THÈSE POUR OBTENIR LE GRADE DE DOCTEUR DE L'UNIVERSITÉ DE MONTPELLIER

En biologie Santé

École doctorale CBS 2 (Chimie et Biologie pour les sciences de la Santé)

Unité de recherche PhyMedExp INSERM U1046

Marqueurs pronostiques biologiques et morphologiques du TAVI à l'ère de l'évolution des pratiques

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Le 22 Novembre 2019

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Remerciements

Aux membres du jury :

A Monsieur le Professeur Eric Bonnefoy-Cudraz: je vous remercie d'avoir accepté de juger ce travail. Vous avez joué un rôle majeur dans ma formation de cardiologue. Je vous exprime toute ma gratitude.

A Madame le Professeur Hélène Eltchaninoff: Je vous remercie d'avoir accepté de juger ce travail. Vous et votre équipe avez révolutionné l'histoire de la cardiologie interventionnelle avec l'avènement du TAVI. Soyez assurée de mon profond respect.

A Monsieur Alain Lacampagne: Merci d'avoir accepté de participer à ce jury et pour cette année de Master 2. J'ai beaucoup appris au laboratoire au sein de ton équipe.

A Madame le Professeur Claire Bouleti: Merci d'avoir accepté de participer à ce jury de thèse et pour tous tes conseils. Tu es et resteras pour moi un modèle.

A Madame le Professeur Florence Leclercq: Je vous remercie d'avoir accepté de diriger ce travail et pour tout ce que vous m'avez apporté pendant mon cursus. Votre expertise dans la thématique est précieuse et vous avez su me transmettre votre passion pour le TAVI et pour l'enseignement.

A Monsieur le Professeur François Roubille : Je te remercie d'avoir accepté de diriger ce travail. Je ne pourrai jamais assez te remercier de m'avoir accordé ta confiance dès l'internat.

A Monsieur le Docteur Thierry Lefèvre : Merci d'avoir accepté de participer à ce jury. Difficile de résumer en quelques mots toute la gratitude et l'admiration que je te porte.

A Madame le Docteur Marie-Jeanne Bertrand : Merci d'avoir accepté de participer à ce jury. Tu es un modèle de réussite et de force de caractère.

A mes parents, je n'oublierai jamais ces valeurs chères à vos yeux.

A Youyou, merci pour ton soutien (encore et toujours).

A mes frères et sœurs, **neveux et nièces, à ma belle-famille.**

A mes amis et ma meilleure amie, merci d'être là.

A toutes **l'équipe de cardiologie du CHU de Montpellier** pour tout ce que j'ai pu apprendre à vos côtés, **à l'«angio» de l'hôpital Privé Jacques Cartier** pour cette année exceptionnelle que je ne pourrai jamais oublier, **à l'équipe du laboratoire PhyMedExp, INSERM U1046,** je vous remercie pour votre accueil, **à l'équipe de cardiologie et de radiologie du CHU de Nîmes** où j'ai fait mes premiers pas d'interne, **à l'équipe de l'unité 51 du CHU de Lyon** qui m'a accueillie pendant 6 mois mémorables.

A **mes ex co-internes, co-fellows, co-chefs et amis :** Rim, Kader, Marion, Christelle, Erwan, Toto, Céline, Pierre M et R, Alexandra, Juliette, Marco, Vincenzo, Andréa(s), Charly, Giulio, Giulia…..
A Grégory, merci pour ta réactivité hors-norme et à Claire avec qui j'aime beaucoup travailler.

Aux internes, étudiants, infirmiers et aides-soignants avec qui j'ai le plaisir de travailler chaque jour et qui font la beauté de notre métier.

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ABREVIATIONS

AVC: Accidents Vasculaires Cérébraux

CA 125: Carbohydrate Antigen 125

CHU: Centre Hospitalo-Universitaire

CRP: C-Reactiv Protein

FEVG: Fraction d'Ejection Ventriculaire Gauche

GDF-15: Growth Differentiation Factor-15

Hs-cTn: Troponine Hypersensible

IMC: Indice de Masse Corporel

RR: Risque Relatif

SC: Score Calcique

sSt2: Soluble Suppression of Tumorigenicity 2

STS score: Society of Thoracic Surgeons score

TAVI: Transcatheter Aortic Valve Implantation

UH: Unité Hounsfield

VARC-2: Valve Academic Research Consortium 2

INTRODUCTION GENERALE

I. Rétrécissement aortique et TAVI

Le rétrécissement aortique, le plus souvent d'origine dégénératif (maladie de Monckeberg), est la pathologie valvulaire la plus fréquente dans les pays industrialisés, représentant environ 30% des valvulopathies (1). Sa prévalence est de 4-7% après 85 ans et est en augmentation constante avec le vieillissement de la population (1). Il s'agit d'un processus pathologique actif et multifactoriel dans lequel l'inflammation chronique, le métabolisme lipidique et les calcifications jouent un rôle majeur avec, sur le plan histologique, la présence de lésions fibro-calcifiantes (2,3).

Le rétrécissement aortique est longtemps asymptomatique et est suspecté sur les données de l'examen clinique avec la présence d'un souffle caractéristique « rude et râpeux » au foyer aortique irradiant dans les carotides avec abolition du B2 en cas de sténose serrée. Le diagnostic formel est porté à l'échocardiographie, examen permettant de préciser le caractère serré du rétrécissement aortique par un gradient moyen transvalvulaire aortique > 40 mmHg et une surface valvulaire <1cm^2 (4). L'échocardiographie permet également d'évaluer les valvulopathies associées, la fonction ventriculaire gauche, l'hypertrophie ventriculaire, la fonction ventriculaire droite, la présence ou non d'une hypertension artérielle pulmonaire, paramètres permettant notamment d'évaluer le retentissement de la valvulopathie. Sur le plan clinique, dès l'apparition de symptômes (dyspnée, angor ou syncope initialement d'effort puis de repos), le pronostic s'aggrave rapidement en l'absence de prise en charge adaptée avec un risque de mort subite entre 1 et 4% par an (5) (Figure 1).

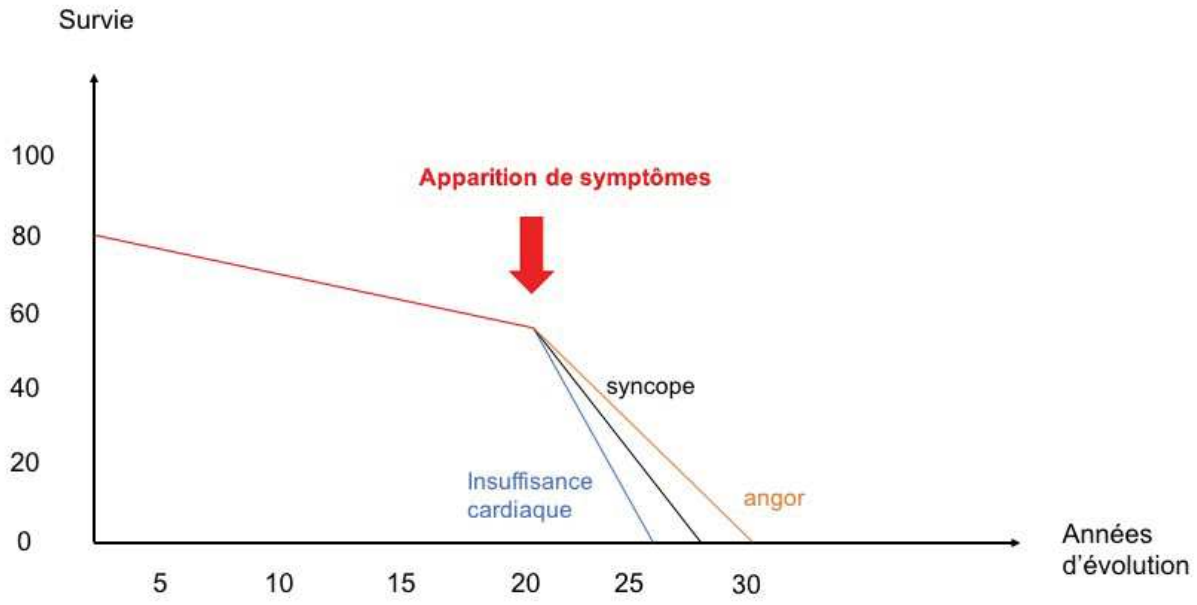


Figure 1 : histoire naturelle du rétrécissement aortique serré à partir de l'apparition des symptômes en l'absence de remplacement valvulaire aortique chirurgical ou percutané (adapté de Bohbot *et al.* (5))

Le remplacement valvulaire aortique chirurgical est le traitement de première intention du rétrécissement aortique serré et symptomatique en classe I des recommandations européennes (4). Cependant, considérant une population de plus en plus vieillissante, une nouvelle technique de prise en charge du rétrécissement aortique a été développée ciblant initialement les patients récusés au traitement de référence, sans alternative thérapeutique jusqu'alors. Il s'agit du remplacement valvulaire aortique percutané ou Transcatheter Aortic Valve Implantation (TAVI), avec une première implantation réalisée en 2002 par le Pr Alain Cribier et son équipe au CHU de Rouen (6). Initialement réservée aux patients à risque chirurgical rédhibitoire, la technique s'est développée avec d'excellents résultats à court, moyen et long terme permettant l'élargissement des indications à des patients à moindre risque chirurgical. En effet, les dernières recommandations européennes de 2017 proposent

une extension des indications du TAVI chez les patients de plus de 75 ans en cas d'anatomie ilio-fémorale favorable après décision de la **« Heart Team »**, équipe multidisciplinaire composée de chirurgiens cardiaques, de cardiologues, de gériatres et d'anesthésistes (4) (Figure 2).

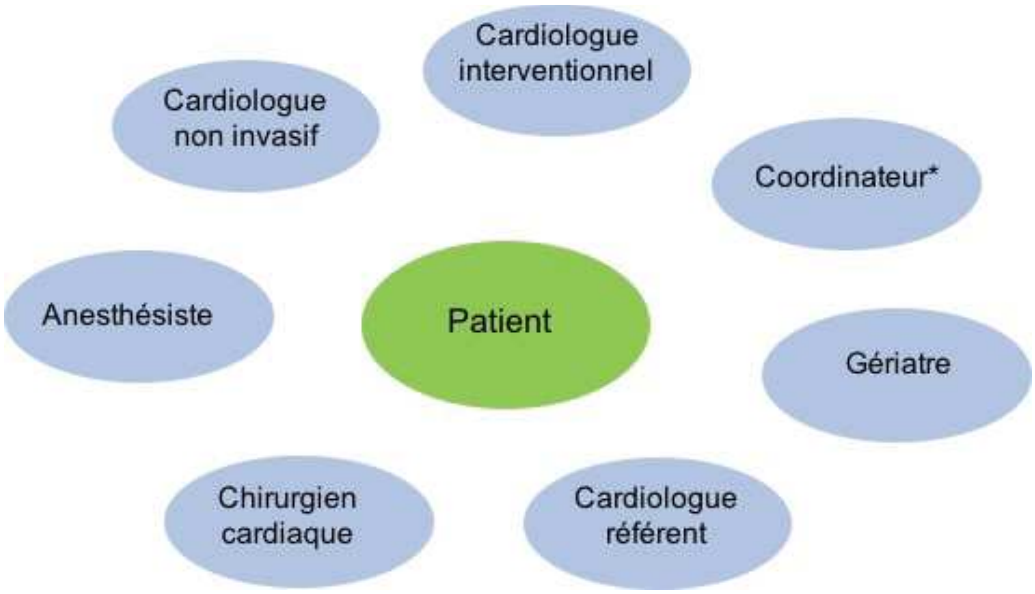


Figure 2 : composition de la « Heart Team » avec décision à l'issue du staff pluridisciplinaire de la prise en charge du rétrécissement aortique

* Le coordinateur est la personne en charge sur le plan logistique de l'organisation du bilan pré-TAVI et de la programmation de la procédure

Depuis plusieurs années, le TAVI s'est largement répandu à travers le monde avec plus de 350 000 implantations réalisées à ce jour et une augmentation de plus 2000% des implantations entre 2009 et 2015. Une évolution exponentielle des implantations est attendue ces prochaines années compte tenu de l'extension inéluctable des indications de la technique à

des patients à moindre risque (7,8). Cependant, malgré les résultats très favorables de la technique, le TAVI présente encore des complications, dont certaines sont spécifiques à la procédure. Les principales complications sont les troubles de conduction avec implantation de pacemaker, les complications vasculaires au niveau de la voie d'abord, les accidents vasculaires cérébraux (AVC), les fuites aortiques péri et intra-prothétiques et l'insuffisance rénale post-procédure. Certaines complications, plus rares mais dramatiques comme la rupture d'anneau aortique, la perforation ventriculaire et l'occlusion coronaire sont devenues exceptionnelles mais sont spécifiques à la technique (9-14) (Tableau 1).

Risque chirurgical	**Elevé** ***Sapien***	**Intermédiaire** ***Sapien XT/ Corevalve-Evolut R***	**Bas** ***Sapien 3/ Corevalve-Evolut R-Pro***
Implantation de pacemaker	3,8%	8,5/ 25,9%	6,6/ 17,4%
Fibrillation atriale	8,6%	9,1/ 12,9%	5,0/ 7,7%
Complications vasculaires	11%	7,9/ 6,0%	2,2/ 3,8%
AVC sévères	3,8%	3,2/ 1,2%	0/ 0,5%
Mortalité	6,6%	3,9/ 2,2%	0,4/ 0,5%
Fuite aortique > grade 2	12,2%	3,7/ 3,5%	0,8/ 4,3%
Insuffisance rénale	4,1%	1,3/ 1,7%	0,4/ 0,9%
Ré-intervention	4,6%	0,4/ 0,9%	0/0,4%
Saignements majeurs	9,3%	10,4/ 12,2%	3,6/ 2,4%
Occlusion coronaire	NK	0,4/ 0,2%	0,2/ 0,9%

Tableau 1 : incidence des complications à 1 mois après TAVI dans les études randomisées comparant TAVI et remplacement valvulaire aortique chirurgical chez les patients à haut

risque (PARTNER (10)), à risque intermédiaire (PARTNER 2 (11) et SURTAVI (12)) et à bas risque chirurgical (PARTNER 3 (13) et Evolut Low Risk (14))

Depuis le début de l'expérience, l'incidence des complications de la technique a nettement diminué (tableau 1). En effet, les dernières études randomisées comparant le TAVI au remplacement valvulaire aortique chirurgical chez les patients à bas risque chirurgical, rapportent des résultats désormais en faveur du TAVI. En effet, dans l'étude PARTNER 3 avec la valve montée sur ballon Edwards Sapien 3 (Edwards Lifesciences LLC, Irvine, CA, USA) incluant 1000 patients, le TAVI est non seulement non-inférieur mais également supérieur (analyse pré-spécifiée) à la chirurgie conventionnelle sur un critère composite de mortalité globale, AVC et ré-hospitalisation à 1 an (13). De même, l'étude Evolut Low risk comparant le TAVI avec les valves auto-expansibles Corevalve, Evolut R et Evolut Pro (Medtronic, Inc., Minneapolis, Minnesota) au remplacement valvulaire aortique chirurgical chez 468 patients retrouve également une non-infériorité du TAVI sur un critère composite de décès et AVC invalidants à 2 ans (14).

La diminution des complications est liée d'une part à l'amélioration des prothèses valvulaires et cathéters utilisés lors de la procédure mais également à l'amélioration de l'expérience des opérateurs et à la meilleure sélection des patients. En effet, une sélection plus rigoureuse des patients pouvant bénéficier de la technique s'effectue à plusieurs niveaux. Tout d'abord, l'évaluation des comorbidités, du degré d'autonomie et de la « fragilité » du patient est une première approche majeure de l'évaluation du risque permettant, grâce à l'approche multidisciplinaire, de distinguer les indications « légitimes » des indications « futiles ». Par ailleurs, l'analyse précise par l'imagerie en coupe (scanner) des caractéristiques anatomiques de l'appareil valvulaire aortique et des voies d'abord potentielles (axes ilio-fémoraux, anneau

aortique, caractère bicuspide ou tricuspide de la valve aortique, calcifications…) permet l'anticipation d'éventuelles difficultés en amont de la procédure et peut même, dans certains cas, faire récuser un patient à la procédure (Figure 3).

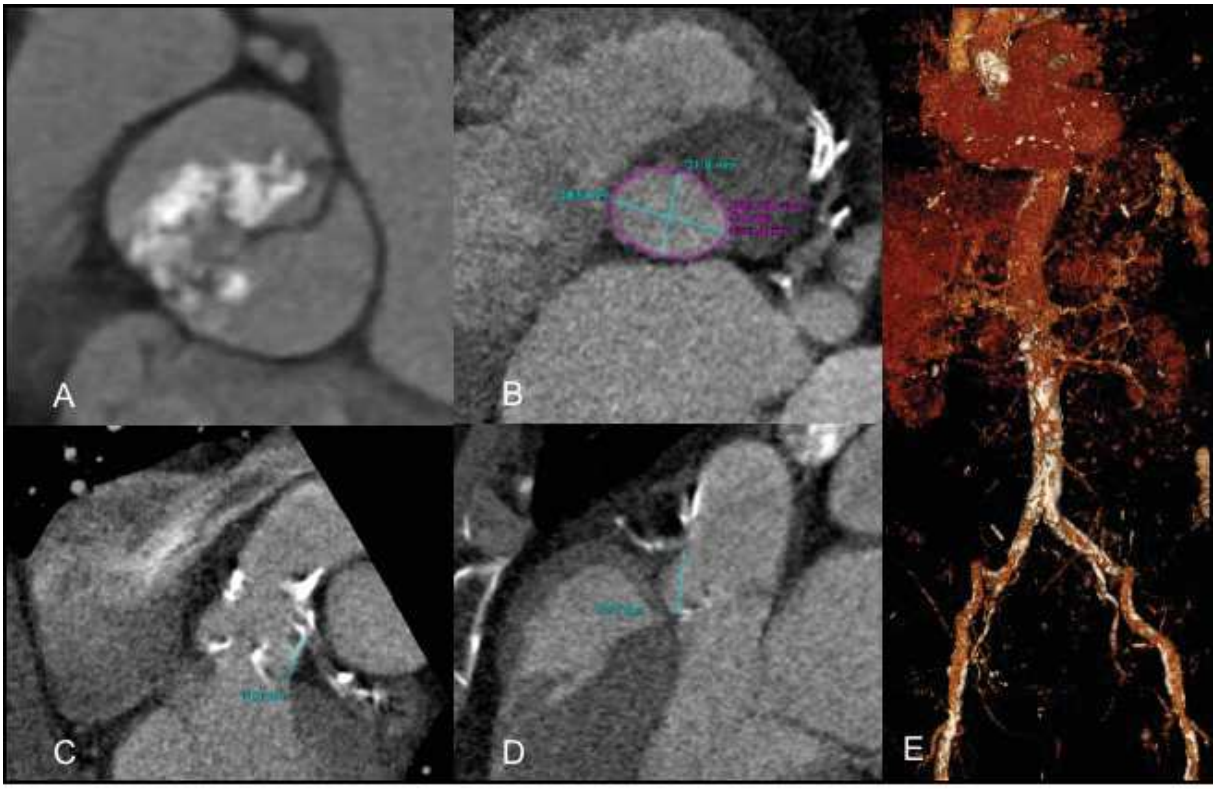


Figure 3 : analyse pré-TAVI par scanner avec gating cardiaque et injection de produit de contraste permettant une évaluation morphologique précise avant la procédure avec caractère tricuspide ou bicuspide de la valve aortique (A), mesure des diamètres minimal, moyen, maximal, de la surface et du périmètre de l'anneau aortique (B), hauteur des ostia coronaires (C, D) et évaluation du diamètre, des calcifications et des tortuosités des axes vasculaires (E).

D'autre part, d'autres éléments morphologiques incluant les données échocardiographiques (fraction d'éjection ventriculaire gauche, fonction ventriculaire droite, valvulopathies associées…) participent à l'évaluation globale du profil de risque du patient (15).

Enfin, certains biomarqueurs peuvent également jouer un rôle dans l'évaluation globale du profil de risque des patients. En effet, certains biomarqueurs ont une valeur pronostique confirmée dans d'autres pathologies cardiovasculaires comme l'insuffisance cardiaque, la cardiopathie ischémique et l'embolie pulmonaire (16-18). Ces biomarqueurs pourraient également trouver leur place dans la stratification du risque des patients porteurs d'une cardiopathie valvulaire et plus particulièrement chez les patients avec rétrécissement aortique bénéficiant d'un TAVI (19-21). La mise en évidence de facteurs pronostiques chez les patients bénéficiant d'un TAVI est donc primordiale pour déterminer le profil de risque dans le but d'améliorer les résultats de la technique et d'anticiper les principales complications. De même, avec l'extension de la technique aux patients à plus faible risque, par définition non contre indiqué à la chirurgie, une meilleure stratification du risque permettrait de mieux sélectionner les « bons » candidats au TAVI. Enfin, la réévaluation de certains facteurs pronostiques décrits au début de l'expérience de la procédure, est indispensable à l'ère de l'évolution des pratiques et de l'amélioration des résultats de la technique.

II. Evolution des pratiques

Depuis les premières procédures de remplacement valvulaire aortique percutané au milieu des années 2000, de nombreuses améliorations techniques et procédurales ont eu lieu avec à l'heure actuelle une simplification de la procédure elle-même mais également une simplification du parcours de soins après la procédure.

Cependant, pour permettre cette simplification de la technique, une planification rigoureuse en amont de la procédure est indispensable afin d'assurer la faisabilité et la sécurité d'une approche minimaliste.

1. Simplification de la procédure

a. Type d'anesthésie

Malgré une première procédure réalisée sous sédation légère et anesthésie locale en 2002 (6), l'expérience initiale du TAVI s'est développée sous anesthésie générale, stratégie encore utilisée en routine en Amérique du Nord (22). En effet, à la différence de l'anesthésie locale avec sédation consciente, l'anesthésie générale permet notamment l'utilisation de l'échographie transoesophagienne pendant la procédure et pourrait être associée à une meilleure stabilité du déploiement de la prothèse et à un meilleur confort du patient et de l'opérateur (23-25). Cependant, l'anesthésie générale est plus invasive et est associée dans certains centres à un sondage urinaire et à la mise en place d'une voie veineuse centrale et d'un cathéter artériel. Tous ces gestes augmentent la durée de la procédure et sont potentiellement associés à un risque d'iatrogénie et notamment à un risque infectieux potentiel. De plus, certains registres rapportent un risque accru d'instabilité hémodynamique, une augmentation des infections pulmonaires, une identification tardive des complications, une augmentation des saignements majeurs et de la durée d'hospitalisation par rapport à la

sédation consciente (23,26). Ainsi, l'anesthésie locale au niveau de la voie d'abord fémorale associée à une sédation légère a progressivement supplanté l'anesthésie générale dans la majorité des centres en France (27). Cette approche moins invasive est réalisable dans la grande majorité des cas et s'est révélée sûre. Dans une méta-analyse récente, les résultats des deux approches étaient similaires en termes de mortalité, de conversion chirurgicale, de complications vasculaires et hémorragiques majeures ainsi que d'AVC (26). Cependant, les besoins en catécholamines et en transfusions étaient moins fréquents chez les patients sous anesthésie locale, de même que les durées d'hospitalisation et de séjour en unité de soins intensifs (26, 28, 29). De plus, la conversion de l'anesthésie locale vers l'anesthésie générale était nécessaire uniquement chez un faible nombre de patients (environ 6%) en raison de complications procédurales ou d'instabilité hémodynamique. Un seul essai randomisé a comparé la désaturation cérébrale entre les deux approches et n'a révélé aucune différence (29). Aucune donnée issue d'étude randomisée n'est disponible actuellement concernant l'impact de l'anesthésie sur les évènements cliniques.

b. Simplification des abords vasculaires

L'approche minimaliste concernant la voie d'abord principale du TAVI ne peut s'envisager actuellement qu'en cas d'accès transfémoral. En effet, l'avènement de l'abord transfémoral « percutané » avec l'apparition de systèmes de fermetures dédiés, a supplanté en grande partie l'abord initialement « chirurgical » depuis 2009 (30-33). Cette évolution des pratiques est liée en grande partie au meilleur profil des cathéters et à la diminution de la taille des introducteurs passant de 24 French dans l'expérience initiale du TAVI à 14 French avec les dernières générations de prothèses (13, 14, 34) (Figure 4).

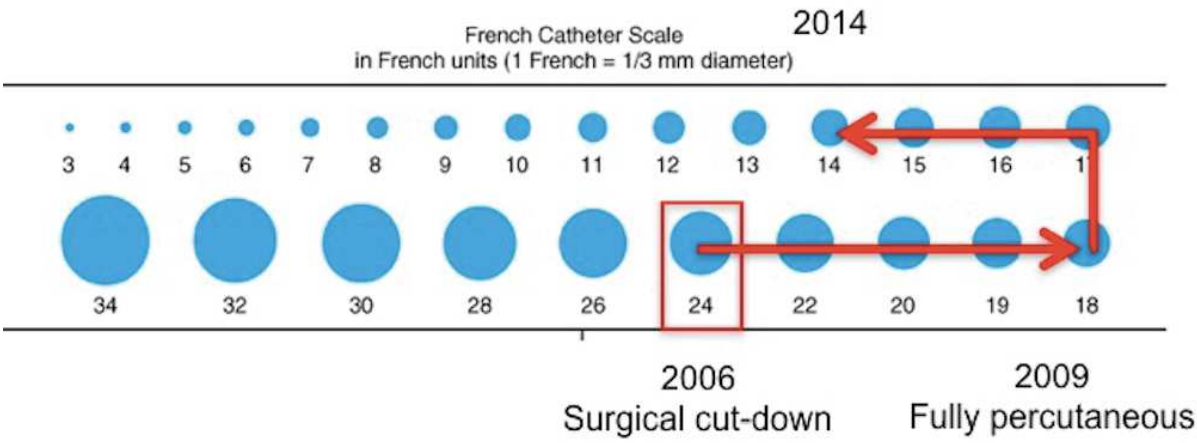


Figure 4 : diminution de la taille des introducteurs entre 2006 (24 French) et 2014 (14 French) permettant l'abord transfémoral percutané.

Ainsi, l'abord percutané, considéré comme moins invasif, a été adopté en routine dans la plupart des centres avec très peu de complications vasculaires dans les dernières études (13, 14, 27). Cette approche pourrait également être associée à une durée d'hospitalisation plus courte (30). En ce qui concerne les dispositifs de fermeture, les systèmes Prostar et Proglide (Abbott Vascular Devices, Redwood City, Californie, États-Unis) sont couramment utilisés (31). Enfin, plus que le type de dispositif percutané, la technique percutanée doit être rigoureuse pour limiter les complications au site d'accès. En effet, le site de ponction de l'artère fémorale commune doit être sélectionné sur le scanner avant la procédure dans une zone sans calcium et au-dessus de la bifurcation et la ponction est réalisée sous guidage angiographique ou échographique au centre de la paroi artérielle antérieure (35,36).

Une autre approche permettant de limiter les complications vasculaires est l'utilisation de plus en plus fréquente de l'accès radial comme voie d'abord controlatérale. En effet, bien que les complications vasculaires aient considérablement diminué au fil du temps, un tiers de ces complications surviennent encore au niveau de l'accès fémoral controlatéral (37). La sélection

d'un accès radial comme voie d'abord secondaire apparaît alors séduisante pour réduire les complications vasculaires et a été décrite précédemment (25). Cependant, dans certains cas, une approche fémorale en cross-over peut être nécessaire, en particulier en cas de nécessité d'implantation d'endoprothèse couverte lors de la gestion d'une complication vasculaire sur la voie d'abord principale. Dans la littérature, l'approche secondaire radiale dans le TAVI s'est avérée faisable et sûre avec une réduction des complications vasculaires lors des interventions percutanées en général et des procédures TAVI en particulier (35, 38-40).

c. Stimulation sur le guide ventriculaire gauche

Au cours de la procédure TAVI, une stimulation ventriculaire rapide est obligatoire pour les valves montées sur ballon dans le but de provoquer une hypotension sévère transitoire nécessaire lors du déploiement de la valve évitant ainsi une embolisation de la prothèse. En routine, une stimulation rapide est effectuée dans le ventricule droit par un accès veineux et une implantation d'une sonde de stimulation temporaire (6). Cependant, cette technique peut être difficile en cas de variations anatomiques et peut entraîner une exposition accrue aux rayons X et des complications spécifiques. En effet, la ponction veineuse peut être associée à la survenue de complications vasculaires telles qu'un hématome, une fistule artério-veineuse ou une thrombose. De même la mise en place de la sonde au niveau du ventricule droit peut être associée à un risque de perforation ventriculaire et de tamponnade (41). Récemment, une stimulation ventriculaire rapide à travers le guide positionné dans le ventricule gauche a été décrite dans le but de simplifier la procédure en supprimant un accès vasculaire supplémentaire lors de procédures de valvuloplastie aortique au ballon ou de TAVI (35,36,41) (Figure 5). Cette nouvelle technique, faisable, sûre avec un taux de complications faible et une

stimulation stable pourrait réduire le temps de procédure (41). Un essai randomisé comparant les deux techniques de stimulation a récemment terminé les inclusions (NCT02781896).

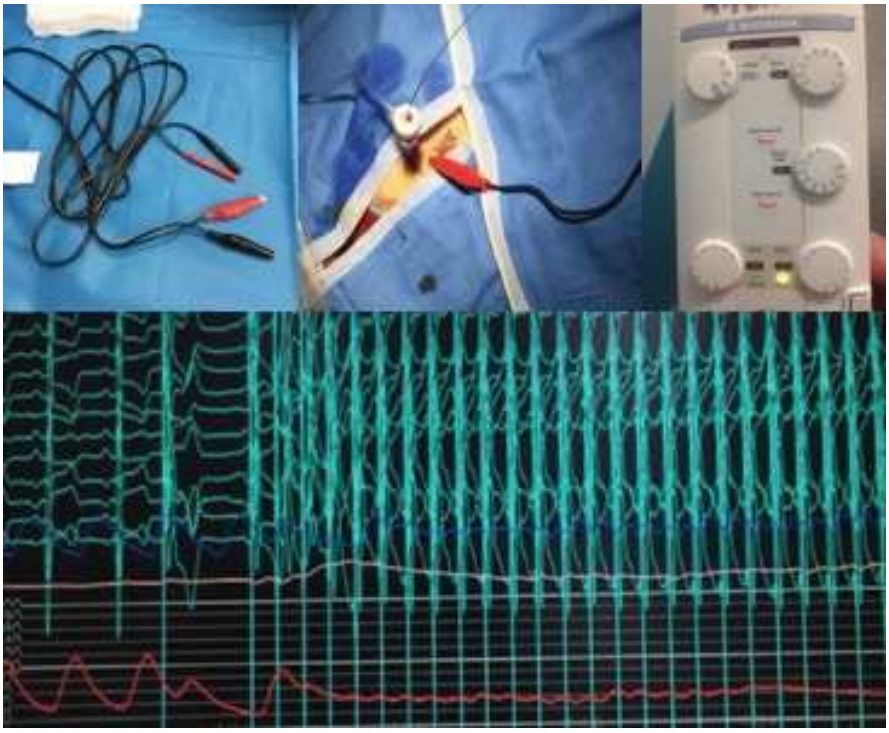


Figure 5 : technique de stimulation sur le guide mis en place dans le ventricule gauche. La stimulation est réalisée à l'aide de pinces crocodiles, la pince noire est raccordée au guide (anode) et la pince rouge est raccordée à la peau via une aiguille métallique (cathode). Le stimulateur est réglé en amplitude maximale (36).

d. TAVI sans prédilatation systématique

Lors de l'expérience initiale du TAVI, la prédilatation au ballon était systématique afin de permettre le passage de la prothèse et d'optimiser son déploiement. Cependant, la réalisation de TAVI sans prédilatation a été évaluée pour la première fois en 2011 par Grübe *et al.* (42) et s'est avérée réalisable dans des études non randomisées (43, 44). Actuellement, avec les dispositifs de nouvelle génération ayant un meilleur profil de franchissement, la prédilatation

au ballon ne semble pas indispensable avant l'implantation de la prothèse et cette approche en « direct TAVI » a été adoptée par plusieurs centres (45). De plus, la prédilatation pourrait présenter quelques inconvénients comme un risque accru d'embolisation cérébrale ou la survenue d'une fuite aortique massive mal tolérée sur le plan hémodynamique (46-49). Cependant, une prédilatation doit être parfois envisagée dans les cas d'une sténose aortique sévèrement calcifiée avec une surface aortique <0,5 cm2, afin de réduire le risque de sous-expansion de la prothèse et le besoin de post-dilater (44). Ainsi le « direct TAVI » est la tendance actuelle dans un but de simplification de la procédure avec pour la première fois une non-infériorité démontrée avec la valve auto-expandable (50). Notre équipe avait pour objectif d'évaluer la faisabilité et l'efficacité du DIRECT TAVI avec la valve de nouvelle génération Sapien 3 montée sur ballon (51) (NCT NCT02729519).

2. Simplification en post-procédure

Un autre aspect de la simplification de la procédure TAVI concerne le parcours de soins. Cette simplification du parcours de soins peut se faire selon différentes modalités avec un passage non systématique en soins intensifs pour certains patients sélectionnés et un raccourcissement de la durée d'hospitalisation.

a. TAVI sans soins intensifs systématique

Après la procédure TAVI, une surveillance rapprochée est systématique dans le but de détecter de façon précoce les complications périprocédurales. Dans de nombreux centres, la surveillance en soins intensifs est effectuée au moins 12 à 24 heures avant le transfert du patient dans une unité de soins conventionnelle en l'absence de complications. Récemment, la réalisation d'un TAVI sans admission systématique en unité de soins intensifs a été évaluée

et s'est avérée faisable et sûre chez certains patients après une évaluation rigoureuse et une surveillance de 2 heures en salle de réveil (52). En effet, l'un des risques à anticiper est le risque de trouble de conduction retardé. Dans l 'étude de Toggweiller *et al*., environ 30% des patients avec un ECG de base normal et l'absence de trouble conductif après TAVI pourraient être orientés d'emblée vers une unité conventionnelle avec un risque de trouble conductif retardé nul (53). Ces données sont consistantes avec la littérature avec environ 30% des patients ayant pu être orientés vers une unité conventionnelle sans complications (52). Cette approche s'intègre parfaitement dans la prise en charge minimaliste et une meilleure stratification du risque pourrait améliorer la sélection des patients pouvant bénéficier de cette approche.

b. Raccourcissement de la durée d'hospitalisation

Une sortie d'hospitalisation précoce a été évaluée dans la littérature démontrant l'innocuité de cette approche chez les patients hospitalisés moins de 48 heures (54-56). En effet, la durée médiane d'hospitalisation était d'un jour dans le groupe « sortie précoce », sans différence en termes de mortalité, d'accident vasculaire cérébral et de réadmission à 1 mois entre les groupes « sortie précoce » et « sortie > 48 heures ». Une procédure de TAVI « minimaliste » avec anesthésie locale, moins de prédilatation au ballon et moins de monitoring invasif, permettait de prédire une sortie précoce dans cette étude. Ainsi cette approche s'envisage avant même la réalisation de la procédure en sélectionnant en amont les patients pouvant bénéficier de cette approche selon le profil de risque (comorbidités) et la présence ou non d'un entourage comme précédemment décrit (57). L'équipe du Dr Webb a également développé un algorithme permettant d'anticiper un raccourcissement de la durée d'hospitalisation selon des critères prédéfinis (58). Ainsi avec l'extension prochaine du TAVI

aux patients à plus faible risque, le raccourcissement de la durée d'hospitalisation reste un objectif prioritaire, nécessitant une sélection rigoureuse des patients et une réflexion sur les structures d'aval.

L'évolution des pratiques dans le TAVI intègre donc une simplification sur le plan de la procédure elle-même mais également en post-procédure (Figure 6).

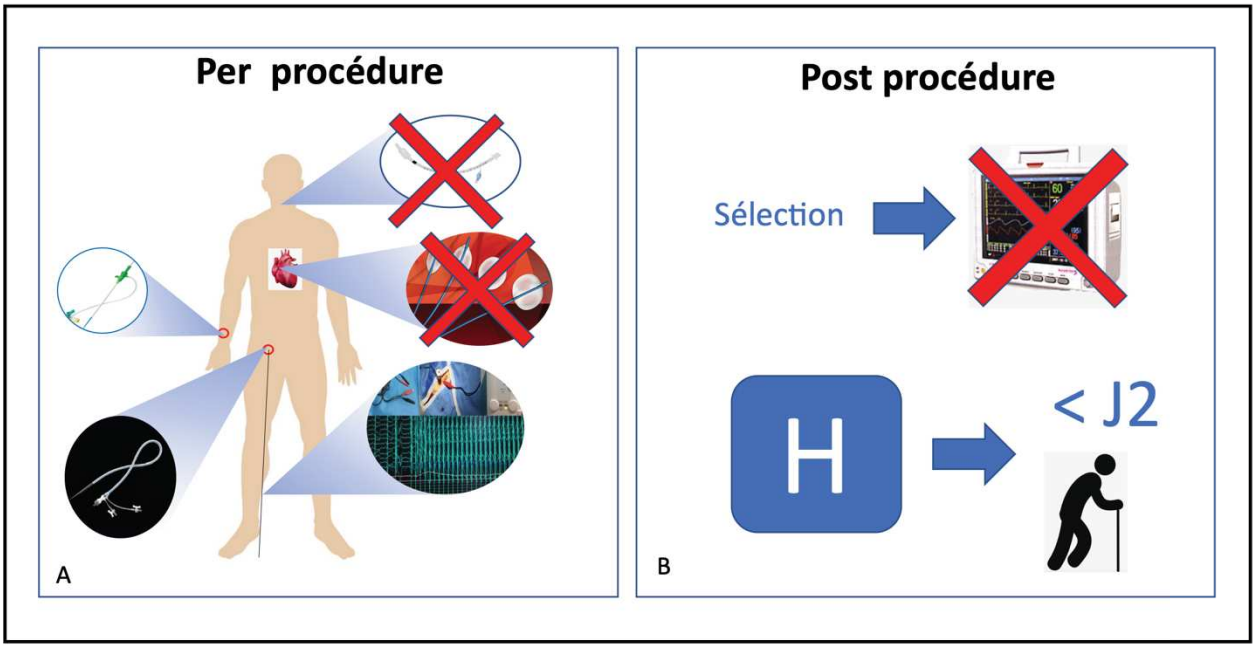


Figure 6 : évolution des pratiques avec éléments de simplification de la procédure TAVI elle-même (A) (sédation consciente, abord fémoral percutané, abord radial secondaire, absence de prédilatation systématique et stimulation sur guide ventriculaire gauche), et des suites de procédure (B) (absence d'hospitalisation systématique en soins intensifs et sortie précoce).

Cette évolution des pratiques a déjà été adoptée en routine dans les centres expérimentés avec un taux de complications faible, un temps de procédure plus court, un meilleur confort du patient, une réduction des coûts et de la charge de travail du personnel. Cependant, une sélection rigoureuse des patients et une stratification précise du risque de complications sont

la clé pour assurer la sécurité de cette approche minimaliste. Ainsi l'identification de nouveaux marqueurs pronostiques cliniques, morphologiques et biologiques ainsi que l'évaluation des marqueurs pronostiques précédemment décrit à l'ère de l'évolution des pratiques sont indispensables pour sélectionner les patients pouvant bénéficier d'une approche minimaliste.

III. Marqueurs pronostiques reconnus en pré-procédure TAVI

Depuis les débuts de la technique, de multiples facteurs pronostiques, cliniques et paracliniques ont été étudiés dans le but de mieux stratifier le risque des patients mais également afin d'identifier les patients pour lesquels le TAVI serait « futile » (figure 7).

a. Facteurs cliniques

Tout d'abord, des facteurs pronostiques cliniques dès l'évaluation initiale du patient ont été mis en évidence. En effet, certaines comorbidités comme la présence d'une pathologie pulmonaire chronique, d'une insuffisance rénale chronique ou d'une « fragilité », concept plus récent, sont associées à une surmortalité chez les patients bénéficiant d'un TAVI dans la littérature (15). En effet, chez les patients porteurs d'une pathologie pulmonaire chronique représentant environ 30% des patients dans l'étude de Mok *et al.* (59), le TAVI était considéré comme futile dans 40% des cas avec absence d'amélioration sur le plan fonctionnel et surmortalité à 6 mois. Ces données ont été confirmées a posteriori chez les patients de l'étude PARTNER (10). Les facteurs pronostiques majeurs de surmortalité dans cette population étaient une distance de marche réduite lors du test de marche de 6 minutes, une mobilité réduite et une oxygéno-dépendance (10,15,59). Hormis l'insuffisance respiratoire chronique, l'insuffisance rénale chronique, présente chez près de la moitié des patients bénéficiant d'un TAVI, a également été démontrée comme étant un facteur pronostique de mortalité dans ce contexte (60-62). En effet, dans l'étude d'Allende *et al.* (63) incluant plus de 2000 patients bénéficiant d'un TAVI, la présence d'une insuffisance rénale chronique sévère (débit de filtration glomérulaire <30 mL/min) était associée à une surmortalité à moyen et long terme. Les facteurs pronostiques associés à cette insuffisance rénale sévère étaient la présence d'une fibrillation atriale et la dialyse avec une mortalité de l'ordre de 40% et 70% à 1 an en post-

TAVI respectivement, avec notamment un surrisque hémorragique et de décompensation cardiaque (15,63).

Enfin, la « fragilité » ou « frailty », concept développé en gérontologie, a été démontrée comme étant un facteur pronostique indépendant de mortalité chez le sujet âgé et de la survenue de complications chez les patients bénéficiant d'un TAVI (22,64). Cette notion intègre l'évaluation de plusieurs fonctions simples comme la mobilité, les capacités cognitives et l'évaluation nutritionnelle avec pour but de donner un reflet de la réserve physiologique en réponse à un stress spécifique (64). Ainsi, dans la littérature, malgré l'absence de définition consensuelle d'indice de fragilité, celle-ci a toutefois été démontrée comme étant associée à une surmortalité post-TAVI, d'autant plus si elle est combinée à d'autres éléments comme les scores de risque chirurgicaux (65-67). Plus récemment, l'étude FRAILTY-AVR a évalué 7 échelles différentes de fragilité et recommandait l'utilisation d'une échelle simple incluant une faiblesse des membres inférieurs, une altération des fonctions cognitives, une anémie et une hypoalbuminémie (68). En effet, cette échelle était la plus fortement associée à une surmortalité à 1 an chez les patients bénéficiant d'un TAVI ou d'une chirurgie conventionnelle (68). D'autres paramètres cliniques comme un indice de masse corporel extrême ou un antécédent de cirrhose ont également été démontrés comme étant des facteurs pronostiques indépendant de mortalité chez ces patients (69,70).

b. Eléments biologiques

Hormis les éléments cliniques, certains facteurs biologiques ont également démontré leur valeur pronostique en pré-TAVI. En effet, le taux d'hémoglobine avant la procédure est reconnu comme étant un facteur classique associé à une surmortalité et à une augmentation de la morbidité après TAVI (71). De même, une hypoalbuminémie, s'intégrant dans un

contexte de dénutrition a également été rapportée comme prédictive de surmortalité après la procédure, mortalité essentiellement d'origine non cardiovasculaire (72).

Plus récemment, le brain natriuretic peptide (BNP) et le NT-proBNP à l'admission ont été rapportés comme facteurs prédictifs de mortalité dans ce contexte. En effet, lors d'une surcharge pressive ou volumique, les cellules myocardiques étirées, essentiellement au niveau du ventricule gauche, sécrètent des peptides natriurétiques sous 2 formes après clivage du préproBNP puis du proBNP : le NT-proBNP inactif et le BNP actif. Ces biomarqueurs ont démontré leur valeur diagnostique et pronostique en contexte d'insuffisance cardiaque (17,73,74). De plus, ces peptides natriurétiques semblent être des marqueurs pronostiques intéressants dans le rétrécissement aortique pour en prédire la sévérité, chez les patients bénéficiant d'une chirurgie de remplacement valvulaire aortique et plus particulièrement chez les patients bénéficiant d'un TAVI (75-77). Dans la littérature, les données concernant l'impact pronostique du BNP et du NT-proBNP dans le TAVI semblent concordantes en faveur d'un impact pronostique réel du BNP en pré-procédure mais également dans les suites immédiates de la procédure sur la survenue d'évènements à moyen et long termes (77,78). De même, Koskinas et son équipe rapportent un impact du NT-proBNP surtout et du BNP d'admission sur la mortalité à 2 ans après TAVI, surtout si le taux de peptides natriurétiques ne diminue pas après la procédure (79).

Cependant, de nombreuses limites sont à apporter à ces données. En effet, le BNP et dans une moindre mesure le NT-proBNP sont directement influencés par d'autres éléments physiologiques (âge, sexe) ou pathologiques sous-jacents (insuffisance rénale, obésité, cirrhose, choc septique…) avec des seuils variables rendant l'homogénéisation des données complexe. De plus, le coût associé aux prélèvements répétés de ces biomarqueurs rend difficile leur utilisation en routine chez les patients bénéficiant d'un TAVI.

c. Eléments morphologiques

Sur le plan morphologique, des paramètres échographiques et scannographiques ont également été décrits comme facteurs pronostiques indépendants de la survenue d'évènements chez les patients bénéficiant d'un TAVI. Tout d'abord, l'altération de la fraction d'éjection ventriculaire gauche (FEVG) < 40%, fréquente dans cette population de patients (jusque 46% avec FEVG <50%) (80), est associée à une surmortalité précoce et tardive avec une surmortalité cardiovasculaire dans les 2 années suivant la mise en place du TAVI (81). Plus que la FEVG, d'autres éléments comme la diminution du volume d'éjection systolique ou la présence d'un rétrécissement aortique « bas débit » (volume d'éjection systolique indexé ≤ 35 mL/m^2), ont été démontrés comme étant associés à une surmortalité au long cours après TAVI indépendamment de la FEVG (82,83). Enfin d'autres paramètres échographiques comme une hypertension artérielle pulmonaire ou une insuffisance mitrale associées sont également évoqués comme facteurs pronostiques de mortalité en post-TAVI (84-87).

Sur le plan morphologique, l'importance des calcifications de l'aorte ascendante a également été rapportée comme prédictive de mortalité chez les patients bénéficiant d'un TAVI (88). En effet, cette rigidité de l'aorte modifierait les conditions de charge et serait associée à un risque accru d'insuffisance cardiaque après la procédure.

d. Scores de risques

Devant ces multiples facteurs pronostiques mis en évidence, plusieurs scores de risque ont été développés dans le but de mieux appréhender le profil de risque des patients bénéficiant d'un TAVI. Tout d'abord, les scores de risque EUROSCORE logistic, EUROSCORE 2 et STS score, utilisés en routine dans le cadre des chirurgies de remplacement valvulaire aortique et de pontage coronaire, ont été évalués chez les patients bénéficiant d'un TAVI. Or, ces scores de risque sont plutôt utilisés comme aide à la décision entre chirurgie conventionnelle et TAVI et

sont peu discriminants en termes d'évaluation du risque de mortalité chez les patients bénéficiant d'un TAVI en particulier (89,90). D'autres scores ont donc été proposés spécifiquement dans la population de patients bénéficiant d'un TAVI, basés sur les facteurs prédictifs de mortalité et de qualité de vie altérée post-TAVI issus des registres (91-93). Ces scores, bien qu'insuffisamment discriminants, permettent d'appréhender le profil de risque des patients après évaluation par des critères simples.

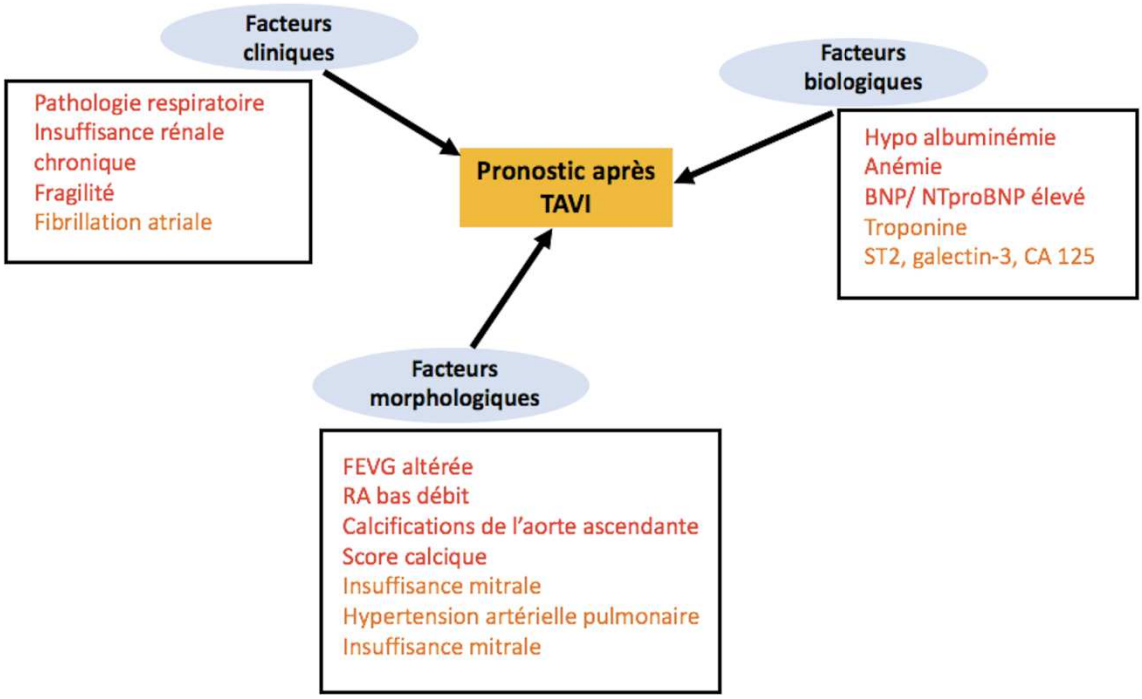


Figure 7 : facteurs pronostiques de mortalité cliniques et paracliniques, reconnus (en rouge) et discutés ou émergents (en orange), chez les patients bénéficiant d'un TAVI

IV Marqueurs pronostiques émergents et/ou discutés

1. Biomarqueurs :

a. La troponine

La troponine est un complexe protéique composant les fibres musculaires des muscles striés et du myocarde. Elle a été découverte en 1965 par Ebashi et Kodama, lors de travaux de recherche portant sur les mécanismes de contraction des muscles striés (94,95).

Les sous-unités de la troponine n'ont été découvertes que plusieurs années après.

Ce complexe protéique est formé par 3 sous-unités protéiques I, C et T (figure 8) (96).

- **La troponine C** (TnC) est aspécifique et est présente également au niveau du muscle strié à l'opposé des troponine T et I qui comportent des isoformes spécifiques du myocarde. La troponine C est responsable de la liaison avec le calcium. Le complexe formé troponine-calcium se déplace et permet la liaison entre actine et myosine. Du fait de ce caractère aspécifique, cette sous-unité ne peut être utilisée pour le diagnostic de lésions myocardiques ou « myocardial injury ».
- **La Troponine I** (TnI) présente 3 isoformes, spécifiques des muscles squelettiques à contraction lente ou rapide et du myocarde (c-TnI). Cette troponine a une fonction d'inhibition permettant la décontraction musculaire en inhibant la liaison actine-myosine (le site de liaison actine-myosine est masqué sur l'actine).
- **La Troponine T** (TnT) est responsable de la liaison avec la tropomyosine. Elle est présente sous 5 à 12 isoformes pour le muscule squelettique (sTnT) et 4 isoformes pour le muscle cardiaque (cTnT).

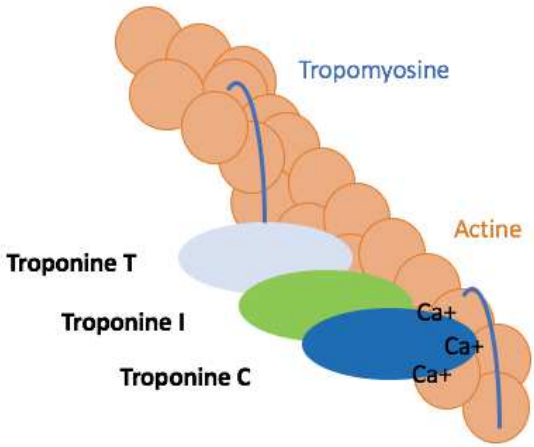


Figure 8 : interaction entre les 3 sous-unités de troponine au niveau des fibres musculaires. La troponine C lie le calcium, le troponine I affecte la liaison actine/myosine et la troponine T interagit avec le tropomyosine.

Ces isoformes cTnT et cTnI se distinguent par une séquence spécifique d'acides aminés et ont pour utilité de déceler une atteinte myocardique (figures 9 et 10). Elles sont mesurées par méthode immunoenzymatique spécifique (96,97).

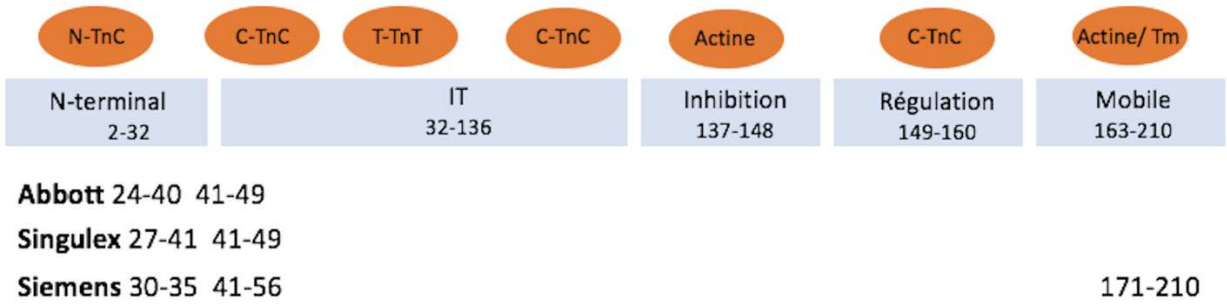


Figure 9 : structure de la troponine I (rectangles bleu clair) et protéines au niveau de la structure musculaire se liant à chaque région de la troponine I (cercles orange). Marques des dosages utilisés pour la troponine I ultrasensible avec séquences des acides aminés (adapté de Adamcova *et al.* (97))



Figure 10 : structure de la troponine T (rectangles bleu clair) et protéines au niveau de la structure musculaire se liant à chaque région de la troponine I (cercles orange). Marque du dosage utilisé pour la troponine T ultrasensible avec séquences des acides aminés (adapté de Adamcova *et al.* (97))

L'utilité diagnostique de la troponine cardiaque en tant que marqueur de souffrance myocardique n'a été mise en évidence dans les études que plus de 30 ans après sa découverte avec l'intégration du biomarqueur dans la définition de l'infarctus du myocarde en 2000 (98,99). Plusieurs mécanismes peuvent expliquer une élévation de troponine : une nécrose, une apoptose, un « stretching » des myocytes avec augmentation de la perméabilité membranaire et un turnover cellulaire (97).

Dans le cadre d'un syndrome coronarien aigu, la troponine est détectée entre 2 à 4 heures après l'atteinte myocardique et fait partie du bilan de routine chez tout patient avec symptômes évocateurs d'un syndrome coronarien aigu (100).

On distingue les troponines « conventionnelles » et les troponines « hypersensibles » (Hs-cTn) de dernière génération, plus récemment utilisées. Ces troponines « hypersensibles » se caractérisent par une précision à 10% pour des valeurs proches et des valeurs du 99° percentile basses (101,102). Il existe plusieurs dosages de troponine, les plus fréquemment utilisés étant les dosages Abbott et Roche. Ces troponines de dernière génération permettent une détection plus importante de leur variation, même minime, avec toutefois un risque de

surdétection. En effet, un dosage de troponine « hypersensible » permet de détecter une élévation de troponine chez le sujet sain dans 50% des cas.

Hormis l'intérêt diagnostique de ce biomarqueur, l'intérêt pronostique a également été mis en évidence dans plusieurs situations.

Tout d'abord chez le sujet sain, la troponine pourrait jouer un rôle de dépistage dans la population générale. En effet, une méta-analyse récente incluant plus de 150 000 patients a mis en évidence un surrisque de mortalité et d'évènements cardiovasculaires chez les patients avec une troponine de base plus élevée (103). De même, une étude prospective a également mis en évidence une association entre Hs-cTn et insuffisance cardiaque et décès d'origine cardiovasculaire chez les patients de plus de 65 ans après un suivi de 12 ans. Enfin, un lien entre Hs-cTn et cardiopathie structurelle (hypertrophie et dysfonction ventriculaire gauche) a également été mis en évidence (104,105).

Hormis chez le sujet sain, l'impact pronostique de la troponine a également été démontré dans diverses pathologies cardiovasculaires (106,107).

En effet, dans le rétrécissement aortique, la Hs-cTn s'est révélée être un facteur pronostique indépendant chez les patients présentant une sténose aortique, indépendamment du traitement proposé (108). Dans ce contexte, le taux de troponine a été mis en évidence comme étant associé à l'hypertrophie ventriculaire et au degré de fibrose myocardique sur des études IRM (107).

De même, le taux de troponine en pré et post-opératoire est un facteur pronostique indépendant chez les patients bénéficiant d'un remplacement valvulaire aortique chirurgical (109, 110). En ce qui concerne le TAVI, les données provenant de petites séries suggèrent que la Hs-cTn pré-procédure pourrait être un facteur pronostique indépendant de mortalité à 1 mois et 1 an (111,112). De plus, la survenue de lésions myocardiques objectivées par

l'élévation de la troponine en post-procédure (« myocardial injury ») après TAVI est fréquente (112-114) et peut être liée à différents facteurs tels que le positionnement de la valve, la stimulation rapide ou aux embols calcaires (113). L'impact pronostique de la troponine en pré et post-procédure reste cependant peu clair avec des données contradictoires dans de petites séries (111-115).

b. Marqueurs de calcifications

D'autres biomarqueurs, reconnus comme facteurs pronostiques dans l'insuffisance cardiaque, émergent chez les patients avec rétrécissement aortique et plus particulièrement chez ceux bénéficiant d'un TAVI. Parmi ceux-ci, les marqueurs biologiques de calcifications semblent prometteurs et pourraient être corrélés à la sévérité de la valvulopathie. L'ostéoprotégérine est l'un des biomarqueurs de calcification se liant au récepteur activateur du facteur nucléaire κβ inhibant l'ostéoclastogénèse avec un rôle potentiel dans le processus d'athérogénèse coronaire et une corrélation avec le score calcique coronaire (116). Une seule étude a évalué la relation entre l'importance des calcifications de la valve aortique et l'ostéoprotégérine sans lien mis en évidence chez des patients porteurs d'un rétrécissement aortique modéré ou serré (117). Aucune donnée n'est disponible dans la littérature concernant le lien entre biomarqueurs de calcifications et score calcique valvulaire chez les patients bénéficiant d'un TAVI. De même, aucune donnée n'est disponible en contexte de TAVI pour la sclérostine, autre marqueur de calcification.

c. Marqueurs de fibrose

Les marqueurs de fibrose sont également étudiés. En effet, le sSt2 (soluble suppression of tumorigenicity 2), membre de la famille des récepteurs à l'interleukine 1, est un marqueur reconnu du remodelage ventriculaire et est corrélé à la sévérité de la cardiopathie chez les

patients insuffisants cardiaque. Ce marqueur est également corrélé à l'apparition de symptômes chez les patients porteurs d'un rétrécissement aortique et est prédictif de mortalité chez les patients bénéficiant d'un remplacement valvulaire aortique chirurgical (118). Dans le TAVI, 3 études ont montré qu'une élévation du sSt2 avant la procédure était corrélée à la mortalité à 1 an (119-121), sans supériorité par rapport au BNP.

De même, la galectin-3 est un marqueur reconnu impliqué dans les processus de fibrose, d'inflammation et de calcifications chez les patients porteurs d'un rétrécissement aortique (122). Ce marqueur présente une valeur pronostique reconnue dans l'insuffisance cardiaque et serait également associé à la survenue d'évènements à court et long terme chez les patients bénéficiant d'un TAVI, surtout s'il est combiné au BNP (123). Cependant les données sont discordantes, l'équipe de Rheude *et al.* (124) ayant demontré que la galectin-3 n'était prédictive d'évènements qu'en cas d'élévation concomitante du carbohydrate antigen 125 (CA 125).

d. Autres biomarqueurs

D'autres mécanismes, comme l'inflammation, pourraient jouer un rôle dans le remodelage ventriculaire post TAVI. En effet, la C reactiv protein (CRP) et le growth differentiation factor (GDF)-15, marqueurs de l'inflammation, ont été rapportés comme étant corrélés à la survenue d'évènements après TAVI dans des séries de petite taille (125).

Le CA 125 est un marqueur tumoral reconnu essentiellement chez les patientes avec tumeur de l'ovaire. Cependant, en dehors du contexte tumoral, ce marqueur peut être produit par les séreuses en réponse à une inflammation et à une stase. En effet, on note une élévation de ce biomarqueur en cas d'inflammation des séreuses et il est également corrélé à la sévérité de l'insuffisance cardiaque (126). Ainsi, les taux de CA 125 avant et après TAVI sont corrélés à la

mortalité et à la survenue d'évènements chez les patients bénéficiant d'un TAVI dans de petites séries (127-129). Plus récemment, l'impact pronostique du CA 125 chez les patients bénéficiant d'un TAVI a été démontré avec une meilleure valeur pronostique que le NTproBNP (124).

Enfin, différents aspects de l'hémostase peuvent êtres altérés chez les patients porteurs d'un rétrécissement aortique. En effet, les forces de cisaillement élevées dans ce contexte à travers la valve aortique entrainent une altération du facteur von Willebrand, une activation plaquettaire et une dégranulation plaquettaire (130-132). Tous ces éléments entraînent un risque accru d'évènements hémorragiques et thromboemboliques, corrélés, lorsqu'ils sont sévères, à la mortalité chez les patients bénéficiant d'un TAVI (130). Cependant, la valeur pronostique de ces éléments n'a pas été démontrée directement hormis pour le facteur von Willebrand et la prédiction des fuites aortiques significatives en post-procédure (132).

Ainsi, de nombreux biomarqueurs émergent comme facteurs pronostiques potentiels chez les patients bénéficiant d'un TAVI. En effet, leur élévation chez les patients porteurs d'un rétrécissement aortique serré s'explique par différents mécanismes, impliquant la valve aortique et le myocarde, reflétant ainsi l'importance des calcifications, du stress exercé sur les myocytes, de l'inflammation chronique, du remodelage et de la fibrose ventriculaire gauche (Figure 11).

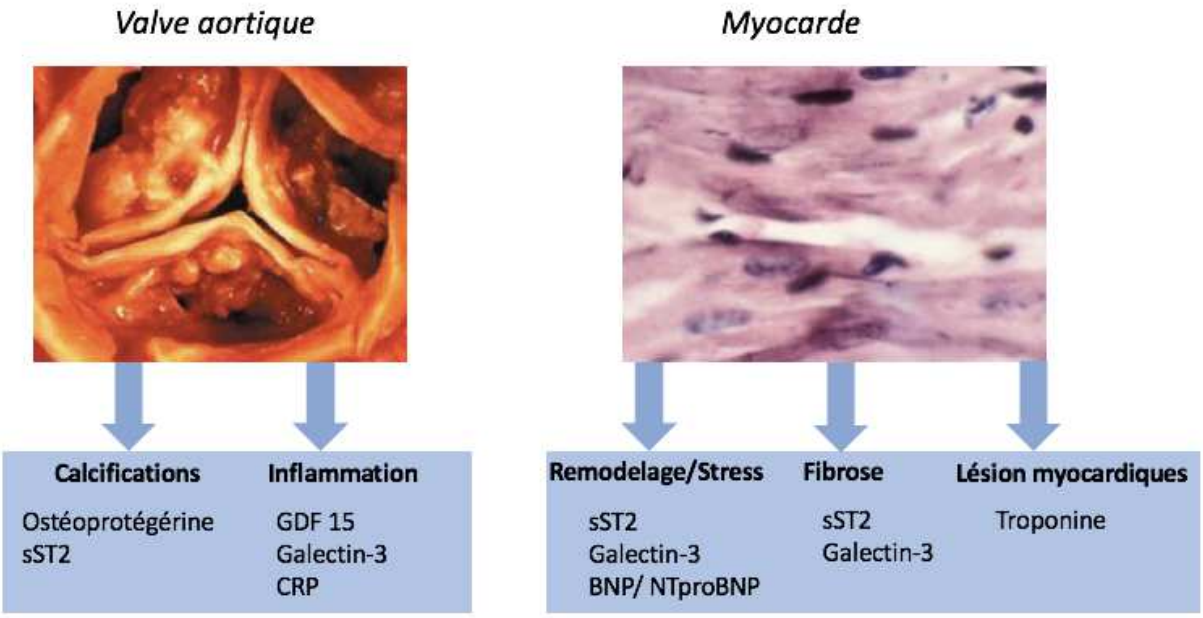


Figure 11 : différents biomarqueurs et mécanismes principaux impliqués dans leur élévation chez les patients porteurs d'un rétrécissement aortique

Ces biomarqueurs pourraient ainsi être corrélés à la sévérité de la maladie et présenter un intérêt pronostique dans ce contexte aidant à la stratification du risque. Cependant, les données sont contradictoires selon les études et aucune donnée sur de larges cohortes de patients n'est disponible. De même, ces outils doivent être réévalués à l'ère de la simplification des procédures et devant les modifications notables du profil de risque des patients orientés vers un TAVI à l'heure actuelle.

2. Marqueurs pronostiques en imagerie : le score calcique

a. Importance des calcifications valvulaire et annulaire aortique

Sur le plan physiopathologique, les mécanismes conduisant au développement des calcifications valvulaires ne semblent pas encore totalement élucidés. En effet, 3 principaux mécanismes ont été rapportés. Tout d'abord une matrice osseuse serait présente au niveau de la valve aortique (cellules ostéoïdes, collagène et ostéoclastes) dans environ 20% des cas (133). De plus, une minéralisation active de la valve par des cellules exprimant des gènes ostéogéniques a également été rapportée (134-137) ainsi que l'accumulation de dépôts calciques au sein de la valve aortique elle-même (133,138). Ainsi, l'importance des calcifications a été démontré comme étant corrélée à la sévérité du rétrécissement aortique (139,140) et peut parfois permettre de conclure au caractère serré du rétrécissement aortique dans les cas litigieux (score calcique > 2000 unités Hounsfield (UH) chez l'homme et 1200 UH chez la femme) (4).

Lors de la planification initiale de la procédure de TAVI, une attention particulière est portée aux calcifications de l'anneau et de la valve aortique. En effet, la quantité de calcifications et leur localisation sont des éléments à prendre en compte afin d'anticiper d'éventuelles complications. En effet, un minimum de calcifications est requis, nécessaire à l'impaction de la prothèse valvulaire au niveau de la valve aortique. Cependant, des calcifications massives ou de distribution inhomogène peuvent gêner l'expansion de la prothèse et conduire à un résultat imparfait ou à la survenue de complications (141,142).

b. Evaluation des calcifications : le score calcique d'Agatston

Le score calcique (SC) d'Agatston est une méthode de quantification scannographique des calcifications de l'appareil valvulaire aortique. Ce score a été décrit pour la première fois en 1990 pour l'évaluation des calcifications coronaires (143) puis adapté pour l'évaluation de la valve aortique (144,145). Le SC est une méthode d'évaluation des calcifications simple, fiable et reproductible. En effet, le SC peut être évalué sur un scanner thoracique sans injection de produit de contraste synchronisé à l'électrocardiogramme. La région d'intérêt, centrée sur le massif cardiaque, est délimitée de la partie supérieure de la chambre de chasse ventriculaire gauche au sommet des cusps aortiques avec une épaisseur de coupes de 3mm. L'analyse du volume est réalisée à l'aide du logiciel spécifique SmartScore 4.0 (General Electric Healthcare, Waukesha, Wisconsin, USA) permettant une détection automatique de l'ensemble des calcifications du volume acquis avec un seuil de 130 UH. La délimitation et l'évaluation des calcifications de la zone d'intérêt est réalisée par l'opérateur, avec l'utilisation du score calcique d'Agatston, exprimé en unités arbitraires, sur les coupes transversales, selon une technique standardisée (146) (figure 12). Le SC est déterminé en tenant compte de la surface des calcifications et de leur densité maximale avec un facteur de 1 à 4 appliqué en fonction de celle-ci. Un facteur 1 est appliqué en cas de densité entre 130 UH et 199 UH, 2 entre 200 UH et 299 UH, 3 entre 300 et 399 UH et 4 si la densité était supérieure ou égale à 400 UH. Le SC est obtenu en multipliant la surface (en mm^2) par le facteur d'ajustement pour chaque région délimitée sur l'ensemble du volume d'acquisition. Les calcifications coronaires sont exclues de l'analyse.

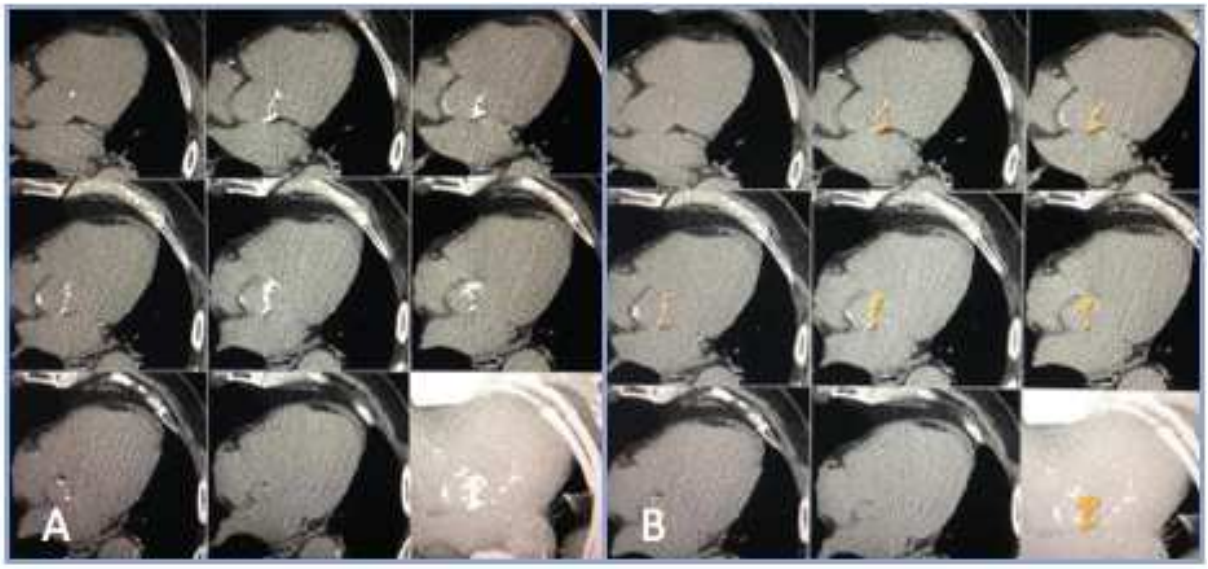


Figure 12 : évaluation du SC sur des coupes de scanner sans injection de produit de contraste. La première étape consiste en une sélection de la zone d'intérêt centrée sur la valve (A) puis les calcifications sont identifiées et sélectionnées (en orange) (B).

c. Impact pronostique du score calcique chez les patients bénéficiant d'un TAVI

L'importance des calcifications de l'appareil valvulaire aortique est un facteur pronostique reconnu de mortalité chez les patients porteurs d'un rétrécissement aortique (139,140). Plus particulièrement chez les patients bénéficiant d'un TAVI, le SC valvulaire est un facteur prédictif de complications, en particulier de la survenue de fuite aortique péri-prothétique, d'implantation de pacemaker (141,147,148) et de rupture d'anneau aortique (142). En particulier, l'impact pronostique du SC sur la survenue de fuites aortiques périprothétiques a été démontré avec la précédente génération de prothèses valvulaires percutanées (Medtronic CoreValve, Edwards Sapien et Sapien XT) avec une augmentation associée de la mortalité (149). Concernant la valve de dernière génération Edwards Sapien 3, commercialisée en Europe depuis janvier 2014, le SC n'apparaît pas comme étant

associé à la survenue de fuite aortique dans une seule étude (150). En effet, les performances de cette prothèse, développée dans le but de palier aux différentes limites de la génération de valve précédente, particulièrement avec l'implantation d'une « jupe » externe, pourrait contrebalancer les effets des calcifications sur l'expansion de la prothèse en limitant l'incidence des fuites aortiques paravalvulaires (150) (figure 13). Aucune donnée n'est disponible concernant l'impact pronostique des calcifications et plus précisément du SC avec les valves auto-expansibles de dernière génération ayant pour principal intérêt la possibilité d'une recapture et d'un repositionnement (figure 13).



Figure 13 : valve montée sur ballon de dernière génération Edwards Sapien 3 (à gauche) et auto-expansible Medtronic Corevalve Evolut R (à droite)

Ainsi, le SC, outil morphologique simple, pourrait être réalisé lors du scanner pré-TAVI dont bénéficient tous les patients avant la procédure. Sa valeur pronostique doit être réévaluée avec les dernières générations de prothèses ayant bénéficiées d'améliorations notables mais également à l'ère de l'évolution des pratiques notamment avec l'absence de prédilatation systématique.

OBJECTIFS

I. Identifier des marqueurs pronostiques biologiques et morphologiques

Le premier objectif de ce travail était **d'identifier des marqueurs pronostiques biologiques et morphologiques, simples**, utilisables en routine chez les patients bénéficiant de la mise en place d'une valve aortique percutanée.

Deux études ont été réalisées chez deux cohortes distinctes de patients.

La première visait à évaluer l'impact pronostique de la troponine en pré et post-procédure chez les patients bénéficiant d'un TAVI.

La deuxième étude évaluait l'impact pronostique du score calcique scannographique, réalisable en routine sur le scanner systématique en pré-procédure, chez les patients bénéficiant d'un TAVI avec 2 générations différentes de prothèses.

En effet, la mise en évidence de facteurs pronostiques supplémentaires pourrait permettre d'améliorer la stratification du risque des patients et de sélectionner les patients avec un profil de risque « favorable » à une procédure TAVI à l'ère de l'évolution des pratiques.

II. Intégrer ces facteurs pronostiques dans l'évolution des pratiques

Le deuxième objectif de ce travail était **d'évaluer la pertinence de ces facteurs pronostiques mis en évidence dans la première partie du travail de thèse à l'ère de l'évolution des pratiques.**

En effet, l'étude DIRECTAVI, étude randomisée visant à évaluer l'intérêt ou non d'une prédilatation systématique au cours de la procédure TAVI, a démontré la non-infériorité d'une procédure de « direct TAVI » (sans prédilatation systématique) chez les patients implantés d'une valve de dernière génération Edwards Sapien 3 (NCT02729519). Une sous-étude concernant l'impact pronostique de la troponine et la survenue d'une « myocardial injury » en post-procédure dans cette population a été réalisée afin de déterminer l'influence de l'évolution des pratiques sur ce facteur pronostique préalablement mis en évidence. En effet, l'absence de prédilatation en particulier pourrait réduire le risque d'élévation de troponine post-procédure, la « myocardial injury », induite lors de cette étape.

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ARTICLES SCIENTIFIQUE

Chapitre 1:

Publication 1: ***Prognostic impact of pre- and post-TAVI troponin: a large cohort study***

Prognostic impact of pre- and post-TAVI troponin: a large cohort study

Mariama Akodad, Marco Spaziano, Bernard Chevalier, Philippe Garot, Hakim Benamer, Annabelle Dinan-Zannier, Xavier Troussier, Thierry Unterseeh, Stéphane Champagne, Thomas Hovasse, Thierry Lefèvre . *J Am Heart Assoc 2019.*

La troponine, marqueur de souffrance myocardique, est un facteur pronostique reconnu dans le rétrécissement aortique et chez les patients bénéficiant d'un remplacement valvulaire aortique chirurgical en pré et post-intervention. Cependant, la valeur pronostique de ce biomarqueur chez les patients bénéficiant d'un TAVI est controversée. En effet, concernant le **taux de troponine pré-procédure**, des données issues de petites séries suggèrent son rôle en tant que facteur pronostique dans ce contexte. En effet, la troponine pré-procédure serait prédictive de mortalité à moyen et long terme et serait en fait un marqueur de sévérité de la cardiopathie sous-jacente.

L'élévation significative de troponine ou lésions myocardiques (« myocardial injury ») après TAVI est définie par une élévation de troponine > 15 × la limite supérieure de la normale et de plus de 50% par rapport à la troponine pré-procédure (9). Cette élévation de troponine est fréquente et concerne entre 30 et 50% des patients bénéficiant d'un TAVI selon les séries (111-113). Elle peut être liée à différents facteurs tels que le positionnement de la valve, la stimulation rapide ou des micro-embols au niveau des artères coronaires (113). Cependant, son impact pronostique reste peu clair et variable selon les séries. Plus récemment, une étude a déterminé que la survenue de lésions myocardiques après TAVI dépendait du type de valve utilisée mais n'était pas prédictive de mortalité (115).

Ainsi, nous avons, dans ce premier travail, évalué la valeur pronostique de la troponine pré- et post-procédure dans une large cohorte de patients bénéficiant d'un TAVI sur une période d'inclusion de 5 ans afin de clarifier l'impact pronostique de ce biomarqueur et d'améliorer la stratification du risque chez les patients éligibles au TAVI.

Concernant la troponine pré-procédure, nous avons divisé la population globale de 1390 patients en 3 tertiles en fonction du taux de troponine initial. Nous avons ensuite évalué l'impact, en fonction du tertile, de la troponine pré-procédure sur la mortalité à 30 jours, 1 an et jusque 3 ans. Nous avons également déterminé les facteurs prédictifs d'élévation de la troponine pré-procédure.

La survenue de lésions myocardiques a été évaluée en fonction du tertile initial afin de pondérer l'élévation de la troponine post-procédure en fonction de la troponine pré-procédure.

Cette étude a permis de confirmer que la troponine pré-procédure était un facteur pronostique indépendant de mortalité à 30 jours, à 1 an et jusqu'à 3 ans. Les patients avec le taux de troponine le plus bas (premier tertile) avaient un profil de risque plus favorable (âge

moins élevé, sexe féminin, moins de troubles conductifs et de fibrillation atriale, moins de coronaropathie et d'atteinte vasculaire périphérique, une meilleure FEVG, moins d'hypertension artérielle pulmonaire et de plus faibles taux de NT-proBNP) avec par conséquent des scores de risques moins élevés (STS et Euroscore logistic). Nous avons également pu déterminer des facteurs prédictifs de troponine pré-procédure élevée (sexe masculin, arythmie auriculaire, faible débit de filtration glomérulaire et taux de NT-proBNP élevé en pré-procédure).

Concernant la survenue de lésions myocardiques après TAVI, nous avons pu démontrer pour la première fois que l'impact pronostique sur la mortalité était dépendant de la troponine pré-procédure. En effet, la survenue de lésions myocardiques était prédictive de la mortalité à 1 an seulement chez les patients ayant une troponine pré-procédurale normale ou quasi-normale.

Ce travail nous a donc permis de **confirmer d'une part la valeur pronostique de la troponine pré-procédure** à moyen et long terme sur une large population de patients et a apporté des données nouvelles concernant **la valeur pronostique de la survenue de lésions myocardiques en fonction de la troponine pré-procédure**. Ce biomarqueur pourrait donc être utilisé en routine pour une meilleure appréhension du profil du risque des patients bénéficiant d'un TAVI.

ORIGINAL RESEARCH

Prognostic Impact of Pre-Transcatheter and Post-Transcatheter Aortic Valve Intervention Troponin: A Large Cohort Study

Mariama Akodad, MD;* Marco Spaziano, MD;* Bernard Chevalier, MD; Philippe Garot, MD; Hakim Benamer, MD; Annabelle Dinan-Zannier, MD; Xavier Troussier, MD; Thierry Unterseeh, MD; Stéphane Champagne, MD; Thomas Hovasse, MD; Thierry Lefèvre, MD

***Background*—**Biomarkers were advocated as prognostic factors in patients undergoing transcatheter aortic valve intervention, with contradictory results concerning prognostic impact of troponin. Our aim was to assess the prognostic impact of preprocedural and postprocedural troponin in transcatheter aortic valve intervention.

***Methods and Results*—**Preprocedural and postprocedural high-sensitivity troponin levels were measured in all patients undergoing transcatheter aortic valve intervention. Primary end point was 1-year mortality. This study included 1390 patients, with a mean age of 83.4±6.8 years. Patients were divided into 3 tertiles according to preprocedural troponin values: tertile 1: 0.001 to 0.023 μg/L; tertile 2: 0.024 to 1.80 μg/L; and T3: 1.81 to 12.1 μg/L. One-year mortality was higher in patients in tertile 2 (hazard ratio, 2.1; *P*=0.001) and T3 (hazard ratio, 1.8; *P*=0.009) compared with those in tertile 1. Myocardial injury was predictive of 1-year mortality (hazard ratio, 1.7; *P*=0.01). This effect may be stronger in the tertile 1 subgroup (hazard ratio, 5.1; *P*=0.03 [*P* value for interaction: 0.18]).

***Conclusions*—**Elevated preprocedural troponin and myocardial injury are associated with 1-year mortality after transcatheter aortic valve intervention. **(*J Am Heart Assoc*. 2019;8:e011111. DOI: 10.1161/JAHA.118.011111.)**

Key Words: transcatheter aortic valve implantation • troponin • aortic stenosis

Transcatheter aortic valve intervention (TAVI) is an alternative to surgery in patients with severe aortic stenosis who are at high surgical risk or in patients for whom conventional aortic valve replacement is contraindicated. Indications were recently extended to patients at moderate surgical risk with Food and Drug Administration approval when the transfemoral approach is considered feasible after Heart Team discussion.[1] Patient selection and risk stratification are key elements for procedural success, but identifying which individuals benefit the most from the procedure remains challenging.[2,3] In this context, several clinical, echocardiographic, and biological prognostic factors have been suggested to predict outcomes.

Among these, biomarkers were identified as potential prognostic factors. New generation high-sensitivity troponin T allows the detection of small increases in troponin levels and was proven to be an independent prognostic factor in patients with aortic stenosis.[4] In addition, preprocedural and postprocedural troponin levels are independent predictors of outcomes in patients undergoing surgical aortic valve replacement.[5,6]

With respect to the TAVI procedure, data from small series suggest that preprocedural high-sensitivity troponin T may be an independent prognostic factor of 1-month and 1-year mortality.[7,8]

Furthermore, myocardial injury after TAVI is frequent[8–10] and may be related to different factors such as valve positioning, rapid pacing, or calcium embolism.[9] The prognostic impact of postprocedural troponin (ie, myocardial injury) remains unclear, with contradictory data in small series.[8–10] More recently, a study determined that myocardial injury after TAVI depended on the type of device used but was not predictive of mortality.[11]

Taking all of these considerations together, assessing the prognostic value of preprocedural and postprocedural troponin in a large prospective cohort of patients may clarify the prognostic value of these parameters, improve risk stratification in patients undergoing TAVI, and ultimately improve periprocedural management.

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Received October 2, 2018; accepted January 17, 2019.

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Clinical Perspective

What Is New?

- Preprocedural troponin is an independent predictor of long-term mortality, as well as myocardial injury in patients with normal or near-normal preprocedural troponin levels.

What Are the Clinical Implications?

- Systematic troponin assessment is routinely feasible and may allow better risk stratification in patients undergoing transcatheter aortic valve intervention.

The aim of this study was to assess the prognostic impact of preprocedural and postprocedural troponin in a large cohort of patients undergoing TAVI.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Population and Procedure

Preprocedural and postprocedural troponin measurements were prospectively collected in all patients undergoing TAVI in our center. We separated the total population in 3 roughly equal tertiles according to preprocedural troponin to compare clinical outcomes. We also assessed the impact of troponin rise (ie, the occurrence of myocardial injury) according to VARC-2 (Valve Academic Research Consortium) criteria. This is defined as troponin T elevations >15 times the upper reference limit of the center's troponin assay (in our center, 0.014 μg/L×15=0.21 μg/L) and at least a 50% increase compared with preprocedural values.[12]

A multidisciplinary heart team involving at least 1 interventional cardiologist and 1 cardiac surgeon discussed all cases, and consensus was achieved regarding therapeutic strategy. Patients underwent TAVI via the transfemoral, transaortic, transapical, subclavian, or carotid approach according to previously described techniques.[13,14] All patients provided informed written consent for the procedure and data collection, and the local ethics committee approved the study.

Data Collection and Study End Points

High-sensitivity troponin T measurement was performed on the Cobas 8000/e602 analyzer (Roche Diagnostics) the day before and the day after the procedure in all included patients. The 99% upper reference limit for this kit is 0.014 μg/L. The total imprecision at the 99th percentile is <6.5%. The limit of detection of this assay is 0.005 μg/L. For patients requiring revascularization before TAVI, percutaneous coronary intervention (PCI) was performed at least 10 days before the valve intervention. Clinical and echocardiographic data at baseline and follow-up were prospectively collected by dedicated personnel and entered in a local database and national registries.[15,16]

The primary end point of this study was 1-year mortality. Secondary end points consisted of 30-day mortality, 3-year mortality, stroke, myocardial injury, new pacemaker implantation, major vascular complication, paravalvular regurgitation greater than mild, and acute kidney injury. End points were defined according to the VARC-2 criteria.[12]

Statistical Analysis

Patients were separated into 3 groups based on preprocedural troponin value. Preprocedural troponin ranged from 0.001 to 12.1 μg/L. Using the 33rd and 66th percentiles of preprocedural troponin, tertiles had the following ranges: tertile 1 (T1): 0.001 to 0.023 μg/L; tertile 2 (T2): 0.024 to 1.80 μg/L; and tertile 3 (T3): 1.80 to 12.1 μg/L.

One-year survival data were fitted in a Cox proportional hazards model and compared in a pairwise fashion for preprocedural troponin tertiles (ie, T1 versus T2, T1 versus T3, and T2 versus T3). Crude and adjusted hazard ratios (HRs) (with 95% CIs) are reported. HRs were adjusted (forward stepwise likelihood ratio) for procedure date (to account for a potential learning effect of time) and for baseline characteristics with a univariate $P<0.10$ for the outcome of 1-year mortality. The covariates that met this criterion and were included in the multivariate model are reported in Table 1. The 1-year model was then extended to 3-year data as an exploratory analysis.

The effect of myocardial injury was assessed as follows: first, we added the myocardial injury variable to the above-mentioned survival model to appreciate its effect. Next, we assessed for interaction of myocardial injury by preprocedural troponin tertile. Finally, as an exploratory analysis, we looked at the HR of myocardial injury in each tertile. Patients who underwent TAVI via the transapical access were excluded from these analyses, as the troponin rise might be less meaningful in that context. Finally, independent predictors of an elevated preprocedural troponin value were assessed by means of a multivariate linear regression model.

Continuous data are reported as mean±SD or median (interquartile range), and categorical variables are reported as number of patients and percentages. Categorical data were compared using chi-square test, and continuous data using 1-way ANOVA or the Kruskal–Wallis test, as appropriate. A $P<0.05$ was considered significant for adjusted models. Statistical analyses were performed with SPSS version 23 (IBM Corp).

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Table 1. Univariate and Multivariate Predictors of 1-Year Mortality

	Univariate Analysis		Multivariate Analysis		
Parameter	HR	*P* Value (Crude)	HR	95% CI	*P* Value (Adjusted)
Preprocedural troponin tertile					
T2 vs T1	2.39	<0.001	2.07	1.38–3.12	0.001
T3 vs T1	2.32	<0.001	1.76	1.15–2.68	0.009
T3 vs T2	0.97	0.52	0.89	0.64–1.21	0.43
Age (per 1-y increment)	1.18	0.006	1.028	1.003–1.053	0.03
Coronary artery disease	1.40	0.03	…	…	…
Peripheral vascular disease	1.47	0.01	1.45	1.07–1.98	0.02
LVEF (per 5% increment)	0.92	<0.001	0.94	0.89–0.98	0.009
Mean aortic gradient (per 5-mm Hg increment)	0.95	0.03	…	…	…
Pulmonary artery systolic pressure (per 5-mm Hg increment)	1.05	0.08	…	…	…
eGFR (per 5-mL/min increment)	0.94	<0.001	0.96	0.93–0.995	0.03
Preprocedural NT-proBNP tertile					
T2 vs T1	1.64	0.04	…	…	…
T3 vs T1	2.60	<0.001			
T3 vs T2	1.59	0.01			

Values are expressed as mean±SD or number (percentage) unless otherwise indicated. For pairwise comparisons, the reference category is stated last (ie, for tertile 2 [T2] vs tertile 1 [T1], the reference category is T1). eGFR indicates estimated glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; T3, tertile 3.

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Results

Between March 2011 and September 2016, 1390 patients underwent TAVI in our center. The mean patient age was 83.4±6.8 years, 52% were men, and mean Society of Thoracic Surgeons (STS) and logistic European System for Cardiac Operative Risk Evaluation (EuroScore) were 5.8±4.0% and 17.3±11.0%, respectively. Several baseline characteristics differed significantly between preprocedural troponin tertiles (Table 2). Patients in T1 (normal or near-normal troponin) were younger, more likely to be female, had less conduction disturbances such as atrial fibrillation or previous pacemaker, were less likely to have undergone previous PCI, and had less peripheral vascular disease (all $P<0.05$). With respect to paraclinical characteristics, patients in T1 had higher left ventricular ejection fraction and lower pulmonary artery pressure, better renal function, and lower NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels (all $P<0.05$). Consequently, patients in T1 also had lower STS and logistic EuroScore (both $P<0.001$).

The distribution of the transfemoral and nontransfemoral approaches was similar among tertiles (Table 3). The use of self-expanding devices differed significantly, with T1 exhibiting the lowest percentage (T1: 26.3% versus T2: 31.9% versus T3: 35.8%, $P=0.008$). Device sizes were also significantly different among tertiles, with patients in T1 receiving smaller valves.

30-Day Clinical Outcomes

Procedural outcomes such as the need for a second device or annulus rupture were similar between tertiles (Table 3). Thirty-day mortality was significantly different between tertiles, with patients in T1 displaying a mortality rate less than half of that in patients in the other tertiles (T1: 3.5% versus T2: 8.3% versus T3: 7.0%, $P=0.007$) (Table 4). Myocardial injury occurred significantly less in patients in T3 compared with the other groups (T1: 66.4% versus T2: 59.7% versus T3: 14.3%, $P<0.001$). Other clinical outcomes such as stroke, new pacemaker implantation, and major vascular complications were similar between preprocedural troponin tertiles.

Patients in T1 had lower rates of significant paravalvular leak (grade 2 or more) at 30 days (T1: 5.8% versus T2: 11.5% versus T3: 8.4%, $P=0.01$). Finally, acute kidney injury occurred twice as often in patients in T2 compared with the other groups ($P=0.001$).

One-Year Mortality

Median follow-up was 360 days. Mortality at 1 year was 18% in the overall cohort (Kaplan–Meier estimate). The mortality rate in T1 was half those of the other tertiles. (T1: 10.0% versus T2: 23.0% versus T3: 21.4%, log-rank $P<0.001$) (Figure 1). After multivariable adjustment, an elevated preprocedural troponin

Table 2. Baseline Characteristics

Variable	All Patients (N=1390)	T1 (n=463)	T2 (n=481)	T3 (n=446)	*P* Value
Age	83.4±6.8	82.2±7.4	83.9±6.2	84.2±6.7	<0.001
Male sex	727 (52.3)	195 (42.1)	262 (54.5)	270 (60.5)	<0.001
STS-PROM, %	5.8±4.0	5.0±3.4	6.2±3.9	6.4±4.6	<0.001
Logistic EuroSCORE, %	17.3±11.0	14.5±8.9	18.7±11.4	18.7±11.9	<0.001
NYHA class 3 or 4	890 (65.3)	287 (62.9)	325 (68.9)	278 (63.9)	0.13
History of syncope	16 (1.5)	4 (1.1)	7 (2.0)	5 (1.5)	0.68
Atrial arrhythmia (flutter or fibrillation)	371 (28.0)	96 (21.4)	139 (30.5)	136 (32.2)	0.001
Diabetes mellitus	380 (27.4)	115 (24.8)	132 (27.5)	133 (29.9)	0.23
Hypertension	751 (68.8)	252 (68.7)	266 (69.8)	233 (67.7)	0.83
Dyslipidemia	539 (49.4)	177 (48.2)	197 (51.7)	165 (48.0)	0.52
Active smoker	30 (2.5)	14 (3.5)	5 (1.2)	11 (3.0)	0.09
Previous PPM	208 (15.1)	46 (10.0)	75 (15.9)	87 (19.6)	<0.001
Coronary artery disease	525 (41.8)	163 (39.0)	190 (44.0)	172 (42.4)	0.33
Previous PCI	370 (27.2)	102 (22.5)	141 (29.9)	127 (29.1)	0.02
Previous CABG	126 (9.3)	46 (10.1)	45 (9.6)	35 (8.0)	0.54
Previous SAVR	23 (1.7)	7 (1.5)	8 (1.7)	8 (1.8)	0.95
Previous BAV	9 (0.6)	1 (0.2)	4 (0.8)	4 (0.9)	0.34
Previous stroke	122 (8.8)	42 (9.1)	37 (7.7)	43 (9.7)	0.56
Peripheral vascular disease	349 (25.2)	98 (21.3)	138 (28.8)	113 (25.4)	0.03
LVEF, %	54.1±13.9	58.0±12.3	52.7±13.9	51.6±14.6	<0.001
LVEF ≤30%	138 (10.2)	32 (7.1)	48 (10.3)	58 (13.4)	0.008
Mean aortic gradient, mm Hg	47.3±15.7	47.7±15.7	47.4±15.5	46.8±16.0	0.74
AVA, cm^2	0.66±0.17	0.67±0.17	0.65±0.16	0.65±0.17	0.06
Pulmonary artery systolic pressure, mm Hg	45.7±12.9	42.8±12.0	46.8±13.5	47.3±12.6	<0.001
Pulmonary artery systolic pressure >50 mm Hg	431 (37.4)	104 (28)	154 (38.1)	173 (46.0)	<0.001
eGFR, mL/min per 1.73 m^2	62.8±23.5	71.0±22.0	59.4±24.3	58.0±21.8	<0.001
eGFR <40 mL/min per 1.73 m^2	199 (14.3)	25 (5.4)	85 (17.7)	89 (20.0)	<0.001
Dialysis	24 (1.9)	0 (0)	15 (3.5)	9 (2.2)	0.001
Preprocedural NT-proBNP, median (IQR), pg/mL	1764 (760–4079)	817 (356–1815)	2458 (1092–6287)	2698 (1292–5394)	<0.001
COPD	251 (18.1)	79 (17.1)	91 (19.0)	81 (18.2)	0.76
BMI, kg/m^2	26.6±5.1	26.6±5.3	26.7±5.0	26.5±5.0	0.84

Values are expressed as mean±SD or number (percentage) unless otherwise indicated. BAV indicates balloon aortic valvuloplasty; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; T1, tertile 1; T2, tertile 2; T3, tertile 3.

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level was an independent predictor of 1-year mortality (T2 versus T1: HR, 2.07 [adjusted *P*=0.001]; T3 versus T1: HR, 1.76 [adjusted *P*=0.009]), (Table 1). No significant 1-year mortality differences were observed in T2 and T3 patients (adjusted *P*=0.43). The other significant independent predictors of mortality at 1 year were age, peripheral vascular disease, left ventricular ejection fraction, and glomerular filtration rate (all adjusted *P*<0.05). When using the same variables in an exploratory model with 3-year mortality data, results remained consistent, with patients in T1 still showing significantly lower mortality than their T2 and T3 counterparts (adjusted *P*=0.002 and 0.003, respectively) (Figure 1).

In a model including STS score and logistic EuroScore (as they integrate most preprocedural variables collected), in addition to preprocedural troponin tertiles, independent predictors of 1-year mortality were STS score (HR, 1.08 per

Table 3. Procedural Characteristics

Variable	All Patients (N=1390)	T1 (n=463)	T2 (n=481)	T3 (n=446)	*P* Value
Approach					0.59
Transfemoral	928 (66.8)	315 (68.0)	317 (65.9)	296 (66.4)	
Transapical	62 (4.5)	22 (4.8)	25 (5.2)	15 (3.4)	
Other	400 (28.8)	126 (27.2)	139 (28.9)	135 (30.3)	
Local anesthesia	768 (63.1)	262 (64.9)	260 (60.9)	246 (63.6)	0.48
Predilatation	675 (48.6)	205 (44.3)	258 (53.6)	212 (47.5)	0.01
Device type					0.004
Balloon-expandable	927 (67.1)	331 (71.5)	326 (68.5)	270 (60.9)	
Self-expandable	431 (31.2)	122 (26.3)	146 (30.7)	163 (36.8)	
Other	24 (1.7)	10 (2.2)	4 (0.8)	10 (2.3)	
Implanted device size (balloon-expandable)					0.03
23 mm	266 (28.7)	108 (32.6)	86 (26.4)	72 (26.7)	
26 mm	421 (45.4)	158 (47.7)	144 (44.2)	119 (44.1)	
29 mm	235 (25.4)	64 (19.3)	94 (28.8)	77 (28.5)	
Implanted device size (self-expandable)					0.04
23 mm	23 (5.3)	7 (5.7)	7 (4.8)	9 (5.5)	
26 mm	101 (23.4)	28 (23.0)	30 (20.5)	43 (26.4)	
29 mm	209 (48.5)	69 (56.6)	77 (52.7)	63 (38.7)	
31 mm	95 (22)	17 (13.9)	32 (21.9)	46 (28.2)	
Postdilatation	113 (8.1)	37 (8.0)	43 (8.9)	33 (7.4)	0.67
Need for second valve implantation	40 (2.9)	9 (2.0)	17 (3.6)	14 (3.2)	0.32
Annulus rupture	13 (0.9)	4 (0.9)	5 (1.0)	4 (0.9)	0.96
Conversion to SAVR	20 (1.7)	9 (2.3)	8 (2.0)	3 (0.8)	0.24
Contrast use, mL	117±57	116±53	121±58	114±59	0.18
Fluoroscopy time, min	16.7±8.8	16.4±8.0	17.1±10.0	16.6±8.4	0.49

Values are expressed as mean±SD or number (percentage). SAVR indicates surgical aortic valve replacement; T1, tertile 1; T2, tertile 2; T3, tertile 3.

1% STS increase; adjusted $P<0.001$) and preprocedural troponin (T2 versus T1: adjusted $P<0.001$; T3 versus T1: adjusted $P=0.001$; T3 versus T2: adjusted $P=0.41$). Both the risk score model and the clinical variables model adjusted the data similarly (−2 log likelihood ratio: 2503.3 and 2496.4, respectively).

Variables Associated With Elevated Preprocedural Troponin

Four independent predictors of elevated preprocedural troponin value were identified by means of multivariate linear regression: male sex (β=0.61 μg/L), atrial arrhythmia (atrial flutter of fibrillation) (β=0.38 μg/L), low glomerular filtration rate (β=0.06 μg/L per 5 mL/min per 1.73 m^2 decrement), and preprocedural NT-proBNP levels (β=0.05 μg/L per 100 pg/mL increment) (all adjusted $P<0.01$) (Table 5).

Incremental Value of Myocardial Injury

Postprocedural troponin was assessed in patients with the nontransapical approach. Myocardial injury was an independent predictor of 1-year mortality in addition to the other preprocedural variables identified, with an HR of 1.69 (95% CI, 1.12–2.55; $P=0.01$). The *P* value for the interaction term of myocardial injury by troponin tertile was not statistically significant (0.18). However, in T1, patients with myocardial injury had a 1-year mortality rate more than 4 times higher than patients without myocardial injury (12.1% versus 2.8%, respectively; HR, 5.11 [adjusted $P=0.03$]) (Figure 2A). This HR was considerably higher than that of the overall cohort and of the other tertiles (T2: HR, 1.41; and T3: HR, 1.08) (Figure 2B and 2C). Patients with previous PCI had a trend for increased risk of myocardial injury (odds ratio, 1.32; $P=0.065$).

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Table 4. Thirty-Day, 1-Year, and 3-Year Outcomes

30-d Outcome	All Patients (N=1390)	T1 (n=463)	T2 (n=481)	T3 (n=446)	*P* Value
Death	87 (6.3)	16 (3.5)	40 (8.3)	31 (7.0)	0.007
Stroke	40 (2.9)	12 (2.6)	16 (3.3)	12 (2.7)	0.76
Myocardial injury*	437 (47.2)	204 (66.4)	190 (59.7)	43 (14.3)	<0.001
New pacemaker implantation†	225 (19.2)	67 (16.1)	78 (19.6)	80 (22.4)	0.08
Major vascular complication	189 (13.6)	60 (13.0)	78 (16.2)	51 (11.4)	0.09
Paravalvular regurgitation >mild	110 (8.6)	25 (5.8)	50 (11.5)	35 (8.4)	0.01
Acute kidney injury	85 (6.1)	18 (3.9)	45 (9.4)	22 (4.9)	0.001
Mean gradient >20 mm Hg	34 (2.8)	13 (3.1)	13 (3.2)	8 (2.0)	0.54
Mean gradient, mm Hg	10.6±5.4	10.6±5.0	10.9±6.6	10.1±4.2	0.14
Hospital stay, d	11.0±8.0	11.0±8.0	11.4±8.7	11.6±10.0	0.58
1-y death‡	190 (18.0)	36 (10.0)	83 (23.0)	71 (21.4)	T1 vs T2: 0.001 T1 vs T3: 0.009 T2 vs T3: 0.43
3-y death‡	241 (38.7)	54 (28.5)	102 (42.6)	85 (47.8)	T1 vs T2: 0.002 T1 vs T3: 0.003 T2 vs T3: 0.96

Values are expressed as mean±SD or number (percentage). T1 indicates tertile 1; T2, tertile 2; T3, tertile 3.
*Patients with transapical approach were excluded from this analysis.
†Patients with a previous permanent pacemaker were excluded from this analysis.
‡Kaplan–Meier estimate; adjusted *P* values (Cox proportional hazards model).

Discussion

This study is the first large prospective registry describing the impact of both preprocedural and postprocedural high-sensitivity troponin in patients undergoing TAVI with second- and third-generation devices. New data on the prognostic value of troponin in patients implanted with TAVI have emerged with 3 main findings:

1. Preprocedural troponin was associated with 30-day mortality and was an independent predictor of 1-year mortality;

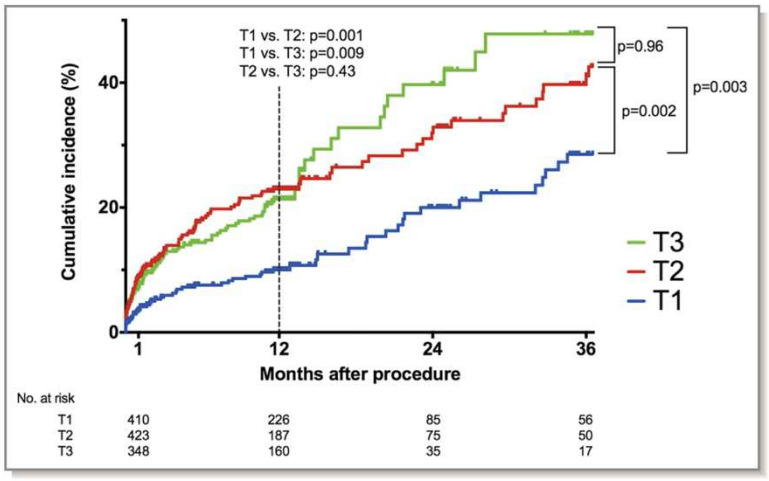


Figure 1. Mortality after transcatheter aortic valve intervention stratified by preprocedural troponin tertile. T1 indicates tertile 1; T2, tertile 2; T3, tertile 3.

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Table 5. Independent Predictors of Preprocedural Troponin Value

Parameter	Multivariate Analysis		
	Coefficient, ng/L	95% CI	*P* Value
Male sex	0.61	0.36–0.87	<0.001
Atrial arrhythmia (flutter or fibrillation)	0.38	0.10–0.66	0.009
eGFR (per 5-mL/min per 1.73 m^2 decrement)	0.06	0.03–0.09	<0.001
Preprocedural NT-proBNP (per 100-pg/mL increment)	0.005	0.003–0.007	<0.001

Values are expressed as mean±SD or number (percentage) unless otherwise indicated. eGFR indicates glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

2. Male sex, atrial fibrillation, low glomerular filtration rate, and preprocedural NT-proBNP levels were independent predictors of elevated preprocedural troponin;
3. Myocardial injury (ie, troponin rise) was independently predictive of 1-year mortality, and its effect may be more pronounced in patients with normal or near-normal preprocedural troponin.

Prognostic Impact of Preprocedural Troponin

In our study, preprocedural troponin was a strong predictor of mortality at 1 month and 1 year and remained a prognostic factor at 3 years after adjustment for potential confounding factors.

These results are consistent with several small series recently published in the literature. Indeed, Frank et al[7] reported a series of 107 patients undergoing TAVI where preprocedural troponin was predictive of short- and long-term mortality in a population at higher surgical risk than our cohort of patients. More recently, these data were confirmed by Köhler et al,[8] who showed that, in a population of Sapien XT valve recipients, preprocedural troponin and NT-proBNP elevation were associated with increased 1-month mortality in 259 patients. Another study of high-sensitivity troponin T showed the same results in 201 patients implanted with both self-expandable and balloon-expandable prostheses,[17] as well as the study by Kofler et al.[18]

The largest study on biomarkers included 847 patients undergoing TAVI.[19] The authors concluded that preprocedural troponin I was not predictive of 1-year mortality. These contradictory results may be explained by the use of standard troponin (not high-sensitivity troponin) in their study.

We confirm here the prognostic value of preprocedural high-sensitivity troponin in a large cohort of patients and suggest the first data demonstrating persistent prognostic value of preprocedural troponin at 3 years. Preprocedural troponin is a biomarker able to predict 1-year mortality in patients undergoing TAVI, thus increasing the predictive value of routine predictors of mortality such as STS score and EuroScore. An elevated preprocedural troponin level may warrant closer postprocedural monitoring and follow-up.

Predictors of Elevated Preprocedural Troponin

Elevated baseline troponin levels may indicate myocardial damage, left ventricular hypertrophy, and advanced stages of cardiomyopathy, as well as other higher-risk profiles for clinical outcomes.[17,20] In the present study, 4 independent predictors of preprocedural troponin value were identified: male sex, atrial arrhythmia, low glomerular filtration rate, and preprocedural NT-proBNP. A significant impact of PCI on pre-TAVI troponin values was unlikely as coronary intervention was performed at least 10 days before the TAVI procedure. Preprocedural NT-proBNP was found to be an independent predictor of elevated preprocedural troponin levels in 2 studies,[7,8] reflecting myocyte stretch, neurohormonal activation, and myocardial hypoxia.[21] Chronic kidney failure was predictive of preprocedural troponin elevation in the study by Köhler et al[8] and in a transfemoral series.[17] Atrial arrhythmia and male sex were not correlated with preprocedural elevated troponin in patients undergoing TAVI in the literature. However, supraventricular tachycardia was described as being associated with elevated troponin baseline level and may be explained by an oxygen supply-demand mismatch defined as a type 2 myocardial infarction.[22]

In our study, several modifiable factors were identified as predictors of preprocedural troponin and may be the target of treatments with the purpose of improving the prognosis of patients undergoing TAVI. Indeed, heart failure reflected by NT-proBNP elevation and atrial arrhythmias may be managed before the procedure with diuretics and rhythm or heart rate control before the procedure, as well as renal function optimization.

Prognostic Impact of Postprocedural Troponin

Myocardial damage during TAVI, resulting in troponin elevation, could be caused by periprocedural conditions with a mismatch between myocardial oxygen supply and oxygen demand.[22] Several mechanisms can be responsible for this mismatch such as balloon valvuloplasty, acute aortic regurgitation, microembolism and temporary hypotension during rapid ventricular pacing, and gradual deployment of the bioprosthesis.[9]

In our study, nearly half of the patients had myocardial injury according to the VARC-2 definition.[12] These data are consistent with recent literature.[8,11] In the present study,

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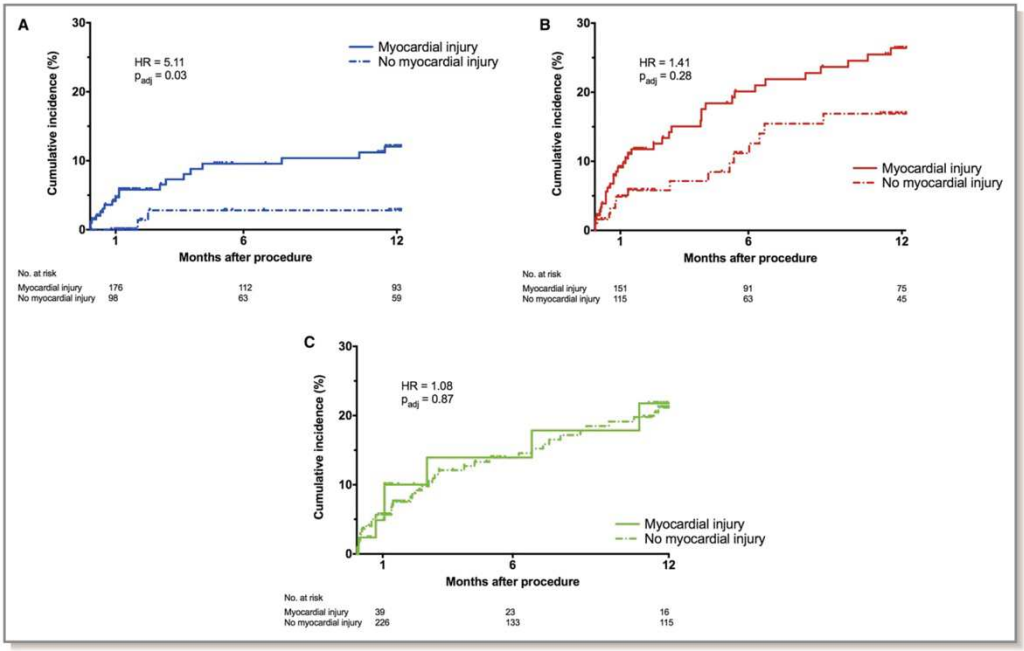


Figure 2. **A**, Mortality after transcatheter aortic valve intervention (TAVI) in tertile 1 (T1) stratified by the presence of myocardial injury. **B**, Mortality after TAVI in tertile 2 (T2) stratified by the presence of myocardial injury. **C**, Mortality after TAVI in tertile 3 (T3) stratified by the presence of myocardial injury. HR indicates hazard ratio.

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myocardial injury was predictive of mortality, and potentially more so in patients with near-normal preprocedural troponin (T1). The prognostic impact of myocardial injury was demonstrated in several studies. In a study including 119 patients, myocardial injury after TAVI was predictive of 1-month mortality.[10] In a larger cohort including 577 patients, Koskinas et al[23] showed that myocardial injury after TAVI was strongly associated with 1-month mortality and remained associated after 2 years. However, contradictory results were found in the literature. In the study by Köhler et al[8] including 259 patients undergoing TAVI, postprocedural elevation of troponin (at days 3 and 7) was not predictive of 1-year mortality, while preprocedural troponin was predictive of survival. However, in this study, the proportion of patients with transapical approach was high (around one third) in comparison to our study cohort (4.5%). In a more recent study including 756 patients undergoing TAVI, myocardial injury assessed by high-sensitivity troponin T depended on the type of device used but was not predictive of 1-year mortality.[11] Baseline troponin level was near normal in patients included in this study and the authors did not evaluate the prognostic value of myocardial injury according to preprocedural troponin level. Studies suggesting prognostic impact of myocardial injury included all patients undergoing TAVI regardless of access routes, which may explain these contradictory data compared with the study by Stundl et al[11] including 97% of patients with transfemoral access. Our study included two thirds of patients with transfemoral access, <5% of patients with transapical route, and 28.8% of patients with transcarotid and transaortic access route. The only variable that was associated with myocardial injury was previous PCI. Although the *P* value did not reach statistical significance, these patients may have a more important atherosclerosis burden leading to an increased risk of myocardial injury during the procedure. These data are consistent with an increased risk of myocardial injury after TAVI in patients with coronary artery disease as reported in the study by Koskinas et al.[23]

Finally, the present study is the first of its kind to suggest that myocardial injury is more predictive of 1-year mortality in patients with near-normal preprocedural troponin. It may appear counterintuitive that troponin elevation in higher-risk patients (ie, those in T2 or T3) had less impact than in a lower-risk group. It is plausible, however, that troponin elevation exerts its effect on mortality upon occurrence, regardless of

whether this is before or after the procedure. For patients in T2 and T3, the elevation in troponin has occurred before the procedure, which placed these patients at increased risk. Any additional increase in troponin may not have had any further impact. In comparison, patients in T1 had normal or near-normal troponin to start. In some, the procedure caused myocardial injury, increasing their risk of death, similarly to patients in T2 and T3. Those without myocardial injury had a 1-year mortality rate of 2.8%, whereas all of the other patients (ie, those with high troponin levels before the procedure and those who developed high troponin levels after the procedure) had a mortality rate >10%.

Study Limitations

The first limitation of this study is its single-center design, which limits the external validity of the findings. However, troponin measurements were performed on a single analyzer, which maximized reproducibility and avoided the use of inaccurate conversion factors to harmonize values from different centers. Second, only 1 preprocedural and 1 postprocedural troponin measurement were performed. Additional assays would have allowed for more refined analyses. However, many patients were discharged early, making multiple measurements impractical. Another limitation is the difference in prosthesis type between groups. Indeed, the use of self-expanding devices was significantly lower in patients in T1. This may be explained by the fact that, in our center, patients with lower risk profiles are less likely to receive a self-expanding valve, because they often present with less extensive valve calcifications. As there were more women in T1, device sizes were also significantly different among tertiles, with patients in T1 receiving smaller valves. However, these characteristics may not have impacted our findings. Another limitation was the use of VARC-2 criteria to define myocardial injury in the entire population. Indeed, this cutoff for troponin elevation may not be suitable for patients in T2 and T3 who have a higher preprocedural troponin level and may explain our findings concerning postprocedural troponin prognostic value, which was observed in patients in T1. The postprocedural troponin analysis suggesting an effect in T1 only should be considered hypothesis-generating as the *P* value for the interaction term was not statistically significant. However, the HRs differed considerably between tertiles and the interaction analysis may have been underpowered.

Conclusions

Preprocedural troponin is an independent predictor of long-term mortality after TAVI. Myocardial injury in patients with normal or near-normal preprocedural troponin is also a predictor of long-term events. Troponin assessment is simple and feasible in routine clinical practice and may improve risk stratification of patients undergoing TAVI. This may, in turn, improve patient selection and allow clinicians to better inform patients and their families about the risks of the procedure as they strive to reach an informed decision.

Disclosures

Dr Akodad received research grants from Edwards Lifescience and Medtronic. Dr Chevalier is a proctor for Medtronic. Dr Lefèvre is a proctor for Edwards LifeSciences. The remaining authors have no disclosures to report.

References

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791.
2. D'Ascenzo F, Ballocca F, Moretti C, Barbanti M, Gasparetto V, Mennuni M, D'Amico M, Conrotto F, Salizzoni S, Omedè P, Colaci C, Zoccai GB, Lupo M, Tarantini G, Napodanno M, Presbitero P, Sheiban I, Tamburino C, Marra S, Gaita F. Inaccuracy of available surgical risk scores to predict outcomes after transcatheter aortic valve replacement. *J Cardiovasc Med (Hagerstown)*. 2013;14:894–898.
3. Silaschi M, Conradi L, Seiffert M, Schnabel R, Schön G, Blankenberg S, Reichenspurner H, Diemert P, Treede H. Predicting risk in transcatheter aortic valve implantation: comparative analysis of EuroSCORE II and established risk stratification tools. *Thorac Cardiovasc Surg*. 2015;63:472–478.
4. Røsjø H, Andreassen J, Edvardsen T, Omland T. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. *Am J Cardiol*. 2011;108:88–91.
5. Saito T, Hojo Y, Hirose M, Ikemoto T, Katsuki T, Kario K. High-sensitivity troponin T is a prognostic marker for patients with aortic stenosis after valve replacement surgery. *J Cardiol*. 2013;61:342–347.
6. Paparella D, Guida P, Caparrotti S, Fanelli V, Martinelli G, Mazzei V, Zaccaria S, Bisceglia L, Scrascia G. Myocardial damage influences short- and mid-term survival after valve surgery: a prospective multicenter study. *J Thorac Cardiovasc Surg*. 2014;148:2373–2379.e1.
7. Frank D, Stark S, Lutz M, Weissbrodt A, Freitag-Wolf S, Petzina R, Rosenberg M, Lutter G, Frey N. Preprocedural high-sensitive troponin predicts survival after transcatheter aortic valve implantation (TAVI). *Int J Cardiol*. 2013;169:e38–e39.
8. Köhler WM, Freitag-Wolf S, Lambers M, Lutz M, Niemann PM, Petzina R, Lutter G, Bramlage P, Frey N, Frank D. Preprocedural but not periprocedural high-sensitive troponin T (hsTNT) levels predict outcome in patients undergoing transcatheter aortic valve implantation (TAVI). *Cardiovasc Ther*. 2016;34:385–396.
9. Rodés-Cabau J, Gutiérrez M, Bagur R, De Larochellière R, Doyle D, Côté M, Villeneuve J, Bertrand OF, Larose E, Manazzoni J, Pibarot P, Dumont E. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2011;57:1988–1999.
10. Yong ZY, Wiegerinck EMA, Boerlage-van Dijk K, Koch KT, Vis MM, Bouma BJ, Henriques JPS, Cocchieri R, Piek JJ, de Mol BAJM, Baan J. Predictors and prognostic value of myocardial injury during transcatheter aortic valve implantation. *Circ Cardiovasc Interv*. 2012;5:415–423.
11. Stundl A, Schulte R, Lucht H, Weber M, Sedaghat A, Shamekhi J, Zur B, Grube E, Mellert F, Welz A, Fimmers R, Nickenig G, Werner N, Sinning J-M. Periprocedural myocardial injury depends on transcatheter heart valve type but does not predict mortality in patients after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10:1550–1560.
12. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es G-A, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J*. 2012;33:2403–2418.

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13. Rodés-Cabau J, Dumont E, De LaRochellière R, Doyle D, Lemieux J, Bergeron S, Clavel M-A, Villeneuve J, Raby K, Bertrand OF, Pibarot P. Feasibility and initial results of percutaneous aortic valve implantation including selection of the transfemoral or transapical approach in patients with severe aortic stenosis. *Am J Cardiol*. 2008;102:1240–1246.
14. Bapat V, Frank D, Cocchieri R, Jagielak D, Bonaros N, Aiello M, Lapeze J, Laine M, Chocron S, Muir D, Eichinger W, Thielmann M, Labrousse L, Rein KA, Verhoye J-P, Gerosa G, Baumbach H, Bramlage P, Deutsch C, Thoenes M, Romano M. Transcatheter aortic valve replacement using transaortic access: experience from the multicenter, multinational, prospective ROUTE registry. *JACC Cardiovasc Interv*. 2016;9:1815–1822.
15. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel J-P, Bourlon F, Bertrand B, Van Belle E, Laskar M; FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med*. 2012;366:1705–1715.
16. Auffret V, Lefevre T, Van Belle E, Eltchaninoff H, Iung B, Koning R, Motreff P, Leprince P, Verhoye JP, Manigold T, Souteyrand G, Boulmier D, Joly P, Pinaud F, Himbert D, Collet JP, Rioufol G, Ghostine S, Bar O, Dibie A, Champagnac D, Leroux L, Collet F, Teiger E, Darremont O, Folliguet T, Leclercq F, Lhermusier T, Olhmann P, Huret B, Lorgis L, Drogoul L, Bertrand B, Spaulding C, Quilliet L, Cuisset T, Delomez M, Beygui F, Claudel J-P, Hepp A, Jegou A, Gommeaux A, Mirode A, Christiaens L, Christophe C, Cassat C, Metz D, Mangin L, Isaaz K, Jacquemin L, Guyon P, Pouillot C, Makowski S, Bataille V, Rodés-Cabau J, Gilard M, Le Breton H; FRANCE TAVI Investigators. Temporal trends in transcatheter aortic valve replacement in France: FRANCE 2 to FRANCE TAVI. *J Am Coll Cardiol*. 2017;70:42–55.
17. Chorianopoulos E, Krumsdorf U, Geis N, Pleger ST, Giannitsis E, Katus HA, Bekeredjian R. Preserved prognostic value of preinterventional troponin T levels despite successful TAVI in patients with severe aortic stenosis. *Clin Res Cardiol*. 2014;103:65–72.
18. Kofler M, Reinstadler SJ, Stastny L, Dumfarth J, Reindl M, Wachter K, Rustenbach CJ, Müller S, Feuchtner G, Mende M, Friedrich G, Metzler B, Grimm M, Bonaros N, Baumbach H. Prognostic implications of pre-procedural high-sensitivity cardiac troponin T in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10:2345–2346.
19. Seiffert M, Sinning JM, Meyer A, Wilde S, Conradi L, Vasa-Nicotera M, Ghanem A, Kempfert J, Hammerstingl C, Ojeda FM, Kim W-K, Koschyk DH, Schirmer J, Baldus S, Grube E, Möllmann H, Reichenspurner H, Nickenig G, Blankenberg S, Diemert P, Treede H, Walther T, Werner N, Schnabel RB. Development of a risk score for outcome after transcatheter aortic valve implantation. *Clin Res Cardiol*. 2014;103:631–640.
20. Hamm CW, Giannitsis E, Katus HA. Cardiac troponin elevations in patients without acute coronary syndrome. *Circulation*. 2002;106:2871–2872.
21. Hall C. NT-ProBNP: the mechanism behind the marker. *J Card Fail*. 2005;11:S81–S83.
22. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon J-L, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035.
23. Koskinas KC, Stortecky S, Franzone A, O'Sullivan CJ, Praz F, Zuk K, Räber L, Pilgrim T, Moschovitis A, Fiedler GM, Jüni P, Heg D, Wenaweser P, Windecker S. Post-procedural troponin elevation and clinical outcomes following transcatheter aortic valve implantation. *J Am Heart Assoc*. 2016;5:e002430. DOI: 10.1161/JAHA.115.002430.

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Publication 2: ***Prognostic Impact of Calcium Score after Transcatheter Aortic Valve Implantation (TAVI) performed with new generation prosthesis***

Akodad, M., Lattuca, B., Agullo, A., Macia, J.-C., Gandet, T., Marin, G., Iemmi, A., Vernhet, H., Schmutz, L., Nagot, N., Albat, B., Cayla, G., Leclercq, F., 2018. Prognostic Impact of Calcium Score after Transcatheter Aortic Valve Implantation Performed With New Generation Prosthesis. *Am. J. Cardiol.2018 ; 121, 1225–1230.*

Après une première procédure réalisée avec succès en 2002, le TAVI s'est largement répandu à travers le monde et s'adresse à des patients avec un profil de risque de moins en moins élevé (4,6). Cependant, de multiples complications péri-procédure peuvent survenir, dont certaines sont spécifiques à la technique. Parmi celles-ci, les fuites aortiques para-prothétiques significatives (≥ grade 2) étaient observées chez 10 à 20% des patients implantés avec les valves aortiques percutanées de la précédente génération (Sapien, Sapien XT et Corevalve) avec une surmortalité à moyen terme chez ces patients (151,152). Dans ce contexte, certains facteurs pronostiques morphologiques ont été décrits. L'importance des calcifications de la valve aortique native est un facteur de risque reconnu de la survenue d'une fuite aortique para prothétique et pourrait être impliquée dans la survenue de rupture d'anneau aortique au cours de la procédure (141,142). L'importance de ces calcifications peut être objectivée de façon quantitative avec le score calcique d'Agatston. Le score calcique est reconnu comme étant un facteur pronostique indépendant de la survenue de fuite aortique para-prothétique avec les valves percutanées Medtronic CoreValve, Edwards Sapien et Sapien XT (141). Cependant, l'évolution de la technique et du matériel utilisé avec notamment le développement de prothèses valvulaires de dernière génération, a permis de limiter l'incidence des complications. Parmi ces complications, on note une diminution drastique des fuites para-prothétiques par l'adjonction d'une « jupe » externe pour la valve Edwards Sapien 3 (montée sur ballon) et par un meilleur positionnement avec recapture possible avec la valve Corevalve Evolut R (auto-expansible).

L'objectif de ce travail était donc d'évaluer l'impact pronostique du score calcique d'Agatston chez les patients bénéficiant de la mise en place d'une valve aortique percutané avec les 2 types de prothèses (montée sur ballon et auto-expansible) pour 2 générations distinctes de valves.

La première partie de cette étude incluait 118 patients implantés avec la génération de prothèse précédente auto-expansible Medtronic Corevalve et montée sur ballon Edwards Sapien XT entre mai 2013 et novembre 2014 (groupe 1). La deuxième partie de ce travail incluait, entre septembre 2014 et octobre 2016, 228 patients implantés avec la dernière génération de prothèse auto-expansible Medtronic Corevalve Evolut R et montée sur ballon Edwards Sapien 3 (groupe 2).

Ces 2 groupes de patients étaient différents en termes de profil de risque avec un Euroscore Logistic moins élevé, moins d'insuffisance rénale chronique et un score calcique également moins élevé dans le groupe 2, probablement témoin de ce profil de risque plus bas dans cette population plus récente.

Ce travail a permis de confirmer la valeur pronostique du score calcique d'Agatston sur la survenue d'évènements (mortalité toutes causes, évènements cardiovasculaires majeurs, infarctus du myocarde, insuffisance cardiaque, réhospitalisation pour cause cardiaque à 1 mois) et sur la survenue de fuites aortiques significatives chez les patients du groupe 1 quel que soit le type de prothèse.

Concernant le groupe 2, le score calcique n'était plus prédictif d'évènements majeurs avec les nouvelles générations de prothèse. En effet, leurs performances semblent contrebalancer l'effet péjoratif du score calcique sur les évènements cliniques. En revanche, le score calcique gardait une valeur pronostique concernant la survenue de fuites aortiques para-prothétiques avec la valve auto-expansible.

Ainsi, cette deuxième étude, réalisée en parallèle de la première étude, a permis de préciser l'impact pronostique du score calcique avec différents types de prothèses de générations successives. Ainsi, le score calcique, perdant sa valeur pronostique avec les dernières

générations de prothèses, pourrait devenir désuet dans l'évaluation du profil de risque des patients hormis chez les patients implantés avec les valves auto-expansibles.

Prognostic Impact of Calcium Score after Transcatheter Aortic Valve Implantation Performed With New Generation Prosthesis

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Calcium score (CS) is a well-known prognostic factor after transcatheter aortic valve implantation (TAVI) performed with first generation prosthesis but few data are available concerning new generation valves. The aim of this study was to evaluate if CS remains a prognostic factor after Sapien 3 and Evolut R valves implantation. Agatston CS was evaluated on multislice computed tomography before TAVI in 346 patients implanted with Sapien XT (n = 61), CoreValve (n = 57) devices, (group 1, n = 118), and with new generation Sapien 3 (n = 147), Evolut R (n = 81) prosthesis, (group 2, n = 228). Major adverse cardiovascular events and aortic regurgitation (AR) were evaluated at 1 month. The 2 groups were similar at baseline except for logistic Euroscore (20.1% in group 1 vs 15.0 % in group 2; p = 0.001), chronic renal failure (44.1% vs 37.2% respectively, p = 0.007) and preprocedural CS (4,092 ± 2,176 vs 3,682 ± 2,109 respectively, p = 0.022). In group 1, 28 patients (23.7%) had adverse clinical events vs 21 (9.2%) in group 2 (p <0.01). In multivariate analysis, a higher CS was predictive of adverse events in group 1 (5,785 ± 3,285 vs 3,565 ± 1,331 p <0.0001) but not in group 2 (p = 0.28). A higher CS was associated with AR in group 1 (6,234 ± 2711 vs 3,429 ± 1,505; p <0.001) and in patients implanted with an Evolut R device from group 2 (4,085 ± 3,645 vs 2,551 ± 1,356; p = 0.01). In conclusion, CS appears as an important prognostic factor of major events after TAVI with first generation valves but not with new generation devices. CS remains associated with AR only with new generation self-expandable Evolut R devices. **© 2018 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2018;121:1225–1230)**

Transcatheter aortic valve implantation (TAVI) was introduced in 2002 by Cribier et al. to treat high surgical risk patients or those who are contraindicated to surgery.[1,2] With the first generation TAVI devices, moderate or severe aortic regurgitation (AR) were observed in 10% to 20% of patients and were associated with midterm mortality after procedure.[3,4] The amount of native aortic valve calcifications is a well-recognized risk factor of AR after TAVI[5,6] and may be involved in annulus rupture.[7] Agatston calcium score (CS) is a method of calcium burden quantification using multislice computed tomography (MSCT) described for the first time in 1990 for coronary arteries evaluation[8] and then adapted for aortic valve assessment.[9,10] CS is a known independent prognostic factor of AR in patients implanted with CoreValve, Sapien, and Sapien XT devices.[11] The last generation devices, Sapien 3 and Evolut R, received approval for use respectively in January 2014 and in June 2015. They were developed to address main issues encountered with previous generation valves, particularly concerning access site complications with a lower profile and AR with an external skirt for the Sapien 3 prosthesis and a retrievability of the Evolut R device. Incidence of AR dramatically decreased with around 3.5% of moderate AR and no severe AR reported with both devices in recent reports.[12–14] However, few data are available concerning the prognostic impact of CS with new generation devices. We aimed to assess the prognostic value of preprocedural CS for major adverse events occurring after new generation Sapien 3 and Evolut R valves implantation in comparison with previous generation valves.

Methods

This prospective monocentric observational study included all consecutive patients who underwent TAVI in Montpellier University Hospital, France. Two groups of patients were compared depending on the generation of valve. Patients included between November 2013 and May 2014 were implanted with a first generation valve (group 1): the balloon-expandable Sapien XT (Edwards Sapien XT, Edwards Lifesciences LLC, Irvine, CA) bovine pericardial device or the self-expandable CoreValve porcine pericardial valve (Medtronic, Inc., Minneapolis, MN). Patients included between

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See page 1229 for disclosure information.

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https://doi.org/10.1016/j.amjcard.2018.02.004

September 2014 and October 2016 were implanted with new generation valves from both companies (group 2): the balloon-expandable Sapien 3 device or the self-expandable CoreValve Evolut R valve. Patients with valve-in-valve procedures were excluded.

A systematic preintervention electrocardiogram-gated, noncontrast and contrast-enhanced MSCT (General Electric LightSpeed VCT) was systematically performed within 2 weeks before the procedure in all patients for valve and vascular access evaluation before TAVI and stored for postprocessing and calcium scoring. The region of interest was selected from the upper part of left ventricular outflow tract to the leaflets tips, with 3 mm thickness slices. Calcifications were automatically detected by the software with a detection cutoff from 130 Hounsfield Unit (HU). Evaluation of aortic valve calcifications was then performed, using the Agatston CS SmartScore 4.0 software (General Electric Healthcare, Waukesha, WI) on transverse view in a standardized technique.[9,10]

Valve size was selected according to manufacturer's recommendation after determination of annulus area, perimeter, and mean diameter of the virtual ring on MSCT. All the patients underwent TAVI procedure under general anesthesia and the transfemoral access was performed through a surgical cut down as previously described.[15,16] Alternative access sites were considered only in case of unsuitable iliofemoral anatomy. Predilatation of the native aortic valve was performed according to operator's choice. The optimal position of the valve was checked by fluoroscopy and a rapid pacing (160 to 200 beats/min) was triggered during the implantation of balloon-expandable devices as previously described.[17] A final control was performed by aortography and transthoracic echocardiography.

The primary endpoint was a composite criterion including all-cause mortality, major cardiac and cerebrovascular events including stroke, myocardial infarction, heart failure, or rehospitalization for cardiac causes occurring within the first month after the procedure according to Valve Academic Research Consortium-2 criteria.[18] The secondary endpoint included postprocedural AR ≥ grade 2. Quantification of AR was performed using transthoracic echocardiography before discharge and classified as none, mild (grade 1), moderate (grade 2), and severe (grade 3) with combined criteria as recommended for native valves.[19]

Data on patient baseline characteristics, procedural details, and in-hospital outcomes were collected from medical records. One month follow-up was obtained by phone questionnaire. All patients were given full study information and consents were collected to data analysis. No additional testing or biological samples were specifically required for the study as MSCT used to evaluate CS was performed for all patients before TAVI. The protocol was approved by the local ethics committee and the institutional regulatory authorities, and conducted according to the principles of the Declaration of Helsinki.

Patients' characteristics were presented using mean ± SD for continuous variables and frequencies and proportions for categorical variables. Groups (primary endpoint vs no primary endpoint) were compared using the Wilcoxon-Mann-Whitney test for continuous variables and the chi-square or Fisher's exact test for categorical ones. To determine the relative importance of the covariates on the occurrence of outcomes, a multivariate analysis using logistic regression was performed. A backward selection of the variables was used, with an alpha-to-exit set at 0.10. Odds ratio (OR) and their 95% confidence intervals were calculated. The goodness-of-fit of the models was assessed using the Hosmer and Lemeshow chi-square test. Furthermore, to analyze the prognostic value of calcium score on the occurrence of outcomes, a sensibility analysis was conducted through receiver operating characteristic (ROC) curves, and the best prognostic value was determined by the Youden method. Statistical analysis was performed using SAS, v.9, statistical software (SAS Institute, Cary, NC). A p value <0.05 was used for statistical significance.

Results

A total of 346 patients were included in this study: 118 in group 1 (n = 61 Sapien XT, n = 57 CoreValve) and 228 in group 2 (n = 147 Sapien 3, n = 81 Evolut R).

Main baseline characteristics did not significantly differ between the 2 groups except for logistic Euroscore and chronic renal failure (Table 1). The transfemoral access was the main access route and all procedural characteristics are presented in Table 1. Calcium scores for each type of valve are summarized in Supplementary Data.

Table 1
Baseline and procedural characteristics in the two study groups*,†

Variables	Corevalve and Sapien XT valves (n = 118)	Sapien 3 and Evolut R valves (n = 228)	p
Mean Age (years)	83.2 ± 6.4	83.8 ± 6.3	0.30
Women	66.0 (56.0%)	131 (57.4%)	0.8
Euroscore 1 (mean ± SD)	20.1 ± 11.4	15.0 ± 9.6	<0.001
Euroscore 2 (mean ± SD)	NA	4.1 ± 2.8	NA
Mean body mass index (kg/m²)	26.6 ± 5.4	25.9 ± 4.8	0.16
Chronic renal failure	52.0 (44.1%)	74 (32.4%)	0.007
Hypertension	89.0 (75.4%)	155 (67.9%)	0.1
Dyslipidaemia	35.0 (29.7%)	63 (27.6%)	0.64
Diabetes mellitus	34.0 (28.8%)	65 (28.5%)	0.89
Coronary artery disease	59.0 (50.0%)	102 (44.7%)	0.3
Peripheral arterial disease	14.0 (11.9%)	28 (12.3%)	0.94
NYHA ≥ 3	60.0 (50.9%)	138.0 (60.5%)	0.07
Mean aortic valve gradient (mm Hg)	48.9 ± 16.1	46.3 ± 14.6	0.10
Mean LVEF (%)	51.9 ± 12.6	52.9 ± 10.7	0.49
Main access site			0.49
TransFemoral	108 (91.5%)	214 (93.9%)	
Transcarotid	1 (0.9%)	12 (5.3%)	
Subclavian	9 (7.6%)	1 (0.4%)	
Transaortic	0 (0%)	1 (0.4%)	
Valve size (mm)			0.18
23 mm	31 (26.3%)	59 (29.2%)	
26 mm	48 (40.7%)	92 (40.3%)	
29 mm	37 (31.4%)	51 (25.3%)	
31 mm	2 (1.7%)	0 (0%)	
Mean Calcium Score (Hounsfield Unit)	4092 ± 2177	3683 ± 2110	0.022

* NYHA = New-York heart association.
† LVEF = Left ventricular ejection fraction.

Table 2
Comparison of the incidence of primary-endpoint and secondary endpoints between the two study groups according to the VARC-2 definition*

Variables	Corevalve and Sapien XT valves (n = 118)	Sapien 3 and Evolut R valves (n = 228)	p
Primary endpoint	**28 (23.73%)**	**21 (9.2%)**	**<0.01**
All-cause mortality	8 (9.4%)	7 (3.1%)	0.10
Stroke	2 (1.8%)	4 (1.8%)	0.99
Myocardial infarction	0 (0%)	0 (0%)	NA
Heart failure (NYHA ≥ 3)	15 (12.71%)	9 (3.9%)	<0.01
Rehospitalisation for cardiac cause	14 (11.9%)	5 (2.2%)	<0.01
Secondary endpoints			
Conduction disorders	55 (53.4%)	79 (34.6%)	<0.01
Aortic regurgitation ≥ 2	27 (22.9%)	19 (8.3%)	<0.01
Pacemaker implantation	12 (11.7%)	35 (15.4%)	0.32

* NYHA = New-York heart association.

At first month, the primary endpoint occurred in 28 patients (23.7%) from group 1 versus 21 patients (9.2%) from group 2 (p <0.01) (Table 2). In group 1, 4 patients (3.4%) died during the index hospitalization, 3 patients (2.5%) died from annulus rupture, and 1 patient (0.9%) died from prosthesis migration. During the follow-up, 4 patients (3.4%) died due to heart failure, 3 (2.5%) of them presented a severe AR and 1 (0.9%) of them presented a moderate AR. In group 2, 3 patients (1.3 %) died during hospitalization, 1 patient died from septic shock, and 2 patients died from heart failure. During follow-up, 4 patients (1.8 %) died from heart failure with no severe AR.

Incidence of post procedural AR ≥ grade 2 was significantly higher in group 1 versus group 2 (p <0.01) (Figure 1, Table 2). Correlation between major adverse cardiac events and calcium score in the 2 groups is represented in Table 3.

In group 1, CS was strongly associated with the occurrence of the primary endpoint (p <0.0001) and with the occurrence of AR (3,429 ± 1,505 HU for no AR or AR grade 1 vs 6,234 ± 2,711 HU for AR grade 2 or 3; p <0.01). A cutoff value of CS >6,000 HU was identified as having the best predictive value, with 82% positive predictive value and 86% negative predictive value. The area under the ROC curve with a CS >6,000 HU was 0.72 (interquartile range 95% 0.61 to 0.84, p = 0.0002) (Figure 2).

In multivariate analysis, a CS >6,000 HU was associated with an increased risk of occurrence of the primary endpoint (OR = 106.0, 95% confidence interval = 15.5 to 727.6, p <0.01) and rehospitalization (OR = 23.24 [2.39 to 100.07] p <0.0001). The type of device implanted was not predictive of the primary endpoint (p = 0.48) or occurrence of AR (p = 0.21).

In group 2, CS did not differ significantly between patients with or without the occurrence of the primary endpoint. Nevertheless, the ROC curve analysis showed that the negative predictive value was 94% for a CS <3,000 HU (Figure 2).

Similarly, CS was not associated with the occurrence of AR in the subgroup of patients implanted with a Sapien 3 device (4,663 ± 3,057 HU for no AR or AR grade 1 vs 4,176 ± 2,149 HU for AR grade 2 or 3; p = 0.9).

Discussion

This study provides new data on prognostic value of CS in TAVI with 3 main findings: (1) CS was an independent predictor of major outcomes after TAVI with first generation devices with a CS cutoff >6000 HU to predict outcomes, (2) CS was not predictive of major outcomes after TAVI with new generation valves, and (3) CS remains predictive of AR > grade 2 with Evolut R device.

Aortic cusp calcium is required for device anchoring during TAVI. However, extensive calcific deposits may lead to significant AR, life-threatening complications such as annulus rupture or coronary obstruction and may increase incidence of postdilation.[7,20] In our study, a higher CS was not only predictive of AR but also of major events with first generation devices. Leber et al. already demonstrated that severe aortic valve calcium correlated with 1 month major adverse cardiac events and with 1 year mortality after CoreValve implantation.[21]

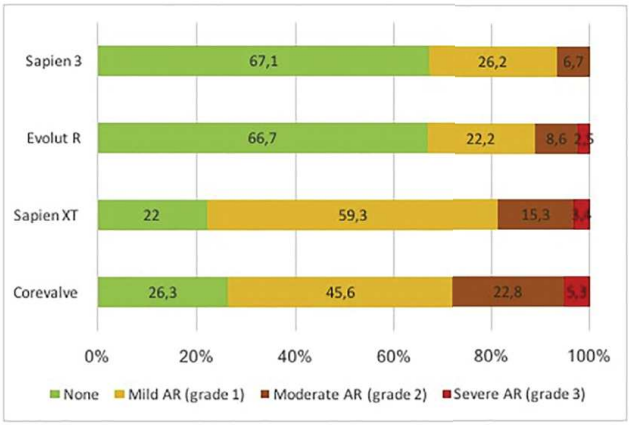


Figure 1. Severity of AR after TAVI according to the type of prosthesis.

Table 3
Predictors of 1-month outcomes in the two study groups in univariate analysis*,†,‡,§

Variables	Corevalve and Sapien XT valves (n = 118)				Sapien 3 and Evolut R valves (n = 228)			
	Outcomes (n = 28)	No outcomes (n = 90)	OR (95% CI)	p	Outcomes (n = 21)	No outcomes (n = 188)	OR (95% CI)	p
Mean age (years)	84.5 ± 4.8	82.8 ± 6.8	**1.05 (0.97–1.13)**	**0.22**	83.8 ± 5.5	83.8 ± 6.6	**1 (0.93–1.07)**	**0.74**
Women	15 (54%)	51 (57%)	**0.88 (0.38–2.07)**	**0.77**	12 (57%)	106 (56%)	**1.03 (0.41–2.65)**	**0.95**
EuroScore 1 (mean ±SD)	24.9 ± 11.5	18.6 ± 10.9	**1.05 (1.01–1.08)**	**0.004**	16.7 ± 12.2	15.2 ± 9.5	**1.01 (0.97–1.06)**	**0.88**
Mean BMI (kg/m²)	24.2 ± 4.0	27.3 ± 5.5	**0.88 (0.80–0.97)**	**0.01**	24.9 ± 4.7	25.9 ± 4.7	**0.96 (0.86–1.07)**	**0.52**
Chronic kidney failure	16 (57%)	36 (40%)	**2.00 (0.85–4.72)**	**0.11**	8 (38%)	56 (30%)	**1.7 (0.31–9.72)**	**0.25**
Hypertension	23 (82%)	66 (73%)	**1.67 (0.57–4.89)**	**0.35**	14 (67%)	124 (66%)	**1.03 (0.39–2.68)**	**0.95**
Dyslipidaemia	12 (43%)	23 (26%)	**2.18 (0.90–5.29)**	**0.08**	7 (33%)	50 (27%)	**1.38 (0.53–3.62)**	**0.51**
Diabetes mellitus	6 (21%)	28 (31%)	**0.60 (0.22–1.65)**	**0.33**	6 (29%)	55 (29%)	**0.97 (0.36–2.62)**	**0.95**
Coronary artery disease	15 (54%)	44 (49%)	**1.21 (0.52–2.82)**	**0.67**	12 (57%)	81 (43%)	**1.76 (0.71–4.38)**	**0.22**
Peripheral arterial disease	3 (11%)	11 (12%)	**0.96 (0.24–3.76)**	**0.82**	4 (19%)	24 (13%)	**1.61 (0.5–5.18)**	**0.49**
NYHA ≥ 3	17 (61%)	43 (48%)	**1.69 (0.71–4.01)**	**0.23**	16 (76%)	105 (57%)	**2.41 (0.85–6.85)**	**0.09**
Mean aortic valve gradient (mm Hg)	48.9 ± 18.9	48.9 ± 15.3	**1.01 (0.98–1.05)**	**0.99**	42.6 ± 13.3	46.4 ± 14.7	**0.98 (0.95–1.02)**	**0.27**
Mean LVEF (%)	49.7 ± 12.8	52.66 ± 12.56	**0.98 (0.95–1.02)**	**0.28**	52.5 ± 9.5	52.8 ± 10.9	**1 (0.95–1.04)**	**0.55**
Mean calcium score	5875 ± 3285	3565 ± 1331	**1.72 (1.32 – 2.24)**	**<0.001**	3139 ± 1464	3815 ± 2172	**0.83 (0.62–1.06)**	**0.28**
Corevalve	18 (64%)	39 (43%)	**2.35 (0.98–5.66)**	**0.056**	NA	NA	NA	**NA**
Femoral access	25 (89%)	83 (92%)	**0.60 (0.14–2.59)**	**0.79**	19 (90%)	175 (93%)	**0.71 (018-4.73)**	**0.66**

Odds-ratio for a calcium score increase of 1000.
* BMI = body mass index.
† CS = calcium score.
‡ LVEF = Left ventricular ejection fraction.
§ NYHA = New-York heart association.

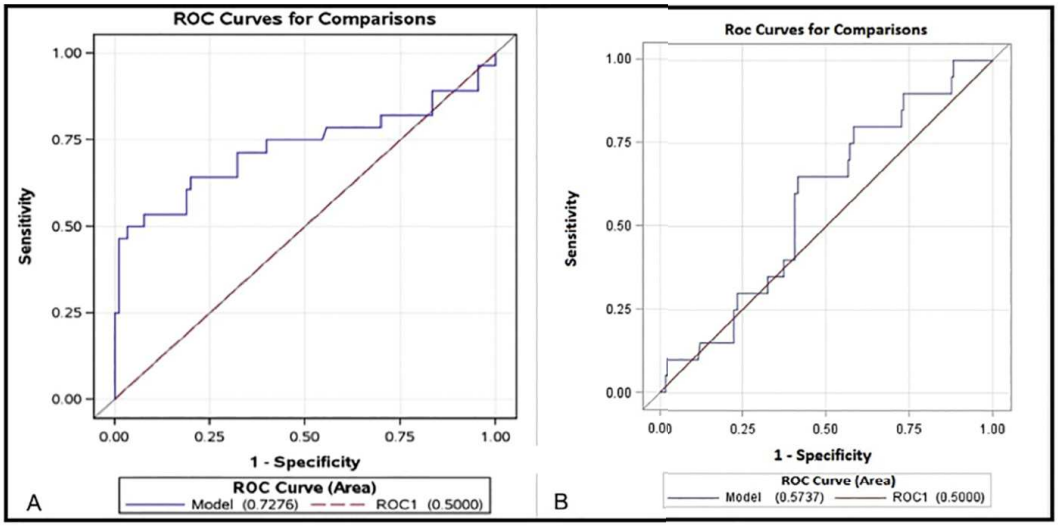


Figure 2. ROC curves with CS in the 2 study groups. ROC curves with a CS cutoff >6,000 to predict major events in the group 1 (*A*), and a CS cutoff <3000 to predict major events in the group 2 (*B*).

A CS cutoff has never been described to predict outcomes. In our study, a CS >6,000 strongly predicted adverse events in patients implanted with first generation valves allowing a risk stratification.

An external skirt was added to Sapien 3 valve to reduce paravalvular regurgitations and to ensure a better anchoring.[22] Our results are consistent with a recent meta analysis comparing Sapien XT with Sapien 3 devices, demonstrating a reduction in significant AR, bleeding, and major vascular complications with this new generation device.[23] However, only 1 recent work studied the association between aortic valve calcification and AR after Sapien 3 valve implantation. Kong et al.[22] compared 3 generations of balloon-expandable devices (Sapien, Sapien XT, and Sapien 3) in 272 patients and

demonstrated that Agatston CS was an independent factor of significant AR with Sapien and Sapien XT but not with Sapien 3 device suggesting that improvements in Sapien 3 design may counterbalance effects of aortic valve calcifications on valve expansion. Our findings may consolidate this hypothesis showing no significant correlation between CS and AR but also between CS and major events with the Sapien 3 device, highlighting the absence of prognostic value of CS with new generation balloon-expandable devices.

Moreover, technical improvements of the self-expandable Evolut R valve allowed reduction of AR by an optimal valve positioning with possible recapture[14,24] as well as reduction of vascular complications by a lower profile delivery system without external sheath.[13,25] Even if correlation between calcifications and AR was demonstrated with first generation CoreValve devices,[26,27] our study suggests that CS was not predictive of outcomes with new generation self-expandable valves. The main hypothesis is that anchoring of self-expandable prosthesis may be reduced by importance of calcifications regarding to the lower radial force compared with balloon-expandable devices. Thus, a higher rate of calcifications may result in an increased risk of AR despite improvements in this new generation device, but without prognostic impact on major cardiovascular and cerebrovascular events.

In our study, CS using Agatston score was higher in patients implanted with first generation devices probably due to a higher risk profile. Indeed, a shift from higher to lower risk profile of patients implanted with TAVI devices is suggested in daily practice and in recent studies with a Logistic Euroscore around 15%.[23] Thus, lower events rates occurred in the group 2, regarding to the learning curve, lower risk patients, and next generation valves. Taken all these considerations together, improvements in devices and in operator's experience leading to an important decrease in complications, may explain the lack of evidence of strongly associated predictive factors of major events.

Finally, this study has to be considered in light of some limitations. First, the studied population is relatively small with a low incidence of adverse events with new generation valves, due to devices improvements, increased operators' experience, and lower risk patients. Moreover, statistic evaluation of the study remains limited to evaluate precisely predictive factors in all study subgroups. Another limitation concerns the different surgical risk between patients in the 2 study groups with a potential bias, but results of this study may not be explained only by these differences with no correlation of risk profile with AR. Finally, AR ≥ 2 was not predictive of major events in patients implanted with Evolut R probably due to the insufficient population size implanted with the device.

In conclusion, although severe aortic valve calcium was an important prognostic factor after TAVI performed with first generation valves, CS does not predict severe adverse outcomes with new generation valves. CS remains a prognostic factor of significant AR with new generation self-expandable valves.

Acknowledgment: The authors thank Valerie Maciocce for her help to revise English language and Marine Chettouh, Research Clinic Assistant, for data collection.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.02.004.

1. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 2002;106:3006–3008.
2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–2198.
3. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB, PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686–1695.
4. Van Belle E, Juthier F, Susen S, Vincentelli A, Iung B, Dallongeville J, Eltchaninoff H, Laskar M, Leprince P, Lievre M, Banfi C, Auffray J-L, Delhaye C, Donzeau-Gouge P, Chevreul K, Fajadet J, Leguerrier A, Prat A, Gilard M, Teiger E, FRANCE 2 Investigators. Postprocedural aortic regurgitation in balloon-expandable and self- expandable transcatheter aortic valve replacement procedures: analysis of predictors and impact on long-term mortality: insights from the FRANCE2 Registry. *Circulation* 2014;129:1415–1427.
5. Yared K, Garcia-Camarero T, Fernandez-Friera L, Llano M, Durst R, Reddy AA, O'Neill WW, Picard MH. Impact of aortic regurgitation after transcatheter aortic valve implantation: results from the REVIVAL trial. *JACC Cardiovasc Imaging* 2012;5:469–477.
6. Feuchtner G, Plank F, Bartel T, Mueller S, Leipsic J, Schachner T, Müller L, Friedrich G, Klauser A, Grimm M, Bonaros N. Prediction of paravalvular regurgitation after transcatheter aortic valve implantation by computed tomography: value of aortic valve and annular calcification. *Ann Thorac Surg* 2013;96:1574–1580.
7. Hayashida K, Bouvier E, Lefèvre T, Hovasse T, Morice M-C, Chevalier B, Romano M, Garot P, Farge A, Donzeau-Gouge P, Cormier B. Potential mechanism of annulus rupture during transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2013;82:E742–E746.
8. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–832.
9. Kizer JR, Gefter WB, deLemos AS, Scoll BJ, Wolfe ML, Mohler ER. Electron beam computed tomography for the quantification of aortic valvular calcification. *J Heart Valve Dis* 2001;10:361–366.
10. Messika-Zeitoun D, Aubry M-C, Detaint D, Bielak LF, Peyser PA, Sheedy PF, Turner ST, Breen JF, Scott C, Tajik AJ, Enriquez-Sarano M. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. *Circulation* 2004;110:356–362.
11. Greason KL, Williamson EE, Suri RM, Mathew V. High Agatston aortic valve calcium score predicts transcatheter paravalvular aortic regurgitation. *J Thorac Cardiovasc Surg* 2014;147:1991.
12. Webb J, Gerosa G, Lefèvre T, Leipsic J, Spence M, Thomas M, Thielmann M, Treede H, Wendler O, Walther T. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. *J Am Coll Cardiol* 2014;64:2235–2243.
13. Piazza N, Martucci G, Lachapelle K, de Varennes B, Bilodeau L, Buithieu J, Mylotte D. First-in-human experience with the Medtronic CoreValve Evolut R. *EuroIntervention* 2014;9:1260–1263.
14. Manoharan G, Walton AS, Brecker SJ, Pasupati S, Blackman DJ, Qiao H, Meredith IT. Treatment of symptomatic severe aortic stenosis with

a novel resheathable supra-annular self-expanding transcatheter aortic valve system. *JACC Cardiovasc Interv* 2015;8:1359–1367.
15. Cailar CD, Gandet T, Cailar MD, Albat B. A simple sheath removal after open trans-femoral catheterization procedure: the ZIP technique. *Eur J Cardiothorac Surg* 2014;45:746–748.
16. Leclercq F, Akodad M, Macia J-C, Gandet T, Lattuca B, Schmutz L, Gervasoni R, Nogue E, Nagot N, Levy G, Maupas E, Robert G, Targosz F, Vernhet H, Cayla G, Albat B. Vascular complications and bleeding after transfemoral transcatheter aortic valve implantation performed through open surgical access. *Am J Cardiol* 2015;116:1399–1404.
17. Nijhoff F, Agostoni P, Samim M, Ramjankhan FZ, Kluin J, Doevendans PA, Stella PR. Optimisation of transcatheter aortic balloon-expandable valve deployment: the two-step inflation technique. *EuroIntervention* 2013;9:555–563.
18. Kappetein AP, Head SJ, Généreux P, Piazza N, Mieghem NM, van Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, Es G-A, van Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012;33:2403–2418.
19. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL, Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;14:611–644.
20. Khalique OK, Hahn RT, Gada H, Nazif TM, Vahl TP, George I, Kalesan B, Forster M, Williams MB, Leon MB, Einstein AJ, Pulerwitz TC, Pearson GDN, Kodali SK. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilation after balloon-expandable transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2014;7:885–894.
21. Leber AW, Kasel M, Ischinger T, Ebersberger UH, Antoni D, Schmidt M, Riess G, Renz V, Huber A, Helmberger T, Hoffmann E. Aortic valve calcium score as a predictor for outcome after TAVI using the CoreValve revalving system. *Int J Cardiol* 2013;166:652–657.
22. Kong WKF, van Rosendael PJ, van der Kley F, de Weger A, Kamperidis V, Regeer MV, Marsan NA, Bax JJ, Delgado V. Impact of different iterations of devices and degree of aortic valve calcium on paravalvular regurgitation after transcatheter aortic valve implantation. *Am J Cardiol* 2016;118:567–571.
23. Ando T, Briasoulis A, Holmes AA, Taub CC, Takagi H, Afonso L. Sapien 3 versus Sapien XT prosthetic valves in transcatheter aortic valve implantation: a meta-analysis. *Int J Cardiol* 2016;220:472–478.
24. Popma JJ, Reardon MJ, Khabbaz K, Harrison JK, Hughes GC, Kodali S, George I, Deeb GM, Chetcuti S, Kipperman R, Brown J, Qiao H, Slater J, Williams MR. Early clinical outcomes after transcatheter aortic valve replacement using a novel self-expanding bioprosthesis in patients with severe aortic stenosis who are suboptimal for surgery: results of the Evolut R U.S. study. *JACC Cardiovasc Interv* 2017;10:268–275.
25. Kalra SS, Firoozi S, Yeh J, Blackman DJ, Rashid S, Davies S, Moat N, Dalby M, Kabir T, Khogali SS, Anderson RA, Groves PH, Mylotte D, Hildick-Smith D, Rampat R, Kovac J, Gunarathne A, Laborde J-C, Brecker SJ. Initial experience of a second-generation self-expanding transcatheter aortic valve: the UK & Ireland Evolut R implanters' registry. *JACC Cardiovasc Interv* 2017;10:276–282.
26. John D, Buellesfeld L, Yuecel S, Mueller R, Latsios G, Beucher H, Gerckens U, Grube E. Correlation of Device landing zone calcification and acute procedural success in patients undergoing transcatheter aortic valve implantations with the self- expanding CoreValve prosthesis. *JACC Cardiovasc Interv* 2010;3:233–243.
27. Di Martino LFM, Soliman OII, van Gils L, Vletter WB, Van Mieghem NM, Ren B, Galema TW, Schultz C, de Jaegere PPT, Di Biase M, Geleijnse ML. Relation between calcium burden, echocardiographic stent frame eccentricity and paravalvular leakage after CoreValve transcatheter aortic valve implantation. *Eur Heart J Cardiovasc Imaging* 2017;18:648–653.

Chapitre 2

Publication 3 (accepté pour publication dans le JACC intervention) : ***Prior Balloon Valvuloplasty vs. Direct Transcatheter Aortic Valve Replacement: Results from the DIRECTAVI Trial***

Leclercq F., Robert P., **Akodad M.**, Macia J-C., Gandet T., Delseny D., Chettouh M., Schmutz L., Robert G., Levy G., Targosz F., Maupas E., Roubille F., Marin G., Nagot N., Albat B., Lattuca B., Cayla G.

Devant l'amélioration drastique des résultats de la technique, le TAVI s'adresse de nos jours à des patients avec un profil de risque de plus en plus favorable avec de meilleurs résultats dans ces populations. De plus, l'évolution du matériel et de l'expérience des opérateurs a conduit de façon inéluctable vers une évolution des pratiques avec une simplification de la procédure à plusieurs niveaux. Cette simplification de la procédure conduisant à la réalisation de TAVI « minimaliste » s'accompagne d'une réduction de la durée de la procédure, de suites de procédure simplifiées avec une sortie précoce et pourrait diminuer l'incidence de certaines complications (36). Parmi ces éléments de simplification, l'implantation de la prothèse sans prédilatation systématique, considérée comme une étape obligatoire dans les débuts de la technique, pourrait réduire l'incidence de certaines complications spécifiques à la prédilatation. En effet, la prédilatation serait associée à un risque accru d'embols systémiques et de fuites aortiques massives (46-49). Seulement quelques études observationnelles ont montré la faisabilité de l'implantation « directe » de la prothèse. Une seule étude randomisée récente a démontré la non-inferiorité d'une stratégie de direct TAVI en comparaison à une prédilatation systématique en termes de succès de la prothèse (« device success ») avec la valve auto-expansible Medtronic Corevalve (50). Aucune donnée randomisée n'est disponible avec la valve montée sur ballon de dernière génération Edwards Sapien 3.

L'objectif de cette étude était donc de comparer les résultats d'une stratégie de « direct TAVI » en comparaison à une prédilatation systématique, chez les patients implantés d'une valve Edwards Sapien 3, en termes de « device success » défini selon les critères VARC-2 à 72 heures (absence de mortalité per-procédure, bon positionnement de la prothèse et absence de missmatch significatif).

Cette étude incluant 236 patients a démontré la non infériorité d'une stratégie de « direct TAVI » dans cette population de patients.

Ainsi, les résultats de cette étude, en faveur de l'évolution des pratiques, nous ont conduit à réévaluer les marqueurs pronostiques précédemment mis en évidence (troponine pré et post-procédure et le score calcique scannographique). En effet, l'étape suivante a été d'une part d'évaluer l'impact pronostique de la troponine pré et post-procédure, dans cette population de patients, et d'autres part d'évaluer le rôle de la prédilatation sur l'élévation de troponine post-procédure ou « myocardial injury » (*publication 4*). Enfin, l'impact pronostique du score calcique dans cette population est également en cours d'évaluation, de même que son impact pronostique en fonction de la stratégie réalisée.

Prior Balloon Valvuloplasty vs. Direct Transcatheter Aortic Valve Replacement: Results from the DIRECTAVI Trial

Brief title: Prior Balloon Valvuloplasty vs. Direct TAVR

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ABSTRACT

Background: Randomized studies are lacking comparing transcatheter aortic valve replacement (TAVR) without balloon aortic valvuloplasty (BAV) to the conventional technique of TAVR with BAV.

Objectives: The aim of the study was to evaluate device success of TAVR using new-generation balloon-expandable prostheses with or without BAV.

***Methods*:** DIRECTAVI was an open-label non-inferiority study that randomized patients undergoing TAVR using the Edwards SAPIEN 3 valve with or without prior balloon valvuloplasty. The primary endpoint was the device success rate according to the VARC-2 criteria which was evaluated with a 7% non-inferiority margin. The secondary endpoint included procedural and 30-day adverse events.

***Results*:** Device success was recorded for 184 of 236 included patients (78.0%). The rate of device success in the direct implantation group (n=97, 80.2%) was non-inferior to the BAV group (n=87, 75.7%) (mean difference 4.5%; 95% CI: -4.4%–13.4%; p=0.02 for non-inferiority). No severe patient-prosthesis mismatch or severe aortic regurgitation occurred in any group. In the direct implantation group, 7 patients (5.8%) required BAV to cross the valve. Adverse events were mainly related to pacemaker implantation (20.9% with BAV group vs. 19.0% with direct implantation; p=0.7). No significant difference was found between the 2 strategies in duration of procedure, contrast volume, radiation exposure or rates of post-dilatation.

Conclusions: Direct TAVR without prior BAV was non-inferior to conventional strategy using BAV with new-generation balloon-expandable valves but without procedure simplification. BAV was needed to cross the valve in a few patients, suggesting a need for upstream selection based on patient anatomy.

CONDENSED ABSTRACT

In this randomized trial including 236 patients, direct transcatheter aortic valve replacement (TAVR) with the new-generation balloon-expandable SAPIEN 3 valve was non-inferior to the conventional technique with prior valvuloplasty considering device success rate (mean difference 4.5%; 95% CI: -4.4% to 13.4%; p-value=0.02 for non-inferiority) and safety of the procedure. However, direct implantation strategy did not simplify TAVR regarding procedural times, contrast volume, radiation doses or rates of post dilatation, which were similar between the 2 groups. In some patients (5.8%), direct implantation was not possible or not attempted suggesting that upstream selection based on patient anatomy is necessary.

Key words: Transcatheter aortic valve replacement; Balloon aortic valvuloplasty; Direct implantation; Device success, Randomized clinical trial

ABBREVIATIONS LIST

AVA: Aortic valve area; AVAi: AVA indexed to body surface area; BAV: balloon aortic valvuloplasty; BMI: Body Mass Index; DW-MRI: Diffusion weight magnetic nuclear imaging; DMSC: Data monitoring and safety committee; DIRECTAVI: direct transcatheter aortic valve implantation; MACCE: major adverse cardiac and cerebral events; MSCT: Multislice computed tomography; MDT: multidisciplinary heart team; PPM: prosthesis–patient mismatch; TAVR: Transcatheter aortic valve replacement; THV: Transcatheter heart valve; VARC: Valve academic research consortium

Trial registration: Clinicaltrials.gov identifier: NCT02729519; July 15, 2016

Introduction

Balloon aortic valvuloplasty (BAV) is typically considered a mandatory step in the transcatheter aortic valve replacement (TAVR) procedure both to facilitate implantation of the transcatheter heart valve (THV) and to reduce the radial counterforce for optimal device expansion (1). However, BAV has been shown to be associated with specific complications including annular rupture, massive aortic regurgitation, destabilization of hemodynamic status related to rapid pacing, or possible cerebral embolization (2-5). Hence, avoiding BAV prior to TAVR is an attractive option that may also simplify the procedure. New-generation balloon-expandable THV are associated with low profile and orientable delivery systems which facilitate valve crossing. These systems have been associated with high TAVR success rates without prior dilatation of the native valve in observational studies and registries (6-9). However, such studies are prone to bias and while the recent randomized DIRECT study showed the feasibility of direct implantation of self-expandable THV (10), no randomized data are currently available concerning the safety and efficacy of this strategy using new-generation balloon-expandable THV.

The aim of the current study was to demonstrate non-inferiority of TAVR without BAV to TAVR with prior BAV on device success rates with the SAPIEN 3 balloon-expandable THV.

Methods

Study design

DIRECTAVI was a prospective, randomized, single-center, open-label trial using the third-generation balloon-expandable Edwards SAPIEN 3 THV. We hypothesized that TAVR without prior BAV of the aortic valve (test arm; direct implantation group) would be non-inferior to

conventional practice using systematic prior valvuloplasty of the aortic valve (control arm; BAV group).

The study protocol was approved by an independent ethics committee before study initiation (Comité de Protection des Personnes Sud Méditerranée, Montpellier, France, ID RCB : 2015-A01823-46) and all patients provided oral and written informed consent. The trial was conducted according to the World Medical Association Declaration of Helsinki and was registered with ClinicalTrials.gov (NCT02729519).

Patient population

From May 2016 to May 2018, 236 consecutive patients undergoing TAVR via transfemoral or trans-carotid approaches were enrolled in the study. Patients were confirmed to be eligible for TAVR by a multidisciplinary heart team including at least an interventional cardiologist, a cardiothoracic surgeon and an anesthetist. The complete list of inclusion and exclusion criteria is provided in **Online Table 1** and was previously published in the study design paper (11). All patients referred for TAVR at our center who met the inclusion criteria were included and randomized between the 2 strategies after checking of the eligibility criteria and collection of the informed consent. Random allocation sequences were computer-generated by an independent statistician in a 1:1 ratio with permuted blocs of 4 and 6. The flowchart of the study is shown in **Figure 1**.

Procedure

All TAVR implantation procedures were performed with the Edwards SAPIEN 3 THV (Edwards Lifesciences, Irvine, CA, USA). For all patients, both vascular access and aortic valve were evaluated before the procedure by multislice computerized tomographic angiography (MSCT) of the entire aorta using vascular windows settings. The prosthesis size (23, 26 or 29 mm) and the vascular access were left to the discretion of the operating team. Transfemoral access was

the first choice when possible. All TAVR procedures were performed in the same hybrid room (in Montpellier University Hospital), by 6 independent medical teams.

The procedure has been previously detailed (11). Briefly, most TAVR were performed under general anesthesia using mild low profile 14–16 French delivery systems and almost exclusive surgical vascular access with a preclosing technique as previously described (12). For the control group, BAV was performed with a 20-, 23- or 25-mm diameter balloon according to the manufacturer's recommendations depending on the annular diameter measured with MSCT. Clopidogrel 75 mg and aspirin 75 mg were administrated to all patients following TAVR except those with indication of long-term anticoagulant therapy who received only aspirin 75 mg in addition to anticoagulant therapy.

Follow-up

Baseline characteristics, clinical and procedural information were collected at the time of randomization (11). Patients were scheduled to undergo clinical evaluation at 72 hours and at 1-month follow-up.

Study endpoints

The primary endpoint was the device success rate at 72 hours post TAVR according to the VARC-2 criteria (13). This composite endpoint was defined as 1) absence of immediate procedural mortality (intra-procedural events resulting in immediate or subsequent death ≤72 hours post-procedure (13) 2) correct positioning of a single THV into the proper anatomical location and 3) no moderate or severe prosthesis–patient mismatch (PPM) and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, and no moderate or severe prosthetic valve regurgitation. Echocardiography assessments used the VARC-2 recommendations. Aortic valve regurgitation was quantitatively assessed (mild, moderate, severe). Aortic valve area (AVA after TAVR) was calculated using the continuity equation. AVA was indexed to body

surface area (AVAi) and PPM was defined as non significant for AVAi >0.85 cm^2/m^2, moderate for AVAi ≥0.65cm^2/m^2 to ≤0.85 cm^2/m^2, and severe for AVAi <0.65 cm^2/m^2. For patients with body mass index (BMI) ≥30 kg/m^2, moderate PPM was defined as AVAi ≤0.70 cm^2/m^2 and severe PPM as AVAi ≤0.60 cm^2/m^2. We also evaluated device success without including PPM in reference to the VARC 1 criteria (14). Secondary endpoints included procedural outcomes (length of procedure, radiation exposure, contrast volume), post-dilatation rate, hospitalization length and clinical events: all-cause mortality, stroke, major bleeding, acute kidney injury (stage 2 and 3), and pacemaker implantation at 1-month follow-up (VARC-2 criteria) (13).

Sample size

The study was designed to evaluate non-inferiority. Based on recent studies and registries, we assumed a procedural success rate of 95% in the control group. Using a non-inferiority threshold of 7%, a power of 80% and a 5% significance level, 240 patients would be necessary to demonstrate non-inferiority of TAVR without predilatation to conventional procedures. All analyses were performed according to the intention-to-treat principle, with the inclusion of all randomized patients according to the original group allocation.

Statistical analyses

Patients' characteristics are presented with proportions for categorical variables and as mean ± standard deviation and median (interquartile range) for quantitative variables. Characteristics were compared between the test and the control group with the Student t-test or the Mann-Whiney U-test for continuous variables, and with Chi square or Fisher exact test for categorical variables. Non-inferiority was assessed by the one-sided Farrington-Manning confidence limit for the risk method. For secondary end points, superiority analysis was used with the appropriate statistical test (either Wilcoxon-Mann-Whitney for quantitative

variables, or Fisher or Chi-square tests for qualitative variables). Statistical analyses were performed using SAS 9.1 software (SAS Institute, Cary, North Carolina).

Results

Study population

Between May 2016 and May 2018, a total of 236 patients were enrolled in the study, 115 patients in the BAV group and 121 in the direct implantation group (**Figure 1**). Baseline characteristics of the population are shown in **Table 1**. Transfemoral access was used for the majority of patients (n=212; 89.8%), while a transcarotid approach was chosen for cases of unsuitable iliofemoral anatomy (n=24; 10.2%). BAV was necessary in seven patients (5.8%) allocated to direct implantation due to failure to cross the valve (n=3) or to a medical decision and anticipation of technical difficulties related to challenging anatomy with severe aortic stenosis and bulky calcification (n=4).

Primary endpoint: device success

Device success according to the VARC-2 criteria at 72 hours follow-up was obtained for 184 patients (78.0%). The device success rate in the direct implantation group (n=97, 80.2%) was non-inferior to the BAV group (n=87, 75.7%) (mean difference 4.5; 95% CI : -4.4% to 13.4%; p=0.02 for non-inferiority, **Figure 2**). The components of the primary end point (**Table 2**, **Central illustration**) were not significantly different between the 2 groups. No severe aortic regurgitation or severe PPM was observed in the population and all patients had correct positioning of a single valve. Excluding PPM evaluation and using the VARC-1 criteria, the device success rate at 72 hours was 95.3% (n=225) without significant difference between the BAV and direct-implantation groups: 94.7% (n=109) and 95.9% (n=116) respectively; mean difference -0.74; 95% CI: -5.1% to 3.5%, p=0.0008 for non-inferiority.

Secondary endpoints (Table 3, Online Figure 1)

No significant difference was observed for any endpoint including mortality and post dilatation rate. The most common event was pacemaker implantation. There was a trend towards lower rates of major vascular complications and acute renal failure in the direct implantation group. No life-threatening bleeding occurred in any group. No patient had severe aortic regurgitation at follow-up.

Discussion

In this prospective, randomized study of an all-comers population of patients with severe aortic stenosis, we found that: 1) direct TAVR with new-generation balloon-expandable SAPIEN 3 valves is non-inferior to conventional procedures using systematic BAV on standardized device success rate (VARC-2); 2) safety of direct TAVR was similar to conventional procedures without significant differences in procedural adverse events, particularly aortic regurgitation or pacemaker rates; 3) procedural times, contrast volume and radiation doses were not statistically different between the 2 strategies; 4) overall use of post-dilatation was low and not higher in the direct strategy group; and 5) in a small number of patients with challenging anatomy, the direct implantation was not possible.

Device success

Improved prosthesis expansion following balloon pre-dilatation during TAVR may in theory reduce the risk of underexpansion of the THV and the need for post dilatation. However, the radial force provided by new-generation TAVR devices, particularly balloon-expandable valves, provided adequate expansion of the prosthesis in most cases (7,15,16). BAV may be helpful for annular sizing and to evaluate the risk of coronary occlusion in case of low sinus height, but with the use of MSCT for detailed assessment of the aortic native valve, optimal selection of patients is possible before the procedure, reducing the need for BAV

during TAVR. The strategy of direct implantation has been suggested to facilitate the procedure with more stable position of the THV in the native annulus during expansion of the device (17). Although recent reports have shown that direct valve implantation without BAV is feasible with high success rates, these studies were mainly historical comparison and non-randomized (9,15,16). Recently, the randomized DIRECT study evaluated 171 patients who underwent TAVR with different generation of self-expandable Corevalve THV and showed that direct implantation was non-inferior to pre-dilatation on device success rates (10). To our knowledge, our study is the first prospective randomized trial powered to investigate non-inferiority of direct TAVR using a new generation of balloon-expandable valves and using the standardized international VARC-2 definition (13). Device success rates in our study were similar to those in the DIRECT trial, which supports the credibility of the results.

Safety and complications

The main component of device failure in our study was PPM, but notably no severe PPM was observed. These results are in accordance with other recent reports with new-generation THV (17,18). That these recent studies show lower rates than earlier and large randomized studies (19,20) is probably due to advances in TAVR technology. No severe aortic regurgitation was reported and moderate aortic regurgitation was rare. In observational studies (9,16), the rate of paravalvular regurgitation after device implantation has been reported to be lower with direct implantation than with prior BAV, an observation attributed to less accurate implantation in the aortic annulus in cases of fractured and separated commissures. Our randomized study did not confirm these results. One explanation may be that significant aortic regurgitation has become a rare event with increasing operator experience and the use of new-generation THV. Furthermore, while a high correlation

between the volume of calcification and the severity of paravalvular leaks has been previously demonstrated (22), the higher rate of aortic regurgitation associated with BAV may have been related to more complex anatomies selected for this strategy in the observational studies (21).

Secondary endpoints

In contrast to prior observational studies (6-9), our randomized comparison found no beneficial effect of the direct implantation for duration of procedure, contrast volume, radiation doses, or hospitalization duration. In observational studies, implantation strategy is usually left to the operator's discretion and patients were selected for suitability for direct implantation (less aortic calcification, favorable femoral and aortic anatomy) as previously showed in the SOURCE 3 registry (21). Contrast injection is not necessary during BAV and radiation doses were probably mostly related to vascular approach difficulties or to the stability of the THV in the native annulus during deployment.

Post-dilatation rates

We found very limited need for post dilatation, with rates consistent with those in prior observational studies and registries using balloon-expandable THV (15,16,23). Notably, the post-dilatation rate was similar in the 2 groups, in contrast to the DIRECT trial (10) which showed a 2-fold increase in the need for post-dilatation in the direct implantation group. As post dilatation appears to be not necessary in most patients after balloon expandable THV, it might be used only for patients with a greater degree of calcifications as reported in the recent EASE-IT TF registry (24).

Failure of valve crossing

The failure of crossing the valve in the direct implantation group was low in our study. An infrequent, but possible need for bailout BAV when TAVI was initially planned without

preimplantation BAV has been reported from an observational study (25). No crossing failure was reported in the DIRECT study (10), which was probably due to the exclusion of patients with complex anatomies such as very calcified or bicuspid valves. Tight valve calcification or bicuspid valve but also aortic anatomy (*i.e* horizontal arch and/or femoral tortuosities) may indicate crossing difficulties. Failure rates can be expected to decrease in future as teams gather experience and device improve, facilitating valve crossings.

Study limitations

A first limitation of this analysis is the relatively small sample size. However, the statistical power was sufficient to demonstrate non-inferiority, the primary objective. A second limitation is related to the use of post dilatation without a formalized indication in the study protocol, instead left to the discretion of the interventional cardiologist.

In conclusion, the DIRECTAVI trial, the first randomized study comparing direct implantation of a third-generation balloon-expandable THV to routine use of prior BAV, found the direct implantation to be non-inferior in terms of device success rate. There was no difference in rates of adverse events or post dilatation. No benefit was found for simplification of the procedure. BAV was required to cross the valve in a small number of patients, suggesting that selection based on patient anatomy is necessary for the strategy.

Clinical Perspectives

Medical Knowledge, Competency in Patient Care and Procedural Skills

TAVR without prior BAV is commonly performed, especially with balloon-expandable THV, but BAV remains a possibility in challenging cases. The efficacy and safety of direct implantation

demonstrated in this study using new-generation balloon-expandable THV may be reassuring for extension of the strategy.

Translational Outlook

The low but relevant failure rate of the direct strategy underlines the need for criteria for selection of patients who need prior BAV, particularly regarding valvular and aortic anatomy. Specific evaluation of patients with greater degree of calcification or bicuspid valve may be particularly relevant considering future extension of TAVR to larger and younger populations.

References

1- Vahanian A, Himbert D. Transcatheter aortic valve implantation: could it be done without prior balloon valvuloplasty? JACC Cardiovasc Interv. 2011;4:758–9.

2- Eltchaninoff H, Cribier A, Tron C, et al. Balloon aortic valvuloplasty in elderly patients at high risk for surgery, or inoperable: immediate and mid-term results. Eur Heart J 1995;16:1079 – 84.

3- Sack S, Kahlert P, Khandanpour S, et al. Revival of an old method with new techniques: balloon aortic valvuloplasty of the calcified aortic stenosis in the elderly. Clin Res Cardiol 2008;97:288 –97.

4- Kahlert P, Al-Rashid F, Döttger P, et al. Cerebral Embolization During Transcatheter Aortic Valve Implantation: a transcranial Doppler study. Circulation 2012;126:1245-55.

5- Nombela-Franco L, Webb J, de Jaegere PP, et al. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. Circulation 2012; 126:3041-53.

6 - Grube E, Naber C, Abizaid A, et al. Feasibility of Transcatheter Aortic Valve Implantation Without Balloon Pre-Dilation A Pilot Study. J Am Coll Cardiol Intv 2011;4:751–7.

7- Fiorina C, Maffeo D, Curello S, et al. Direct transcatheter aortic valve implantation with self-expandable bioprosthesis: Feasibility and safety. Cardiovascular Revascularization Medicine 2014; 15: 200–3.

8- Möllmann H, Kim WK, Kempfert J, et al. Transfemoral aortic valve implantation of Edwards SAPIEN XT without predilatation is feasible. Clin Cardiol 2014;37:667-71.

9- Deharo P, Resseguier N, Koning R, et al. Impact of Direct Transcatheter Aortic Valve Replacement Without Balloon Aortic Valvuloplasty on procedural and clinical outcomes insights from the FRANCE TAVI registry. J Am Coll Cardiol Intv 2018;11:1956–65.

10- Toutouzas K, Benetos G, Voudris V, et al. Pre-Dilatation Versus No Pre-Dilatation for Implantation of a Self-Expanding Valve in All Comers Undergoing TAVR: The DIRECT Trial. JACC Cardiovasc Interv 2019;12:767–77.

11- Leclercq F, Robert P, Labour J, et al. Prior balloon valvuloplasty versus DIRECT transcatheter aortic valve implantation (DIRECTAVI): study protocol for a randomized controlled trial. Trials 2017;18:303-12.

12- Du Cailar C, Gandet T, Du Cailar M, Albat B. A simple sheath removal after open trans-femoral catheterization procedure: the ZIP technique. Eur J Cardiothorac Surg 2014 ;45:746-8.

13- Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012; ;60:1438–54.

14- 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. Eur Heart J 2011; 32: 205–17.

15- Liao YB, Meng Y, Zhao ZG, et al. Meta-analysis of the effectiveness and safety of transcatheter aortic valve Implantation without balloon predilation. Am J cardiol 2016; 117:1629-35.

16 - Auffret V, Regueiro A, Campelo-Parada F, et al. Feasibility, safety, and efficacy of transcatheter aortic valve replacement without balloon predilation: a systematic review and meta-analysis. Catheter Cardiovasc Interv 2017;90:839–50.

17- Herrmann HC, Daneshvar SA, Fonarow GC et al. Prosthesis–Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement from the STS/ACC TVT Registry. J Am Coll Cardiol 2018;72:2701–11.

18- Miyasaka M, Tada N, Taguri M, et al. from the OCEAN-TAVI Investigators. Incidence, predictors, and clinical impact of prosthesis-patient mismatch following transcatheter aortic valve replacement in Asian patients: the OCEAN-TAVI registry. J Am Coll Cardiol Intv 2018;11:771–80.

19- Little SH, Oh JK, Gillam L et al. Self-expanding transcatheter aortic valve replacement versus surgical valve replacement in patients at high risk for surgery: a study of echocardiographic change and risk prediction. Circ Cardiovasc Interv 2016;9:e003426.

20- Pibarot P, Weissman NJ, Stewart WJ, et al. Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: a PARTNER trial cohort analysis. J Am Coll Cardiol 2014;64:1323–34.

21- Wendler O, Schymik G, Treede H, et al. SOURCE 3 Registry: design and 30-day results of the European post approval registry of the latest generation of the SAPIEN 3 transcatheter heart valve. Circulation 2017;135:1123–32.

22- Khalique OK, Hahn RT, Gada H, et al. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilation after balloon-expandable transcatheter aortic valve replacement. JACC Cardiovasc Interv 2014;7:885–94.

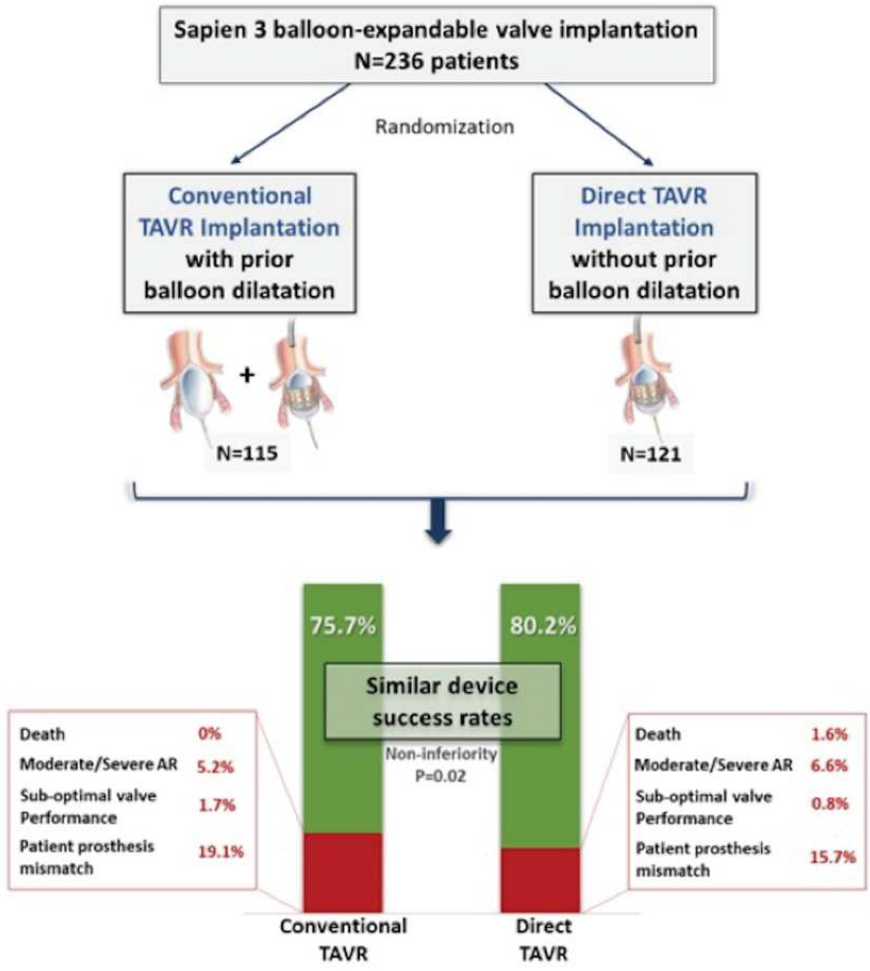
23- Wang N, Lal S. Post-dilation in transcatheter aortic valve replacement: a systematic review and meta-analysis. J Interv Cardiol 2017;30:204–11.

24- Butter C, Okamoto M, Schymik G, et al. Degree of valve calcification in patients undergoing transfemoral transcatheter aortic valve implantation with and without balloon aortic valvuloplasty: Findings from the multicenter EASE-IT TF registry. Catheter Cardiovasc Interv 2019. Mar 13. doi: 10.1002/ccd.28164.

25- Chan PH, Mario CD, Moat N et al. Transcatheter aortic valve implantation without balloon predilatation: not always feasible. Catheter Cardiovasc Interv 2013;82:328-32.

FIGURES TITLE AND LEGEND

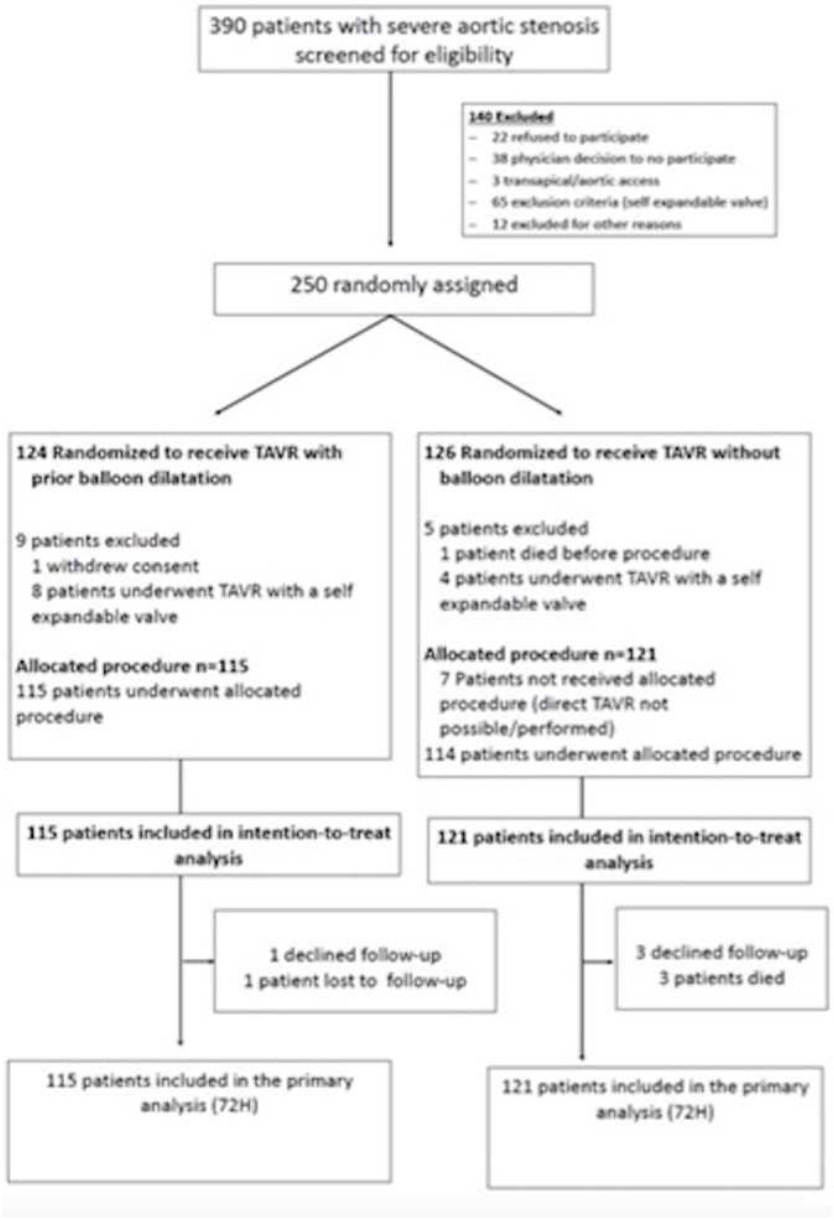
Central illustration: Study design and main results



Green bars represent device success rates in each group and red bans represent the rate of implantation failure and its different components.

TAVR indicates Transcatheter Aortic Valve Replacement and AR, Aortic Regurgitation

Figure 1: Flow chart of the DIRECTAVI study

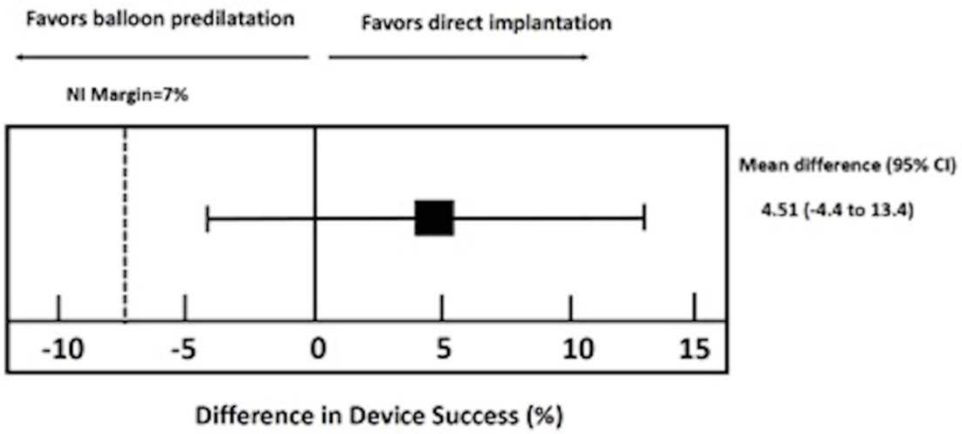


Caption:

Three hundred ninety patients were screened and 140 not meeting the inclusion criteria were excluded, mainly related to use of a self- expandable THV. Among the 240 patients randomly assigned, 16 patients were excluded due to protocol violation or death before TAVR.

TAVR: Transcatheter aortic valve replacement; THV: Transcatheter heart valve

Figure 2: Primary endpoint: Procedural success at 72 hours according to the VARC-2 criteria (non-inferiority analysis)



Caption:

No difference in device success rate was observed between the 2 strategies of pre-dilatation and direct implantation (non-inferiority threshold of 7%, mean difference = 4.5%, 95% CI -4.4% to 13.4%). Immediate device success was defined, according to the VARC-2 criteria, as absence of immediate procedural mortality AND correct positioning of a single prosthetic heart valve into the proper anatomical location AND intended performance of the prosthetic heart valve (no prosthesis–patient mismatch and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s), AND no moderate or severe prosthetic valve regurgitation.

VARC: Valve Academic Research Consortium

Table 1: Baseline characteristics of the population

	Pre-dilatation group (n=115)	**Direct implantation group** (n=121)
Female	45 (39.1)	45 (37.2)
Age, median (years)	83 (79-87)	83 (78-87)
Body mass index, median (kg/m^2)	26 (24.3-29.2)	26.6 (24.5-29.6)
Diabetes mellitus	41 (35.7)	45 (37.2)
Previous PCI	48 (41.7)	53 (43.8)
Previous CABG	6 (5.2)	7 (5.8)
Previous BAV	10 (8.7)	12 (9.9)
Cerebrovascular disease	5 (4.4)	4 (3.3)
Peripheral vascular disease	13 (11.3)	12 (9.9)
COPD	8 (7.0)	20 (16.5)
Atrial fibrillation	31 (27.0)	48 (39.7)
Permanent pacemaker	15 (13.1)	14 (11.6)
Pulmonary hypertension	2 (1.7)	2 (1.7)
Creatinine (µmol/L)	102 (82.0-126.0)	104 (84-131)
Hypertension	81 (70.4)	74 (61.2)
Euroscore 1	10 (7-14)	10 (7-14)
Euroscore 2	3 (2-4)	2.3 (2-3.8)
NYHA class		
I, II	54 (47.0)	58 (47.9)
III, IV	61 (53.1)	63 (52.1)
LVEF, %	60 (50-60)	60 (50-60)
Aortic valve area, cm^2	0.7 (0.6-0.9)	0.8 (0.6-0.9)
Mean aortic valve gradient, mmHg	46 (40-55)	49.5 (40-58)

Values are median or n (%);

* BAV: balloon aortic valvuloplasty; † CABG, coronary artery bypass graft; ‡ COPD: chronic obstructive pulmonary disease; § NYHA: New York Heart Association; ? PCI: percutaneous coronary intervention

Table 2: Primary endpoints at 72 hours follow-up

	Total population (n=236)	**Pre-dilatation group (**n=115)	**Direct implantation group** (n=121)	**Absolute difference**
Device success at 72h	184 (78%)	87 (75.7%)	97 (80.2%)	4.5 (-4.4 to 13.4)
Procedural mortality	2 (0.8%)	0	2 (1.7%)	
Correct performance of the valve				
Moderate PPM	41 (17.4%)	22 (19.1%)	19 (15.7%)	-3.4 (-13.1 to 6.2)
Severe PPM	0	0	0	
Aortic valve gradient > 20mmHg or Peak velocity > 3m/s	3 (1.3%)	2 (1.7%)	1 (0.8%)	-0.9 (-3.8 to 1.9)
Moderate AR	14 (5.9%)	6 (5.2%)	8 (6.6%)	1.4 (-4.6 to 7.4)
Severe AR	0	0	0	
Second valve	0	0	0	
Post dilatation	0	0	0	
Secondary migration	0	0	0	
Improper positioning	0	0	0	

*AR: aortic regurgitation; †: PPM: prosthesis-patient mismatch

Table 3: Secondary outcomes

	Total population (n=236)	**Pre-dilatation group** (n=115)	**Direct implantation group** (n=121)	**P value #**
Procedural outcomes				
Need of post dilatation, n (%)	4 (1.7)	2 (1.7)	2 (1.7)	1.00
Contrast volume (mL), mean ± SD	79.01±31.4	78.2 ±29.3	79.7 ±33.3	0.97
Procedure length (min), mean ± SD	53.06±18.4	54.2±18.2	52.0±18.7	0.31
Radiation (cgrays/cm^2), mean ± SD	3907±3385	3730±3487	4073±3293	0.24
Hospitalization duration (days)	5.0 ±2.7	5.2 ±3.0	4.9 ±2.2	0.90
1-month adverse events, n (%)	60 (25.4)	29 (25.2)	31 (25.6)	0.94
All-cause mortality, n (%)	4 (1.7)	0 (0)	4 (3.2)	0.24
Stroke, n (%)	3 (1.3)	1 (0.9)	2 (1.7)	0.99
Major vascular complications, n (%)	7 (3)	6 (5.2)	1 (0.8)	0.06
Major bleeding, n (%)	8 (3.4)	3 (2.6)	5 (4.1)	0.70
Transfusion, n (%)	4 (1.7)	2 (1.7	2 (1.7)	1.00
Acute kidney injury, n (%)	5 (2.1)	1 (0.9)	4 (3.3)	0.37
Pacemaker implantation, n (%)	47 (19.9)	24 (20.9)	23 (19.01)	0.72
Heart failure, n (%)	3 (1.3)	0 (0)	3 (2.5)	0.24
Aortic regurgitation, n (%)				
- None (grade 0), n (%)	144 (61.5) *	75 (65.2)	69 (58.0) **	0.20
- Mild (grade 1), n (%)	76 (32.5)	34 (29.5)	42 (35.3)	0.90
- Moderate (grade 2), n (%)	14 (6)	6 (5.2)	8 (6.6)	0.90
- Severe (grade 3), n (%)	0 (0)	0 (0)	0 (0)	NA

*Data available for 234 patients

** Data available for 119 patients

Superiority analysis using the appropriate statistical test (either Wilcoxon-Mann-Whitney for quantitative variables, or Fisher or Chi-square tests for qualitative variables)

Publication 4 (en attente de soumission): ***Impact of prior Balloon Valvuloplasty vs Direct Transcatheter Aortic Valve Replacement on myocardial injury: Insight from the DIRECTAVI trial***

Akodad M, Marin G., Cayla G., Macia J-C., Gandet T., Delseny D., Chettouh M., Lattuca B., Robert P., Schmutz L., Robert G., Levy G., Targosz F., Maupas E., Nagot N., Albat B., Roubille F, Leclercq F.,

La valeur pronostique de la troponine pré et post-procédure est suggérée par plusieurs études observationnelles avec néanmoins des données contradictoires (110-115). Dans le premier chapitre de ce travail de thèse, la troponine pré-procédure a été démontrée comme facteur prédictif indépendant de mortalité à 1 mois et jusque 3 ans après la procédure dans une large population de patients. La troponine post-procédure était également prédictive de mortalité à moyen et long terme chez les patients ayant une troponine pré-procédure normale ou presque normale. Certains facteurs prédictifs de troponine pré-procédure élevée ont été mis en évidence dans la littérature et dans les données précédemment décrites dans ce travail. Ces facteurs sont essentiellement liés aux comorbidités du patient et cette élévation de la troponine chronique est en fait un reflet de la sévérité de la cardiopathie (111,112).

Concernant l'élévation de la troponine post-procédure, les facteurs prédictifs suggérés dans la littérature sont essentiellement des facteurs liés à la procédure elle-même. En effet, la durée de la stimulation rapide, une hypotension sévère pendant la procédure ou la prédilatation au ballon ont été mis en cause (113). Or, la prédilatation avant l'implantation de la prothèse, systématique dans les débuts de l'expérience TAVI est de moins en moins réalisée actuellement, à l'ère de la simplification des procédures TAVI.

Une seule étude randomisée publiée à ce jour a démontré la non-infériorité d'une stratégie de « direct TAVI » en comparaison à une prédilatation systématique avec la valve auto-expansible Medtronic corevalve. Notre équipe a réalisé l'étude DIRECTAVI démontrant également la non-infériorité d'une stratégie de « direct TAVI » avec la valve Edwards Sapien 3.

Une seule étude observationnelle avec la valve auto-expansible Medtronic corevalve suggérait que l'implantation de la prothèse sans prédilatation pourrait diminuer l'importance de l'élévation de la troponine et l'incidence de la « myocardial injury » après la procédure

(153). L'objectif de cette étude était donc d'évaluer dans la population de l'étude randomisée DIRECTAVI, d'une part la valeur pronostique de la troponine pré et post-procédure et d'autre part l'impact de la prédilatation sur la survenue de la « myocardial injury » ou élévation significative de troponine post-procédure. L'hypothèse de départ étant que la prédilatation par plusieurs mécanismes comme de micro-embols, la stimulation rapide ventriculaire et l'hypotension induite favoriserait la « myocardial injury ». Dans cette étude ancillaire de l'essai DIRECTAVI incluant 211 patients, la troponine pré-procédure n'était pas associée à la survenue d'évènements à 1 mois. En revanche **la « myocardial injury », présente chez 20% des patients en post-procédure, était prédictive d'évènements majeurs à 1 mois**. La réalisation d'une **prédilatation était associée significativement à la survenue de « myocardial injury » a**vec un risque multiplié par 2,8 par rapport à la stratégie de « direct TAVI ».

Ainsi, l'absence de prédilatation avant l'implantation de la prothèse, s'intégrant dans l'évolution des pratiques, est associée à une diminution de la troponine post-procédure et de la « myocardial injury ». De même, la « myocardial injury » reste associée à un pronostique péjoratif chez les patients bénéficiant d'un TAVI. A noter que la troponine pré-procédure n'était pas associée au pronostique, soit par manque de puissance dans cette population de taille relativement faible, soit par manque de suivi au long cours.

Impact of prior Balloon Valvuloplasty vs Direct Transcatheter Aortic Valve Replacement on myocardial injury: Insight from the DIRECTAVI trial

Brief title: Myocardial injury after Direct TAVR

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This study was funded by the University Hospital of Montpellier, avenue du doyen Giraud, 34295 Montpellier (France) by an unrestricted grant from Edwards Lifesciences, route de l'Etraz 70, 1260 Nyon (Switzerland)

Tweet: Myocardial injury after TAVR was increased by predilatation and remained associated with adverse outcomes

ABSTRACT

***Background**:* Myocardial injury, defined by significant troponin elevation, was described as a predictive factor of short and long term mortality after transcatheter aortic valve implantation and may be increased by balloon aortic valvuloplasty (BAV).

Objectives: The aim of the study was to evaluate the impact of BAV on myocardial injury after TAVR using new-generation balloon-expandable prostheses.

Methods**:** the DIRECTAVI trial, an open-label randomized study, demonstrated non-inferiority of TAVR performed without predilatation (direct TAVR group) in comparison with systematic predilatation (BAV group) in patients undergoing TAVR with the Edwards SAPIEN 3 valve. High-sensitive troponin assessment was performed in all patients before and after the procedure. The incidence of myocardial injury defined by troponin elevation > 15 upper limit reference after the procedure was the main endpoint. Secondary endpoints were adverse events at 1-month follow-up according to VARC-2 criteria.

Results**:** Pre and post-procedure troponin were available in 211 of the 236 patients (89.4%) included in this study (104 (90.4%) in the BAV group and 107 (88.4%) in the direct TAVR group). Baseline characteristics were comparable between both groups. Mean age was 82 y± 6.7 and 145 were male (61.4%). Myocardial injury occurred in 42 patients (19.9%), 13 (12.2%) in the direct TAVR group and 29 (27.9%) in the BAV group, p=0.004. Myocardial injury increased by 2.8-fold in the BAV group in comparison to the direct TAVR group (OR 2.8 IC 95% 1.4-5.8). Myocardial injury was associated with 1-month outcomes (p=0.03).

***Conclusions**:* Predilatation significantly increased myocardial injury in patients undergoing TAVR with new-generation balloon-expandable valves. Myocardial injury was associated with 1-month outcomes.

Key words: Transcatheter aortic valve replacement; Balloon aortic valvuloplasty; Direct implantation; troponin, myocardial injury, Randomized clinical trial

ABBREVIATIONS LIST

BAV: balloon aortic valvuloplasty

DIRECTAVI: direct transcatheter aortic valve implantation

Hs-TnT: hypersensitive troponin T

MSCT: Multislice computed tomography

TAVR: Transcatheter aortic valve replacement

URL: Upper reference limit

VARC: Valve academic research consortium

Introduction

Systematic prior balloon aortic valvuloplasty (BAV) before device implantation was considered as the standard of care in the initial transcatheter aortic valve replacement (TAVR) experience to allow insertion and optimal expansion of the prosthesis (1). However, regarding significant improvements in devices profile and increased operators' experience, this step is not systematically performed nowadays (2-7). This strategy of direct TAVR has been shown to be feasible in observational studies and more recently in a randomized study with the Corevalve self-expandable device (8). Moreover, BAV may be associated with specific complications as annulus rupture, severe aortic regurgitation and cerebral embolization (2, 9-11). On the other hand, rapid pacing, required for BAV, may increase myocardial injury and induce left ventricle (LV) dysfunction after TAVR, particularly in patients with previous LV dysfunction (12,13). Likewise, myocardial injury, defined as troponin elevation> 15 upper reference limit (URL), is a well-known prognostic factor of mortality in patients undergoing TAVR (14-16). Several factors as rapid pacing duration, hypotension, embolization and prosthesis positioning may induce myocardial injury. Only one observational study evaluated the impact of predilatation on post-procedure myocardial injury showing a significant decrease in myocardial injury in patients without BAV before self-expandable Medtronic Corevalve implantation (17). Moreover, in this study, this significant troponin elevation after the procedure was associated with poorer prognosis. The DIRECTAVI trial (NCT02729519), a randomized trial comparing direct TAVR versus predilatation with Edwards Sapien 3 recently conducted by our team showed a non-inferiority of the direct TAVR strategy on device success.

The aim of this study was to evaluate the impact of BAV on myocardial injury in patients included in the DIRECTAVI trial.

Methods

Study design

The DIRECTAVI was a prospective, randomized, single-center, open-label trial using the third-generation balloon-expandable Edwards SAPIEN 3 device (Edwards Lifesciences, Irvine, CA, USA). The main hypothesis was the non-inferiority of direct TAVR in comparison to systematic BAV before prosthesis implantation. The study protocol was approved by an independent ethics committee (Comité de Protection des Personnes Sud Méditerranée, Montpellier, France, ID RCB: 2015-A01823-46) and all patients provided written informed consent. The trial was conducted according to the World Medical Association Declaration of Helsinki and was registered in ClinicalTrials.gov (NCT02729519) as described elsewhere (18).

Patient population

From May 2016 to May 2018, 236 consecutive patients undergoing TAVR via transfemoral or trans-carotid approaches were enrolled in the DIRECTAVI trial after heart team decision. Inclusion and exclusion criteria were previously published in the study design paper. All patients were randomized between the 2 strategies as previously described (18), **figure 1.**

Procedure

All TAVR procedures were performed with the Edwards SAPIEN 3 device after careful evaluation of vascular access and native aortic valve by multislice computerized tomographic angiography (MSCT) of the entire aorta. The prosthesis size and the vascular access were left to the discretion of the operators' with a transfemoral default strategy. TAVR procedure was performed under general anesthesia and surgical vascular access as previously described (19). In the BAV group, balloon diameter was selected according to the manufacturer's recommendations depending on the annular diameter measured with MSCT.

Data collection and follow-up

Baseline characteristics, clinical, biological and procedural data were collected at the time of randomization (18). Pre- and post-procedure troponin measurements were prospectively collected. Patient with either missing pre-or post-procedure troponin were excluded from the analysis. High-sensitivity troponin T measurement was performed on the Cobas 8000/e602 analyser (Roche Diagnostics, Meylan, France) the day before and the day after the procedure. The 99% upper reference limit (URL) for this kit is 0.014 µg/L. For patients requiring revascularization, percutaneous coronary intervention was performed at least 1 week before TAVR. Clinical follow-up was performed at 72 hours and 1-month.

Study endpoints

The primary endpoint was the incidence of myocardial injury depending on the group of patients (direct implantation versus BAV). Myocardial injury was defined according to VARC-2 recommendations as troponin T elevation >15 URL and at least 50% increase compared to pre-procedure value (20). Mean post-procedure troponin in both groups was also evaluated. Prognostic impact of pre-and post-procedure troponin on 1-month outcomes (myocardial infarction, stroke, cardiovascular death, pacemaker implantation, heart failure) was also evaluated. Predictive factors of myocardial injury were studied.

Statistical analyses

Patients' characteristics are presented with proportions for categorical variables and as mean ±standard deviation and median (interquartile range) for quantitative variables. Characteristics were compared between both group with the Student t-test or the Mann-Whiney U-test for continuous variables, and with Chi square or Fisher exact test for categorical variables. The occurrence of myocardial injury was included in the Cox survival model and assessed individually for each pre-procedural troponin tertile. Statistical analyses were performed using SAS 9.1 software (SAS Institute, Cary, North Carolina).

Results

Study population

Between May 2016 and May 2018, a total of 236 patients were enrolled in the DIRECTAVI trial study, 115 patients in the predilatation group and 121 in the direct implantation group. Mean age was 82y± 6.7, mean euroscore 2 was 3.8± 4.2% and 145 (61.4%) were male. Baseline characteristics of population are shown in **Table 1**.

Pre-and post-procedure troponin were available in 211 patients (89.4%), 104 (90.4%) in the BAV group and 107 (88.4%) in the direct TAVR group (**Figure 1**). Pre-procedure troponin, C-reactiv protein, hemoglobin and creatinine were not statistically different between both groups **(Table 1).** Post-procedure hemoglobin was similar between both groups (11.8 g/dL (11-12.9) in the predilatation group versus 11.9 g/dL (10.8-12.8) in the direct TAVR group), p=0.9. Post-procedure creatinine was similar between both groups (90 μmol/L (70-110) in the BAV group versus 91 μmol/L (70-115) in the direct TAVR group), p=0.6.

Device success was obtained for 184 patients (78.0%). Direct TAVR was non-inferior to predilatation regarding to device success, 80.2% versus 75.7%, respectively, p= 0.02 for non-inferiority.

Primary endpoint

Myocardial injury occurred in 42 patients (19.9%), 13 (12.2%) in the direct TAVR group and 29 (27.9%) in the BAV group, p= 0.004, **figure 2** and **figure 3**. Predilatation increased by 2.8 the risk of myocardial injury in comparison to direct implantation group (OR 2.8 IC 95% 1.4-5.8).

Mean troponin value after TAVR procedure was 124.9 ±81.4 ng/L in the direct TAVR group *versus* 170.4± 127.7 ng/L in the BAV group, p= 0.007. The mean increase in hs-TnT after the procedure was 4.4-fold, 3.8-fold in the direct TAVR group and 5-fold in the BAV group.

Secondary endpoints

No significant difference was observed regarding to outcomes between BAV and direct TAVR groups at 1-month follow-up (**Table 2**).

Preprocedural troponin was not predictive of 1-month outcomes, regardless the group of patients (p=0.4). Conversely Myocardial injury was significantly associated with 1-month outcomes, p=0.03.

Predictors of myocardial injury

In multivariate analysis, only BAV was predictive of myocardial injury. No pre-procedural characteristics were predictive of myocardial injury even in case of previous coronary disease. Procedural length or post-dilatation were not predictive of myocardial injury.

Discussion

This study, including patients from the prospective randomized DIRECTAVI study, evaluated for the first time the impact of predilatation on myocardial injury with 3 main findings:

1) Myocardial injury remains frequent, occurring in around 20% of patients after TAVR
2) BAV was associated with a 3-fold increased risk of myocardial injury in comparison to direct device implantation
3) Myocardial injury was predictive of outcomes at 1-month follow-up

Incidence of myocardial injury after TAVR

In the literature, myocardial injury after TAVR was found to occur in 30-50% of cases (14-16). Indeed, in the largest cohort published assessing incidence and prognostic impact of myocardial injury on more than 1300 patients undergoing TAVR, the incidence of myocardial injury was around 50% (16). In our study, myocardial injury occurred in around 1/5 of patients, less frequently than in the literature. Moreover, mean increase in hs-TnT after the procedure was 4.4-fold, less than the 7-fold previously described in the literature (14, 21-23). This difference may be explained by 1/ our more recent population of patients, probably at lower risk profile especially younger, 2/ undergoing TAVR procedure with the last generation of devices 3/ increasing of experience of operators with shorter procedures. Indeed, myocardial injury during TAVR may be induced by peri-procedural conditions with a mismatch between myocardial oxygen supply and oxygen demand (24). Among the factors involved in the occurrence of myocardial injury, BAV but also acute aortic regurgitation, micro-embolism and temporary hypotension during rapid ventricular pacing were advocated (14, 17). In the current TAVR era, with the evolution of the technique and of operators' experience, valve positioning may be more precise and procedural length shortened with less haemodynamic impairments

(25). Taken all these considerations together, incidence of myocardial injury may decrease over the years with growing experience in the field.

Impact of predilatation on myocardial injury

New generation TAVR devices with lower sheath system profile and improved radial force provide adequate expansion in the majority of cases (2-7). Thus, systematic BAV before device implantation may not be a mandatory step in current TAVR era, particularly with balloon-expandable prosthesis. Moreover, as BAV may be associated with specific complications involving aortic regurgitation, systemic embolism and annulus rupture, avoiding BAV may be of interest (3,4,17,18). Indeed, a study showed that cerebral micro embolism during TAVR, assessed by transcranial doppler, occurred both during predilatation and prosthesis implantation (10). In the other hand, rapid pacing, performed during BAV with a hypotensive effect, may induce myocardial injury, ventricular arrhythmias and LV dysfunction (12, 13). Moreover, in the literature, rapid pacing was associated with negative effects on microcirculation (26). Thus, rapid pacing, performed twice in case of balloon-expandable device implantation after BAV, may be reduced to once during device implantation in case of direct TAVR. Only one observational study evaluated the impact of predilatation on myocardial injury. In this study including 164 patients, authors found that direct implantation of self-expandable Corevalve device was associated less myocardial injury (17). The authors also demonstrated a prognostic impact of myocardial injury on 1-month and 1-year outcomes. Taken all these considerations together, direct TAVR, feasible and safe, appears as a seducing option in the aim to simplify TAVR procedure in the “minimalist TAVR” era and to reduce myocardial injury (27,28).

Myocardial injury and prognostic impact

In the present study, myocardial injury was predictive of 1-month outcomes. This is consistent with the literature. Indeed, the prognostic impact of myocardial injury was demonstrated in several studies with increased risk of 1-month and 2-years mortality (14,15,29). In a more recent study with a large cohort of patients, myocardial injury was associated with long-term mortality only in patients with near-normal pre-procedural troponin (16). Our study confirms for the first time the prognostic impact of myocardial injury in a randomized study. Indeed, previous studies were mainly historical comparison and non-randomized and upstream selection of patients with more favorable anatomies for direct implantation cannot be excluded. Finally, our study showed that avoiding myocardial injury may improve patient's prognosis.

Study limitations

A first limitation of this study is the relatively small sample size. However, the statistical power was sufficient to demonstrate the prognostic impact of myocardial injury but not the prognostic value of pre-procedure troponin. The second limitation was the lack of long-term follow-up. The third limitation was the use of VARC-2 criteria to define myocardial injury. Indeed, this cut-off for troponin elevation may not be suitable for all patients, particularly in those with elevated pre-procedure troponin.

In conclusion, this ancillary study of the DIRECTAVI trial is the first randomized study assessing the impact of predilatation on myocardial injury. Direct implantation significantly reduced myocardial injury in patients undergoing TAVR with the last generation of balloon-expandable Edwards Sapien 3 devices. Moreover, myocardial injury was associated with adverse outcomes at 1-month. Thus, direct TAVR is feasible, safe and reduces myocardial injury hence a potential positive impact on early outcomes.

References

1. Vahanian A, Himbert D. Transcatheter aortic valve implantation: could it be done without prior balloon valvuloplasty? JACC Cardiovasc Interv. 2011;4:758–9.
2. Eltchaninoff H, Cribier A, Tron C, et al. Balloon aortic valvuloplasty in elderly patients at high risk for surgery, or inoperable: immediate and mid-term results. Eur Heart J 1995;16:1079 –84.
3. Grube E, Naber C, Abizaid A, et al. Feasibility of Transcatheter Aortic Valve Implantation Without Balloon Pre-Dilation A Pilot Study. J Am Coll Cardiol Intv 2011;4:751–7.
4. Fiorina C, Maffeo D, Curello S, et al. Direct transcatheter aortic valve implantation with self-expandable bioprosthesis: Feasibility and safety. Cardiovascular Revascularization Medicine 2014; 15: 200–3.
5. Deharo P, Resseguier N, Koning R, et al. Impact of Direct Transcatheter Aortic Valve Replacement Without Balloon Aortic Valvuloplasty on procedural and clinical outcomes insights from the FRANCE TAVI registry. J Am Coll Cardiol Intv 2018;11:1956–65.
6. Liao YB, Meng Y, Zhao ZG, et al. Meta-analysis of the effectiveness and safety of transcatheter aortic valve Implantation without balloon predilation. Am J cardiol 2016; 117:1629-35.
7. Auffret V, Regueiro A, Campelo-Parada F, et al. Feasibility, safety, and efficacy of transcatheter aortic valve replacement without balloon predilation: a systematic review and meta-analysis. Catheter Cardiovasc Interv 2017;90:839–50.

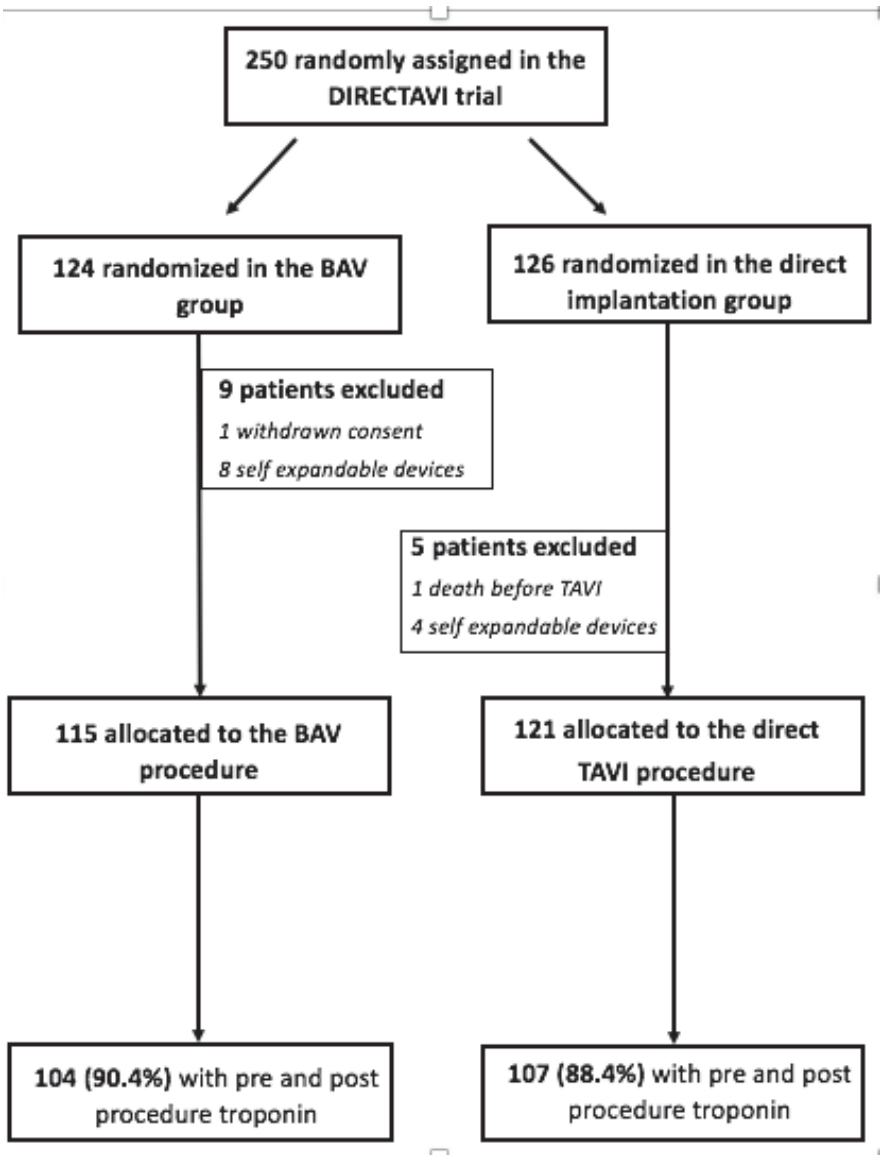
8. Toutouzas K, Benetos G, Voudris V, et al. Pre-Dilatation Versus No Pre-Dilatation for Implantation of a Self-Expanding Valve in All Comers Undergoing TAVR: The DIRECT Trial. JACC Cardiovasc Interv 2019;12:767–77.
9. Sack S, Kahlert P, Khandanpour S, et al. Revival of an old method with new techniques: balloon aortic valvuloplasty of the calcified aortic stenosis in the elderly. Clin Res Cardiol 2008;97:288 –97.
10. P, Al-Rashid F, Döttger P, et al. Cerebral Embolization During Transcatheter Aortic Valve Implantation: a transcranial Doppler study. Circulation 2012;126:1245-55.
11. Nombela-Franco L, Webb J, de Jaegere PP, et al. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. Circulation 2012; 126:3041-53.
12. Ben-Dor I, Pichard AD, Satler LF, et al. Complications and outcome of balloon aortic valvuloplasty in high-risk or inoperable patients. JACC Cardiovasc Interv 2010;3:1150–1156.
13. Holmes DR, Nishimura RA, Reeder GS. In-hospital mortality after balloon aortic valvuloplasty: frequency and associated factors. J. Am. Coll. Cardiol. 1991;17:189–192.
14. Rodés-Cabau J, Gutiérrez M, Bagur R, et al. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. J. Am. Coll. Cardiol. 2011;57:1988–1999.
15. Carrabba N, Valenti R, Migliorini A, Vergara R, Parodi G, Antoniucci D. Prognostic value of myocardial injury following transcatheter aortic valve implantation. Am. J. Cardiol. 2013;111:1475–1481.

16. Akodad M, Spaziano M, Chevalier B, et al. Prognostic Impact of Pre-Transcatheter and Post-Transcatheter Aortic Valve Intervention Troponin: A Large Cohort Study. J Am Heart Assoc 2019;8:e011111.
17. Mirna M, Wernly B, Eder S, et al. Transcatheter aortic valve implantation without prior balloon valvuloplasty is associated with less pronounced markers of myocardial injury. J Cardiovasc Surg (Torino) 2018.
18. Leclercq F, Robert P, Labour J, et al. Prior balloon valvuloplasty versus DIRECT transcatheter aortic valve implantation (DIRECTAVI): study protocol for a randomized controlled trial. Trials 2017;18:303-12.
19. Du Cailar C, Gandet T, Du Cailar M, Albat B. A simple sheath removal after open trans-femoral catheterization procedure: the ZIP technique. Eur J Cardiothorac Surg 2014 ;45:746-8.
20. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012; ;60:1438–54.
21. Chorianopoulos E, Krumsdorf U, Geis N, et al. Preserved prognostic value of preinterventional troponin T levels despite successful TAVI in patients with severe aortic stenosis. Clin Res Cardiol 2014;103:65–72.
22. Yong ZY, Wiegerinck EMA, Boerlage-van Dijk K, et al. Predictors and prognostic value of myocardial injury during transcatheter aortic valve implantation. Circ Cardiovasc Interv 2012;5:415–423.
23. Liebetrau C, Kim WK, Meyer A, et al. Identification of Periprocedural Myocardial Infarction Using a High-Sensitivity Troponin I Assay in Patients Who Underwent Transcatheter Aortic Valve Implantation. Am. J. Cardiol. 2017;120:1180–1186.

24. Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–35.
25. Bourantas CV, Modolo R, Baumbach A, et al. The evolution of device technology in transcatheter aortic valve implantation. EuroIntervention 2019;14:e1826–e1833.
26. Selle A, Figulla HR, Ferrari M, et al. Impact of rapid ventricular pacing during TAVI on microvascular tissue perfusion. Clin Res Cardiol 2014;103:902–911.
27. Colombo A, Michev I, Latib A. Is it time to simplify the TAVI procedure? “Make it simple but not too simple.” EuroIntervention 2014;10 Suppl U:U22-27.
28. Akodad M, Lefèvre T. TAVI: Simplification Is the Ultimate Sophistication. Front Cardiovasc Med 2018;5:96.
29. Koskinas KC, Stortecky S, Franzone A, et al. Post-Procedural Troponin Elevation and Clinical Outcomes Following Transcatheter Aortic Valve Implantation. J Am Heart Assoc 2016;5.

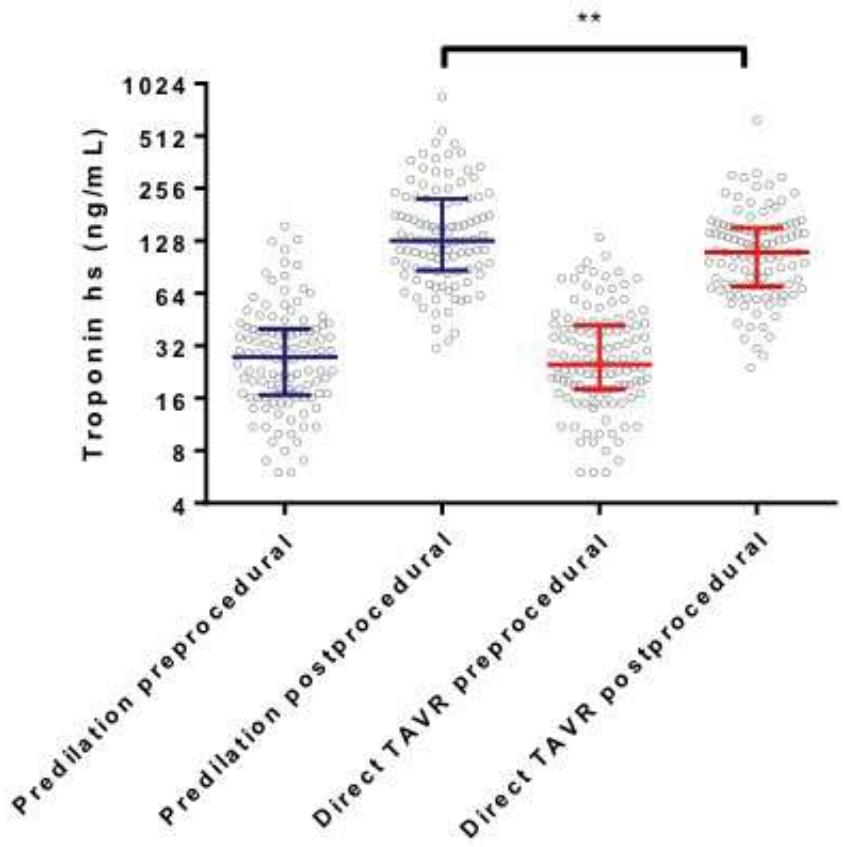
Figures

Figure 1: Flow chart of the DIRECTAVI study and of the myocardial injury sub study



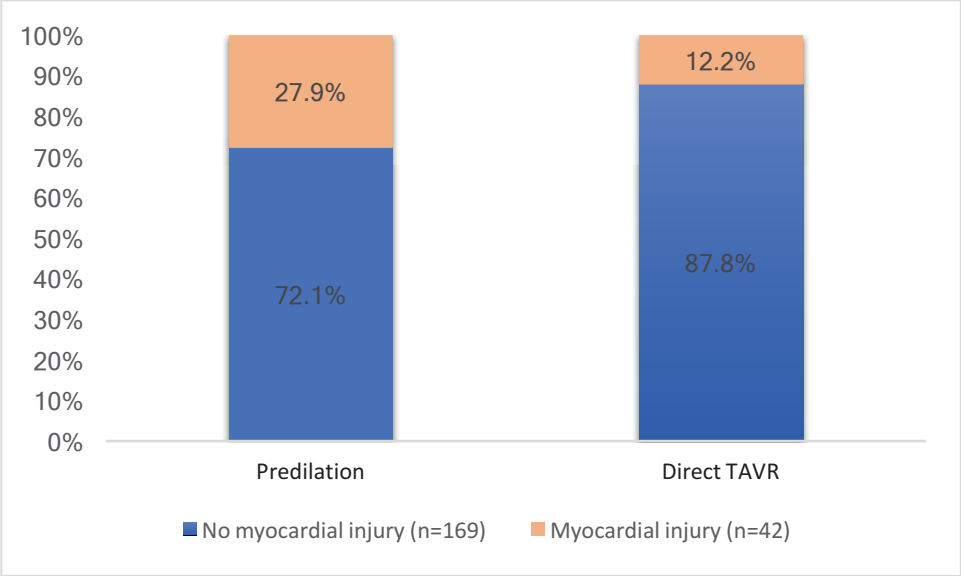
Caption: Among the 240 patients randomly assigned in the DIRECTAVI trial, pre- and post-procedure troponin were available in 211 patients (89.4%), 104 (90.4%) in the BAV group and 107 (88.4%) in the direct TAVR group.

Figure 2: Pre and post procedure troponin according to the group of patients (predilation and Direct TAVR)



Caption: Mean pre procedure troponin level was similar between both groups, (p=0.3). Mean post procedure troponin level was significantly higher in the BAV group in comparison to the direct TAVR group, p=0.007.

Figure 3: Primary endpoint: Myocardial injury according to the VARC-2 criteria in BAV and direct TAVI groups



Caption: Myocardial injury was significantly more frequent in the BAV group in comparison to the direct TAVR group, p=0.004

Table 1: Baseline characteristics of the population

	Pre-dilatation group (n=115)	**Direct implantation group** (n=121)
Female	45 (39.1)	45 (37.2)
Age, median (years)	83 (79-87)	83 (78-87)
Body mass index, median (kg/m^2)	26 (24.3-29.2)	26.6 (24.5-29.6)
Diabetes mellitus	41 (35.7)	45 (37.2)
Previous PCI	48 (41.7)	53 (43.8)
Previous CABG	6 (5.2)	7 (5.8)
Previous BAV	10 (8.7)	12 (9.9)
Cerebrovascular disease	5 (4.4)	4 (3.3)
Peripheral vascular disease	13 (11.3)	12 (9.9)
COPD	8 (7.0)	20 (16.5)
Atrial fibrillation	31 (27.0)	48 (39.7)
Permanent pacemaker	15 (13.1)	14 (11.6)
Pulmonary hypertension	2 (1.7)	2 (1.7)
Creatinine (µmol/L)	102 (82.0-126.0)	104 (84-131)
Hemoglobin (g/Dl)	12.5 (11.8-13.7)	12.3 (11.4-13.4)
C-reactiv protein (UI)	3 (1-7)	3 (1-8)
Troponin (ng/L)	27.5 (17-40)	25.0 (18-42)
Hypertension	81 (70.4)	74 (61.2)
Euroscore 1	10 (7-14)	10 (7-14)
Euroscore 2	3 (2-4)	2.3 (2-3.8)
NYHA class		
I, II	54 (47.0)	58 (47.9)
III, IV	61 (53.1)	63 (52.1)
LVEF, %	60 (50-60)	60 (50-60)
Aortic valve area, cm^2	0.7 (0.6-0.9)	0.8 (0.6-0.9)
Mean aortic valve gradient, mmHg	46 (40-55)	49.5 (40-58)

Values are median or n (%);

* BAV: balloon aortic valvuloplasty; † CABG, coronary artery bypass graft; ‡ COPD: chronic obstructive pulmonary disease; § NYHA: New York Heart Association; ? PCI: percutaneous coronary intervention

Table 2: Outcomes at 1-month follow-up according to the group of patients

	Total population (n=236)	**Pre-dilatation group** (n=115)	**Direct implantation group** (n=121)	**P value** #
Total adverse events, n (%)	60 (25.4)	29 (25.2)	31 (25.6)	0.94
All-cause mortality, n (%)	4 (1.7)	0 (0)	4 (3.2)	0.24
Stroke, n (%)	3 (1.3)	1 (0.9)	2 (1.7)	0.99
Major vascular complications, n (%)	7 (3)	6 (5.2)	1 (0.8)	0.06
Major bleeding, n (%)	8 (3.4)	3 (2.6)	5 (4.1)	0.70
Transfusion, n (%)	4 (1.7)	2 (1.7	2 (1.7)	1.00
Acute kidney injury, n (%)	5 (2.1)	1 (0.9)	4 (3.3)	0.37
Pacemaker implantation, n (%)	47 (19.9)	24 (20.9)	23 (19.01)	0.72
Heart failure, n (%)	3 (1.3)	0 (0)	3 (2.5)	0.24
Aortic regurgitation, n (%)				
- None (grade 0), n (%)	144 (61.5) *	75 (65.2)	69 (58.0) **	0.20
- Mild (grade 1), n (%)	76 (32.5)	34 (29.5)	42 (35.3)	0.90
- Moderate (grade 2), n (%)	14 (6)	6 (5.2)	8 (6.6)	0.90
- Severe (grade 3), n (%)	0 (0)	0 (0)	0 (0)	NA

*Data available for 234 patients

** Data available for 119 patients

Superiority analysis using the appropriate statistical test (either Wilcoxon-Mann-Whitney for quantitative variables, or Fisher or Chi-square tests for qualitative variables)

DISCUSSION GENERALE

Le TAVI représente une véritable révolution dans la prise en charge du rétrécissement aortique. Initialement réservé aux patients inopérables ou à très haut risque opératoire, la technique s'étend peu à peu à des populations à moindre risque en raison des améliorations du matériel et de l'expérience des équipes avec une réduction drastique des complications. Cette extension des indications à des patients avec des profils de risque plus favorables s'accompagne d'une évolution des pratiques qui tend vers la simplification de la procédure à chaque étape et également à celle du parcours de soins en post-procédure. Cependant, la sélection rigoureuse des patients pouvant bénéficier de la technique et une meilleure appréhension de leur profil de risque permettent d'anticiper les potentielles complications et d'adapter leur prise en charge. Les évaluations clinique et échographique, bien que nécessaires, sont insuffisantes pour permettre une stratification précise du risque de ces patients. Ainsi, d'autres éléments, facilement accessible comme certains biomarqueurs ou des éléments d'imagerie comme le score calcique scannographique apparaissent comme complémentaires pour l'évaluation de ce profil de risque.

Dans le premier chapitre de cette thèse, nous avons confirmé la valeur pronostique de 2 éléments, accessibles en routine chez les patients bénéficiant d'un TAVI, la troponine et le score calcique. *La troponine*, biomarqueur ayant démontré sa valeur pronostique dans plusieurs pathologies cardiovasculaires dont le rétrécissement aortique (107-109), nous paraissait être l'un des biomarqueurs clés à étudier chez les patients bénéficiant d'un TAVI. En effet, dans la littérature, la valeur pronostique d'une élévation de la troponine pré-procédure d'une part et de la troponine post-procédure d'autre part, de mécanismes différents, sont discutés. L'élévation de la troponine pré-procédure est liée à la sévérité de la cardiopathie sous-jacente avec plusieurs facteurs favorisants en lien avec les comorbidités du patient (111-

113). Sa valeur pronostique à moyen et long terme a été évoquée dans plusieurs séries incluant des effectifs faibles (111,112). Dans notre étude, nous avons pu confirmer la valeur pronostique de la troponine en pré-procédure sur la mortalité à 1 mois, 1 an et pour la première fois jusque 3 ans. De plus, quatre prédicteurs indépendants d'une élévation de troponine pré-procédure ont été identifiés : le sexe masculin, l'arythmie auriculaire, le faible débit de filtration glomérulaire et le NT-proBNP pré-procédure élevé. Certains de ces éléments reflètent la sévérité du terrain sous-jacent et de la cardiopathie elle-même (hypertrophie et remodelage ventriculaire gauche). Ainsi la troponine pré-procédure est un facteur pronostique chez les patients bénéficiant d'un TAVI et devrait être prise en compte dans l'évaluation du profil du risque dès l'admission sans pour autant pouvoir modifier ce marqueur de risque.

Le mécanisme d'élévation de troponine post-procédure est différent. En effet, la survenue de lésions myocardiques au décours du TAVI, entraînant une élévation de la troponine, pourrait être causée par des conditions périprocédurales délétères avec un déséquilibre entre l'apport et la demande en oxygène du myocarde (113). Plusieurs mécanismes peuvent être responsables de cette discordance, comme une valvuloplastie au ballon, une régurgitation aortique aiguë, une micro-embolie et une hypotension induite pendant la stimulation ventriculaire rapide et le déploiement de la prothèse (113,153). L'impact pronostique de la « myocardial injury » en post-TAVI est plus discuté dans la littérature avec des résultats contradictoires (112-115). Dans notre étude, près de la moitié des patients avaient des lésions myocardiques selon la définition du VARC-2 (9). Ces données sont en accord avec la littérature récente (113-115). De plus, la survenue de lésions myocardiques était prédictive de mortalité uniquement chez les patients ayant une troponine pré-procédurale normale ou quasi-normale. Ces données contradictoires pourraient être expliquées pas le fait que dans notre

étude, seuls les patients avec voie d'abord transfémorale et transcarotide ont été analysés avec exclusion des patients avec une voie d'abord transpicale.

De plus, l'impact pronostique de la troponine post-procédure a été étudié en fonction de la troponine pré-procédure, pour la première fois dans la littérature. Ainsi la mise en évidence de l'impact pronostique de la troponine post-procédure dans ce travail initial confirme certaines données de la littérature dans une large population de patients. De plus, cette élévation de troponine post-procédure étant liée à des facteurs procéduraux essentiellement, la mise en évidence des facteurs prédictifs de cette élévation de troponine pendant la procédure nous semble indispensable. En effet, l'identification de ces facteurs permettrait potentiellement de les moduler et ainsi de limiter l'incidence de la « myocardial injury » dans le but d'améliorer le pronostique chez ces patients.

Dans le deuxième volet de ce premier chapitre, nous avons évalué l'impact pronostique du score calcique en fonction du type et de la génération de prothèse. En effet, la sévérité des calcifications peut conduire à l'apparition de fuites para-valvulaires significatives, de rupture d'anneau ou d'obstruction coronaire et pourrait augmenter l'incidence de la post-dilatation (141,142). Cet impact pronostique sur la survenue de fuites aortiques para-prothétiques et d'évènements à 1 mois et 1 an a été démontré avec les deux types de valves de la précédente génération (154,155). Nous avons pu, dans ce travail confirmer d'une part que le score calcique était prédictif d'évènements à 1 mois avec les deux types de valves de la précédente génération et d'autre part que le score calcique perdait sa valeur pronostique avec les valves de dernière génération hormis pour la survenue de fuites aortiques significatives avec la valve auto-expansible. Ces résultats sont concordants avec les données de la littérature pour la valve Edwards Sapien 3 en termes de survenue de fuites para-prothétiques (150), aucune donnée n'étant disponible avec la valve auto-expansible de dernière génération. Ceci pourrait

être lié au meilleur positionnement des prothèses mais également à leurs améliorations techniques. Cependant, bien que le score calcique soit un outil simple et utilisable en routine sans nécessité d'examen complémentaire autre que le scanner systématique pré-TAVI, il s'agit d'un élément imparfait de l'évaluation des calcifications. De plus, son impact en fonction de la stratégie utilisée à l'ère de la simplification du TAVI est inconnu. Ces questions en suspens ouvrent les perspectives vers plusieurs travaux dans ce domaine.

Dans le deuxième chapitre de ce travail de thèse, nous avons souhaité évaluer l'impact d'une prédilatation systématique ou d'une stratégie d'implantation direct de la prothèse (« direct TAVI »), élément de simplification de la procédure TAVI s'intégrant dans l'évolution des pratiques. Nous avons donc conduit un essai randomisé comparant ces 2 stratégies avec la valve de dernière génération Edwards Sapien 3, l'étude DIRECTAVI (51). En effet, malgré la réalisation en routine de cette stratégie de « direct TAVI », aucune donnée issue d'études randomisées n'est disponible à ce jour avec cette prothèse. Une seule étude randomisée a démontré la non-infériorité du « direct TAVI » avec la valve Medtronic Corevalve. Les résultats de notre étude ont démontré une non-infériorité du « direct TAVI » par rapport à la prédilatation systématique au ballon (50). Cette étude randomisée évalue de façon concrète l'un des éléments clés de l'évolution des pratiques dans le cadre du TAVI, à savoir l'absence de prédilatation systématique. Nous avons donc prévu de réaliser deux sous-études visant à évaluer les facteurs pronostiques étudiés dans le premier chapitre de ce travail de thèse en fonction de la stratégie utilisée. La première sous-étude vise à réévaluer l'impact de la troponine pré et post-procédure dans cette population récente et surtout d'évaluer l'impact d'une prédilatation, facteur incriminé dans la littérature, sur la survenue de lésions myocardique (« myocardial injury ») après TAVI. Dans cette sous-étude, la troponine pré-

procédure n'était pas prédictive d'évènements à 1 mois alors que la survenue d'une « myocardial injury » l'était. Nous avons également pu démontrer pour la première fois que la prédilatation était associée de façon significative (risque multiplié par 3) à la survenue de « myocardial injury » par rapport à une stratégie de « direct TAVI ». Ces résultats sont en faveur de l'absence de prédilatation systématique avec les valves de dernière génération montées sur ballon. En effet, l'incidence des lésions myocardiques, facteur pronostique reconnu dans la littérature pourrait être diminuée à l'ère de l'évolution des pratiques.

La deuxième sous-étude concernant l'impact pronostique du score calcique en fonction de la stratégie utilisée (prédilatation systématique ou « direct TAVI ») est en cours.

CONCLUSION

L'utilisation de biomarqueurs et de marqueurs morphologiques comme le score calcique scannographique semble faisable en routine et peut s'intégrer dans l'évaluation globale du profil de risque du patient bénéficiant d'un TAVI. En particulier, la troponine pré-procédure apparait comme un facteur pronostique corrélé aux comorbidités du patient et à la sévérité de la cardiopathie sous-jacente. De même, la troponine post-procédure, facteur pronostique d'évènements à moyen et long terme, semble être modifiable par des éléments procéduraux. Ainsi, la simplification de la procédure et notamment l'absence de prédilatation pourrait avoir un impact favorable avec la diminution des lésions myocardiques induites. De même, le score calcique, facteur pronostique d'événements avec les valves de la précédente génération, semble perdre sa valeur pronostique avec l'avènement des nouvelles prothèses et doit être réévalué à l'ère de l'évolution des pratiques.

PERSPECTIVES

Ce travail de thèse a ouvert le champ sur plusieurs perspectives s'intégrant dans les suites de ce projet.

Perspective 1 : sous-étude DIRECTAVI sur l'impact pronostique du score calcique en fonction de la stratégie utilisée

Le score calcique d'Agatston est un facteur pronostique reconnu de la survenue d'évènements et de fuites aortiques chez les patients bénéficiant d'un TAVI avec la précédente génération de prothèses (154,155). L'amélioration notable de l'expérience des opérateurs avec un meilleur positionnement des prothèses et les améliorations du matériel avec des éléments limitant le risque de fuites para-prothétiques comme la jupe externe ou la possibilité de recapture de la prothèse ont contrebalancé la valeur pronostique du score calcique. Cependant, aucune donnée n'est disponible concernant l'impact pronostique du score calcique en fonction de la stratégie utilisée, prédilatation ou « direct TAVI ». Cette sous étude de l'essai randomisée DIRECTAVI vise à évaluer l'impact pronostique du score calcique en fonction de la stratégie utilisée avec la valve Edwards Sapien 3.

Perspective 2 : corrélation score calcique d'Agatston et biomarqueurs de calcifications

Le score calcique d'Agatston est un outil simple, réalisable en routine sans nécessité d'autres examens que le scanner réalisé lors du bilan pré-TAVI. Cependant, il s'agit d'un outil imparfait pour l'évaluation des calcifications valvulaires. Certains biomarqueurs de calcifications la sclérostine et l'ostéoprotégérine, obtenus par simple prélèvement sanguin, pourraient permettre une évaluation plus précise de ces calcifications valvulaires. Une seule étude a évalué la relation entre l'importance des calcifications de la valve aortique et l'ostéoprotégérine sans lien mis en évidence chez des patients porteurs d'un rétrécissement

aortique modéré ou serré. Aucune donnée n'est disponible dans une population uniquement de rétrécissement aortique serré et a fortiori à l'ère du TAVI.

Un projet évaluant la corrélation entre le score calcique d'Agatston et ces marqueurs chez les patients bénéficiant d'un TAVI va débuter prochainement au CHU de Montpellier. Ceci permettrait d'évaluer de façon simple l'importance des calcifications chez les patients avec rétrécissement aortique serré par simple prélèvement sanguin. Cette approche pourrait permettre dans un deuxième temps d'évaluer l'impact pronostique de ces biomarqueurs chez les patients implantés d'un TAVI et d'ainsi mieux appréhender leur profil de risque et d'anticiper les complications potentielles.

Annexes :

Annexe 1 :

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Feasibility and Safety of Transcatheter Aortic Valve Implantation Performed Without Intensive Care Unit Admission

Florence Leclercq, MD, PhD[a,*], Anais Iemmi, MD[a], Benoit Lattuca, MD[a], Jean-Christophe Macia, MD[a], Richard Gervasoni, MD[a], Francois Roubille, MD, PhD[a], Thomas Gandet, MD[b], Laurent Schmutz, MD[c], Mariama Akodad, MD[a], Audrey Agullo, MD[a], Marine Verges, MD[a], Erika Nogue, MD[d], Gregory Marin, MD[d], Nicolas Nagot, MD[d], Francois Rivalland, MD[e], Nicolas Durrleman, MD[f], Gabriel Robert, MD[g], Delphine Delseny, MD[h], Bernard Albat, MD, PhD[b], and Guillaume Cayla, MD, PhD[c]

Admission to the intensive care unit (ICU) is a standard of care after transcatheter aortic valve implantation (TAVI); however, the improvement of the procedure and the need to minimize the unnecessary use of medical resources call into question this strategy. We evaluated prospectively 177 consecutive patients who underwent TAVI. Low-risk patients, admitted to conventional cardiology units, had stable clinical state, transfemoral access, no right bundle branch block, permanent pacing with a self-expandable valve, and no complication occurring during the procedure. High-risk patients included all the others transferred to ICU. In-hospital events were the primary end point (Valve Academic Research Consortium 2 criteria). The mean age of patients was 83.5 ± 6.5 years, and the mean logistic EuroSCORE was 14.6 ± 9.7%. The balloon-expandable SAPIEN 3 valve was mainly used (n = 148; 83.6%), mostly with transfemoral access (n = 167; 94.4%). Among the 61 patients (34.5%) included in the low-risk group, only 1 (1.6%) had a minor complication (negative predictive value 98.4%, 95% confidence interval [CI] 0.91 to 0.99). Conversely, 31 patients (26.7%) from the high-risk group had clinical events (positive predictive value 26.7%, 95% CI 0.19 to 0.35), mainly conductive disorders requiring pacemaker (n = 26; 14.7%). In multivariate analysis, right bundle branch block (odds ratio [OR] 14.1, 95% CI 3.5 to 56.3), use of the self-expandable valve without a pacemaker (OR 5.5, 95% CI 2 to 16.3), vitamin K antagonist treatment (OR 3.8, 95% CI 1.1 to 12.6), and female gender (OR 2.6, 95% CI 1.003 to 6.9) were preprocedural predictive factors of adverse events. In conclusion, our results suggested that TAVI can be performed safely without ICU admission in selected patients. This strategy may optimize efficiency and cost-effectiveness of procedures. **© 2016 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2016;■:■−■)**

Transcatheter aortic valve implantation (TAVI) is now the standard of care for inoperable patients with severe symptomatic aortic stenosis and an accepted alternative to surgery for high-risk patients.[1−6] TAVI is less invasive and associated with fewer complications than the traditional approach for aortic valve replacement through median sternotomy and cardiopulmonary bypass.[7,8] However, TAVI is an interventional technique with specific postoperative complications related to the procedure itself but also to multiple comorbidities of the patients. These complications were standardized and defined by the Valve Academic Research Consortium (VARC-2), updated in 2013.[9] With the improvement in operator experience and valve technology, combined with better screening and trend to include lower risk patients, contemporary studies have shown a dramatic decrease of in-hospital complications after TAVI.[6,10−13] Recent reports showed the possibility to decrease hospital length of stay in selected patients with subsequent decrease of procedural costs.[7,14−16] Although there are currently no specific guidelines concerning immediate medical care after TAVI, admission to intensive care unit (ICU) with monitoring has been regarded as an essential step for the patients after the procedure. However, both the improvement of the results of the procedure and the risk of overload of the ICU associated with the development of TAVI call into question this systematic strategy. The objective of this prospective cohort study was to evaluate feasibility and safety of TAVI performed without subsequent ICU admission in patients

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See page 7 for disclosure information.

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0002-9149/16/$ - see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjcard.2016.04.019

carefully selected using simple clinical, electrocardiographic (ECG), and echocardiographic selection criteria.

Methods

Between December 2014 and July 2015, all consecutive patients who underwent TAVI in our center were included in a monocentric prospective study. Exclusion criteria included valve-in-valve procedures and transaortic or transapical approaches. The procedures were performed in the catheterization laboratory using the new-generation balloon-expandable Edwards SAPIEN 3 bovine pericardial device (Edwards Lifesciences, Irvine, California) or the self-expandable CoreValve porcine pericardial device (Medtronic, Inc., Minneapolis, Minnesota). All patients had severe symptomatic aortic stenosis secondary to degenerative disease confirmed by transthoracic echocardiography (TTE) (mean gradient >40 mm Hg and/or valve area <1 cm^2) and were not candidates for surgical aortic valve replacement according to guidelines and after internal discussions about the therapeutic options within the multidisciplinary heart team.[4] The choice of the valve was left to the decision of the interventional cardiologist. The self-expandable valve was usually preferred in small aortic annulus considering the good hemodynamic performances of this prosthesis or to avoid balloon inflation in case of high risk of annulus rupture (mechanical compression of a "vulnerable area" by calcifications). Patients were divided into 2 groups (low or high risk) according to the presence or absence of risk factors of severe in-hospital complications requiring admission to ICU.[3,4,12–14] Preprocedural and postprocedural simple clinical, ECG, and TTE selection criteria (Table 1) were recorded prospectively. Of note, the use of self-expandable prosthesis in patients without previous pacemaker and the occurrence of any new conductive disorder during the procedure, including PR interval >200 ms, QRS >120 ms, QRS widening >10 ms, or complete atrioventricular block (AVB) were considered as high-risk criteria. For patients included in the low-risk group, clinical events were collected with monitoring during 2 hours after the procedure in an anesthesia recovery room, and then, when no complications occurred, they were admitted to the conventional cardiology unit (CCU) for standard medical care without monitoring. Patients included in the high-risk group were transferred to the ICU for at least 24 hours. The ICU in our center is a 16-bed unit with a full-time staff composed of 6 certified physicians and 1/3 nurse per patient ratio. The ICU allowed ECG monitoring and hemodynamic support, if necessary, and only noninvasive ventilation assistance. The CCU is a standard cardiology unit with 1/15 nurse per patient ratio (1/30 during the night) and no ECG monitoring. Importantly, the final clinical decision to transfer the patient to ICU was left to the physician (cardiologist or anesthetist), even if it concerned a "low-risk" patient according to our predetermined criteria. During hospital stay, ECG was recorded daily. TTE was performed at the admission to ICU in the high-risk group and before hospital discharge in all patients. Permanent pacing requirements were considered according to European Society of Cardiology (ESC) guidelines 2013.[17] Briefly, in case of high-degree or complete AVB, permanent pacemakers were most of the time implanted between the first and the fifth day. In case of persistent new left (LBBB) or right bundle branch block (RBBB), an electrophysiological study was performed between day 2 and day 5, and permanent pacing was considered when His ventricle interval was >60 ms. A combination of clopidogrel 75 mg and aspirin 75 mg was introduced in all patients after the procedure except in those with an indication of vitamin K antagonists (VKAs) or direct oral anticoagulant therapy who had only aspirin 75 mg. The primary end point of the study included in-hospital events considered as requiring ICU admission, with reference to the VARC-2 criteria[9] (Table 2). Medical decision to secondarily transfer a patient initially admitted in the CCU to the ICU was considered as an event regardless of the reason of the transfer. Our objective was firstly to validate the safety of the strategy of TAVI performed without subsequent admission to ICU (negative predictive value [NPV]). Incidence of major adverse events was also evaluated in the 2 groups (positive predictive value), and predictive factors of in-hospital complications requiring ICU admission were assessed to validate our triage strategy. We also evaluated incidence of minor complications (not requiring ICU admission) and duration of hospitalization in the 2 groups of patients. Adverse events were also compared between the 2 implanted prostheses. Patients' characteristics are presented using mean and SD for continuous variables and frequencies and proportions for categorical variables. Groups (high vs low risk) were compared using a Student *t* test or Mann-Whitney Wilcoxon rank test for continuous variables, depending on the normality of each variable's distribution as attested by a Shapiro-Wilk test and chi-square or Fisher exact test for categorical ones. To determine the relative importance of the preprocedural and

Table 1
High versus low-risk groups of patients according to the predefined criteria

	Low-risk group	High-risk group
Before procedure		
Preexisting pulmonary disease with oxygen dependence.	-	+
Permanent pace-maker for patients with CoreValve	+	-
Hemodynamic state	Stable	Unstable
Complete right bundle branch block (QRS width >120 ms)	-	+
Left ventricular ejection fraction > 40%	+	-
Systolic arterial pulmonary pressure < 60 mmHg (according to Euroscore definition)	+	-
Transfemoral approach	+	-
During and 2 hours after procedure		
Hemodynamic state	Stable	Unstable
Thrombotic/embolic complications	-	+
Minor or major vascular complication (according to VARC 2 definitions)	-	+
New conductive disorder	-	+
New atrial or ventricular arrhythmia	-	
Good positioning of the prosthesis and Aortic regurgitation ≤2	+	-
Medical decision	-	+

Table 2
Clinical end-points in the 2 groups of patients

Complications	Clinical events considered
Death	Death from any cause
Hemodynamic instability	Mean arterial pressure <65 mm Hg inquiring volume replacement or vasopressors Acute pulmonary edema
Major, life threatening or fatal bleeding	Loss of hemoglobin level of at least 3.0 g/dL with hypovolemic shock Transfusion of 2 or more blood units
Major and minor vascular complications	Vascular dissection Vascular rupture Surgical or endovascular or percutaneous intervention/repair
Stroke	Transient ischemic attack or stroke of any cause
Pacemaker requiring	All new conduction defect requiring permanent or transient pacemaker implantation
Acute myocardial infarction < 72 hours	Ischemic symptoms or ECG suggestive of ischemia with elevation of cardiac biomarkers (peak value exceeding 15x as the upper reference limit for troponin)
Acute kidney injury (Stage 2 or 3 according to RANKIN classification)	Oligoanuria between 12h and 24h Anuria for > 12h Increase in serum creatinine of more than 200% compared with baseline
Pericardial effusion	Requiring medical intervention
Secondary Transfer to intensive care unit	Any medical reason (physician decision)

periprocedural covariates on the occurrence of major complications (VARC-2 criteria), a multivariate analysis using logistic regression was performed. A stepwise selection of the variables was then used, with an alpha-to-enter and alpha-to-exit, respectively, set at 0.15 and 0.05. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated along with p values. The significance of adding or removing a variable from the logistic model was determined by the maximum likelihood ratio test. The goodness-of-fit of the models was assessed using the Hosmer and Lemeshow chi-square test. Statistical bilateral significance threshold was set at 5%. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Results

The study enrolled 177 patients, 61 (34.5%) were classified in the low-risk group and 116 (65.5%) in the high-risk group according to the predefined criteria. Except for the risk factors in the criteria defining low- versus high-risk groups in our study, the clinical characteristics between the groups of patients only differed by the logistic EuroSCORE ($p = 0.011$; Table 3). Most TAVIs were performed under general anesthesia with orotracheal intubation (n = 170, 96.1%) and with transfemoral approach (n = 167, 94%). We did not usually use echocardiography for position or deployment of the valve. The SAPIEN 3 prosthesis was mainly used (n = 148, 83.6%). Surgical access was exclusive in our center. Considering their clinical preprocedural characteristics, 76 patients (42.9%) were directly assigned to the high-risk group and transferred to ICU regardless of the course of the procedure (Figure 1). The 3 main reasons were left ventricular ejection fraction <40% (n = 31), CoreValve implantation without previous pacemaker (n = 25), and complete RBBB (n = 14). During and until 2 hours after the procedure, 40 additional patients (22.6%) converted from low- to high-risk group because of occurrence of predefined complications requiring ICU transfer, mainly new conductive disturbance (n = 34, 85%). Among the 116 patients of the high-risk group, 73 (62.9%) developed at least 1 conductive disorder during the procedure ($p < 0.001$; Table 4). We observed 8 patients who did not have any complication or high-risk criteria but who were nevertheless transferred to ICU after decision of the cardiologist or the anesthetist owing to frailty (Figure 1). Postprocedural outcome of the population is presented in Table 5. According to our study end points, 32 patients (18.1%) experienced ≥1 clinical events, mostly represented by conduction disturbances requiring permanent or transient pacing (n = 26; 14.7%). Major vascular complications or bleeding were observed in 2 patients (1.1%). One patient died because of major bleeding. All these events occurred exclusively in patients admitted to ICU and included in the high-risk group. No major complication occurred in the low-risk group. Only 1 patient developed a noncompressive pericardial effusion (<10 mm on TTE) and not defined as a significant event in our predefined criteria. According to medical decision, the patient was transferred to ICU and could go back to CCU 12 hours later. Considering these results, the NPV of our decision-making criteria was 98.4% (95% CI 0.91 to 0.99) with a sensitivity of 96.9% (95% CI 0.84 to 0.99), whereas the positive predictive value was 26.7% (95% CI 0.19 to 0.36) with a specificity of 41.4% (95% CI 0.32 to 0.49). Minor complications, not included in our end point criteria, had favorable evolution and did not require secondary transfer to ICU. Manual compression controlled by Doppler was required for minor vascular events (low-risk group: n = 4; 1.6% and high-risk group: n = 15; 1.3%, $p = 0.12$). aortic regurgitation occurred, respectively in 43 (24.3%) and 16 (9%) patients of the low- and high-risk group ($p = 0.58$). Although the risk level did not significantly influence the length of hospital stay in our study (Table 3), patients who developed a complication stayed longer than patients who did not (5.4 ± 3.6 vs 3.7 ± 1.8 days, respectively; $p < 0.001$). Some patients of the high-risk group developed at least 1 mild or transient conductive disorder (mostly LBBB) during monitoring in the ICU that did not require pacing (n = 20; 11.3%). The predictive factors of complications requiring ICU are presented in Table 6. In multivariate analysis, use of the self-expandable valve without a pacemaker (OR 5.5, 95% CI 2 to 16.3), RBBB (OR 14.1, 95% CI 3.5 to 56.3), VKA treatment (OR 3.8, 95% CI 1.1 to 12.6), and female gender (OR 2.6, 95% CI 1.003 to 6.9) were preprocedural predictive factors of in-hospital adverse events, whereas periprocedural occurrence of LBBB (OR 8.8, 95% CI 2.7 to 28.8) and complete AVB (OR 19.7, 95% CI 5 to 77.3) were highly predictive of complications during ICU stay ($p < 0.001$). As expected, prevalence of permanent pacemaker requirement was higher with the self-expandable CoreValve compared with the balloon-expandable SAPIEN 3 valve (n = 11, 44% vs n = 15, 11.8%, respectively; $p < 0.0001$).

Table 3
Baseline and procedural characteristics of the 2 groups of patients

Variables	Total population (n=177)	Low risk group (34%, n=61)	High risk group (66%, n=116)	P value
Age (years)	83.5 +/- 6.9	84.2 +/- 6.3	83.1 +/- 7.1	0.312
Male gender	87 (49.2%)	29 (47.5%)	58 (50%)	0.756
Body Mass Index (kg/m^2)	26.3 +/- 6.1	26.3 +/- 4.5	26.3 +/- 6.9	0.362
Euroscore II (%)	5.3 +/- 4.2	4.3 +/- 2.4	5.9 +/- 4.8	0.028
Logistic Euroscore (%)	14.6 +/- 9.7	12.2 +/- 6.3	15.9 +/- 10.9	0.011
Hypertension	114 (64.4%)	42 (68.9%)	72 (62.1%)	0.370
Diabetes mellitus	49 (27.7%)	19 (31.2%)	30 (25.9%)	0.455
Active smoker	3 (1.7%)	1 (1.6%)	2 (1.7%)	1.000
Pulmonary disease with O2 dependence	9 (5.1%)	0	9 (7.8%)	0.026
Systolic PAP > 60mmHg	10 (5.7%)	0	10 (8.6%)	0.018
Coronary artery disease	87 (49.2%)	29 (47.5%)	58 (50%)	0.755
Peripheral artery disease	14 (7.9%)	4 (6.6%)	10 (8.6%)	0.629
Atrial fibrillation	50 (28.3%)	13 (21.3%)	37 (31.9%)	0.137
Cirrhosis	6 (3.4%)	2 (3.3%)	4 (3.5%)	1.000
NYHA				0.099
I	16 (9.4%)	4 (6.8%)	12 (10.7%)	-
II	46 (26.9%)	19 (32.2%)	27 (24.1%)	-
III	87 (50.9%)	33 (55.9%)	54 (48.2%)	-
IV	22 (12.9%)	3 (5.1%)	19 (17.0%)	-
ECG				
First degree AVB	24 (13.6%)	9 (14.8%)	15 (12.9%)	0.736
Complete LBBB	13 (7.3%)	5 (8.2%)	8 (6.9%)	0.767
Complete RBBB	14 (7.9%)	0	14 (12.1%)	0.005
Treatment				
Vitamin K antagonists	20 (11.3%)	3 (4.9%)	17 (14.7%)	0.052
Dual antiplatelet (aspirin + clopidogrel)	46 (26.0%)	16 (26.2%)	30 (25.9%)	0.958
Direct oral anticoagulants	7 (4.0%)	2 (3.3%)	5 (4.3%)	1.000
Dual antiplatelet + Vitamin K antagonists	16 (9.0%)	5 (8.2%)	11 (9.5%)	0.777
Left ventricular ejection fraction				<0.001
< 30%	2 (6.8%)	0	12 (10.3%)	-
30-40%	19 (10.7%)	0	19 (16.4%)	-
>40%	146 (82.3%)	61 (100%)	85 (73.3%)	-
Pacemaker	25 (14.1%)	12 (19.7%)	13 (11.2%)	0.124
Creatinine clearance (mL/min)	50.2 +/- 19.6	50.0 +/- 18.2	50.3 +/- 20.4	0.936
Hemoglobin (g/dL)	12.3 +/- 1.6	12.3 +/- 1.7	12.3 +/- 1.6	0.833
CRP (g/l)	10.7 +/- 20.9	10.8 +/- 22.7	10.7 +/- 20.0	0.651
Anesthesia				
General	170 (96.1%)	59 (96.7%)	111 (95.7%)	-
Local	7 (3.9%)	2 (3.3%)	5 (4.3%)	-
Procedure length (hours)	1.37 +/- 0.44	1.31 +/- 0.34	1.41 +/- 0.49	0.295
Access				0.058
Right transfemoral	44 (24.9%)	17 (27.9%)	27 (23.3%)	-
Left transfemoral	123 (69.5%)	44 (72.1%)	79 (68.1%)	-
Subclavian	0	0	0	-
Transcarotid	10 (5.7%)	0	10 (8.6%)	-
Prosthesis				0.010
Edwards SAPIEN 3	148 (83.6%)	57 (93.4%)	91 (78.5%)	-
Medtronic CoreValve	29 (16.4%)	4 (6.6%)	25 (21.6%)	-

Discussion

The main results of this study were as follows: (1) TAVI may be performed safely without subsequent ICU admission using simple patient and procedural selection criteria; (2) postprocedural complications included mainly conductive disorders with a very low rate of major vascular and bleeding events; (3) the main predictive factors of complications in our study included preprocedural RBBB, self-expandable prosthesis implantation, use of VKA therapy, and conductive disorders occurring during the procedure; (4) this new "minimalist" strategy avoided ICU admission for 1/3 of our patients.

The improvement of the technique including the use of new low-profile devices, combined with the increase of operator experience and the precise screening of patients, has decreased complications of TAVI.[6,11–13,18] In-hospital adverse events observed currently with both self- and balloon-expandable prostheses included mainly complete AVB requiring permanent pacing or vascular and bleeding

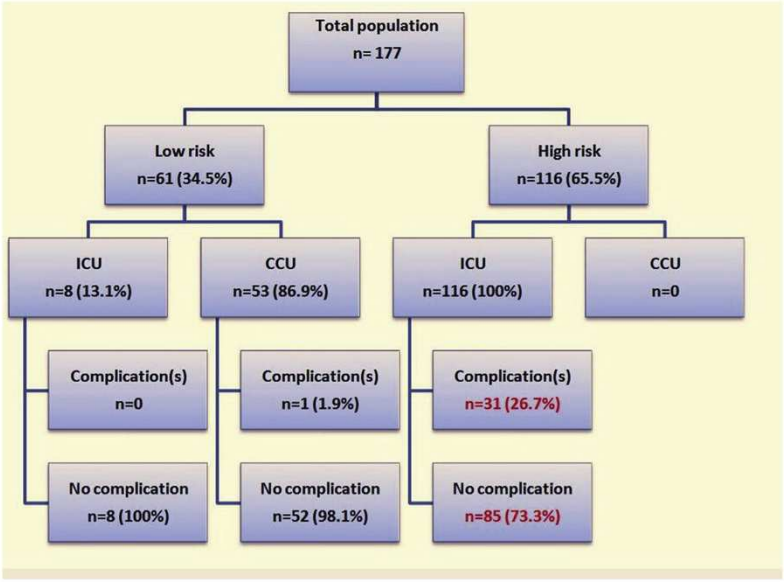


Figure 1. Orientation of the patients in the ICU or CCU according to the triage strategy.

Table 4
Preprocedural and periprocedural events observed in the population

Variables	Total population (n177)	High-risk group (n=116)	P value
Before procedure			
Pulmonary disease with O2 dependence	9 (5.1%)	9 (7.8%)	0.03
CoreValve prosthesis without pacemaker	25 (14.1%)	25 (21.6%)	<0.005
Complete right bundle branch block	14 (7.9%)	14 (12.1%)	0.004
Left ventricular ejection fraction < 40%	31 (17.5%)	31 (26.7%)	<0.005
Systolic pulmonary arterial pressure > 60mmHg	10 (5.6%)	10 (8.6%)	0.018
During Procedure			
Unstable hemodynamic	5 (2.8%)	5 (4.3%)	0.17
Mean arterial pressure < 65mmHg + vasopressors	4 (2.3%)	4 (3.4%)	0.299
Mean arterial pressure < 65mmHg + volume replacement	1 (0.6%)	1 (0.9%)	0.545
Vascular complications	6 (3.4%)	6 (5.2%)	0.55
Vascular rupture necessity surgery	2 (1.1%)	2 (1.7%)	0.545
Hematoma with manual compression	4 (2.3%)	4 (3.4%)	0.552
Second prosthesis	1 (0.6%)	1 (0.9%)	1
Stroke	1 (0.6%)	1 (0.9%)	1
New conductive disorder	73 (41.2%)	73 (62.9%)	<.000001
Complete atrio ventricular block	26 (14.7%)	26 (22.4%)	<.001
Complete left bundle branch block	49 (27.7%)	49 (42.2%)	<.001
Complete right bundle branch block	3 (1.7%)	3 (2.6%)	0.55
First degree atrio ventricular block	15 (8.5%)	15 (12.9%)	0.003
Pericardial effusion requiring medical intervention	1 (0.6%)	1 (0.9%)	1
Aortic regurgitation > grade 2 or pericardial effusion on echocardiography	4 (2.3%)	4 (3.4%)	0.299
Supraventricular arrhythmia	1 (0.6%)	1 (0.9%)	1
Ventricular arrhythmia	1 (0.6%)	1 (0.9%)	1
Transfert on medical decision	8 (4.5%)	8 (6.9%)	-

events.[6,11–13,19] Noncardiovascular mortality (sepsis or renal failure) may also explain mortality particularly in inoperable patients.[10] All these adverse events warranted ICU admission after the procedure. In our study including mainly patients undergoing TAVI with the SAPIEN 3 prosthesis, clinical adverse events occurred in 18.1% of our

Table 5
In-hospital complications observed in the total population and in the 2 groups of patients

Variables	Total population (n=177)	Low risk group (n=61)	High risk group (n=116)	P value
Death from any cause	1 (0.6%)	0	1 (0.9%)	1
Unstable hemodynamic	1 (0.6%)	0	1 (0.9%)	1
Volume replacement	0	0	0	-
Vasopressors	0	0	0	-
Acute pulmonary oedema	1 (0.6%)	0	1 (0.9%)	-
Major bleeding	1(0.6%)	0	1 (0.9%)	1
Major vascular complications	1 (0.6%)	0	1 (0.9%)	1
Vascular rupture with surgery	1 (0.6%)	0	1 (0.9%)	-
Stroke	1(0.6%)	0	1(0.9%)	1
Conductive disorder requiring pacemaker	26 (14.7%)	0	26 (22.4%)	<.001
Myocardial infarction	0	0	0	-
Acute kidney injury (stage 2 or 3 according to Rankin classification)	3 (1.7%)	0	3 (2.5%)	0.55
Pericardial effusion requiring medical intervention	2 (1.1%)	0	2 (1.7%)	0.54
Secondary transfer to intensive care unit	1 (0.6%)	1 (1.6%)	0	-

Table 6
Predictors of in-hospital complications in univariate and multivariate analysis

Variables	Total population (n=177)	Complication(s) (n=32)	No complication (n=145)	P value	OR [95% CI]	P value multivariate
Female gender	90 (50.8%)	22 (68.7%)	68 (46.9%)	0.025	2.6 [1-6.9]	0.04
Logistic Euroscore (%)	14.6 +/- 9.7	17.6 +/- 14.7	13.9 +/- 8.2	0.554	-	-
Medical history						
Atrial fibrillation	50 (28.3%)	11 (34.4%)	39 (26.9%)	0.4	-	-
NYHA class				0.09	-	-
I	16 (9.4%)	4 (12.9%%)	12 (8.6%)	-		
II	46 (26.9%)	4 (12.9%)	42 (30%)	-		
III	87 (50.9%)	16 (51.6%)	71 (50.7%)	-		
IV	22 (12.8%)	7 (22.6%)	15 (10.7%)	-		
ECG before procedure						
Complete left bundle branch block	13 (7.3%)	1 (3.1)	12 (8.3%)	0.47	-	-
Complete right bundle branch block	14 (7.9%)	9 (28.1%)	5 (3.4%)	<.0001	14.1 [3.5-56.3]	0.0002
Vitamin k antagonist treatment	20 (11.3%)	7 (21.9%)	13 (8.9%)	0.058	4.5 [1.1-12.6]	0.03
No pacemaker with CoreValve	25 (14.1%)	13 (40.6%)	12 (8.3%)	<.0001	5.5 [2-16.3]	0.001
Procedure length (hours)	1.37 +/- 0.44	1.48 +/- 0.47	1.35 +/- 0.44	0.08	-	-
New conductive disorder during procedure						
First degree atrio ventricular block	15 (8.5%)	5 (15.6%)	10 (6.9%)	0.15	-	-
Complete right bundle branch block	3 (1.7%)	1 (3.1%)	2 (1.4%)	0.45	12.5 [2-77.6]	0.007
Complete left bundle branch block	49 (27.7%)	17 (53.1%)	32 (22%)	<.0001	8.8 [2.7-28.8]	<.0001
Complete atrioventricular block	26 (14.7%)	19 (59.4)	7 (4.8%)	<.0001	19.7 [5-77.3]	<.0001

patients and only in the high-risk group. According to previous data, these adverse events were mainly related to high conductive disorders requiring permanent pacing (n = 26, 14.7%), and as expected, these conductive disorders were more frequent with the self-expandable prosthesis.[6,11,20] The rate of other adverse events was low, particularly major vascular events or bleeding (n = 2, 1.1%). The use of new-generation prosthesis with low-size sheaths (14Fr to 16Fr) may have contributed to the low rate of bleeding in our study. The open surgical access exclusively used in our center is also associated with a low rate of vascular complications and bleeding.[21,22] The low rate of other post-procedural complications is concordant with that recently reported with the new generation of prosthesis SAPIEN 3 and CoreValve.[6,12] Surgical risk scores, such as the logistic EuroSCORE and Society of Thoracic Surgeons score, are commonly used to identify high-risk or "inoperable" patients but appear to be poor predictors of immediate outcome of patients after TAVI.[23,24] Prediction of high degree of conductive disturbances is particularly important, considering the possibility of abrupt occurrence. In most studies, the main predictors of pacemaker implantation were preexisting conducting disturbances and particularly RBBB or QRS duration >150 ms.[25–27] Considering these main predictors of immediate adverse events requiring close medical observation and monitoring, we developed a protocol of ICU admission. As previously reported, we did not consider EuroSCORE as a risk factor of immediate adverse events, and our results warranted this choice. To increase the NPV of our strategy, we used "hard" ECG and vascular

criteria to exclude patients from CCU (Table 1). Occurrence of any conductive disturbance during the procedure, expecting first-degree AVB, was therefore highly predictive of complications ($p < 0.001$). Considering the risk of heart block associated with the self-expanding CoreValve,[11,18,20] only patients with previous permanent pacemaker were included in the low-risk group with this device. Finally, at any time, the ultimate decision to transfer the patient to the ICU depended on the physician (cardiologist or anesthetist). Therefore, 8 frail patients without high-risk criteria were anyway admitted to the ICU but did not develop any complication. As previously reported, left ventricular ejection fraction appears to be a weak predictive criterion of events in our study ($p = 0.09$), and women have more complications after TAVI than men, as after any invasive intervention.[13,16,19,24] Although we observed a tendency toward more VKA therapy in the high-risk group ($p = 0.052$), the relation between adverse events and VKA is surprising while majority of complications were conductive disturbances and not vascular or bleeding events. Conductive disturbances requiring a pacemaker, occurring more frequently in these patients, may be partially explained by association with atrial fibrillation, the main indication of VKA in our patients, which can be associated with masked sinus dysfunction or AVB. Considering our selection criteria, patients admitted to CCU (1/3 of the cohort) can be managed safely without any major complication, and therefore, the NPV of this triage strategy was very high (98.4%), with only 1 minor complication in the low-risk group. Previous reports showed that the vast majority of intraoperative events that are diagnosed and/or treated after TAVI occurred before the patient was transferred to the ICU.[8,27] Our results indicated that patients with uneventful recovery until 2 hours after the procedure have no risk of subsequent significant adverse events. Recent reports showed that early discharge after TAVI is feasible and safe in patients selected by clinical judgment, concerning also almost 1/3 of patients.[14–16] This strategy is cost-effective in comparison to the conventional approach.[7] Patients considered for early discharge in these studies were selected with criteria close to ours and may probably be partly concerned by the procedure of TAVI without ICU. Considering the rapid development of TAVI with the future trend to extend its indications to lower risk population,[28] an increased number of patients admitted to ICU after the procedure may be a crucial problem, particularly in high-volume centers because the number of critical care beds is limited.[29] Although recent data showed the need to optimize ICU triage for patients who will truly benefit, identification of risk of immediate cardiac events requiring ICU after TAVI may also be particularly relevant.[30] The monocentric design of the study is the first limitation and does not allow to extend these results to all centers. Our selection criteria were defined arbitrarily according to previous data evaluating risks factors of immediate outcome after TAVI. However, this pragmatic strategy may be improved, and a randomized trial may be useful to validate our selection criteria. Frailty measurement may also be added to improve patient assessment.

In conclusion, on the basis of single-center experience, this study suggests that TAVI can be performed safely without ICU admission in at least 1/3 of selected patients. According to simple clinical, ECG, and echocardiographic criteria evaluated before, during, and until 2 hours after the procedure, it is possible to identify a "low-risk" group of patients for whom ICU admission seems to be unnecessary. Combined with the possibility of early discharge, this "minimalist" approach of TAVI may optimize efficiency and cost-effectiveness of the procedure and may be evaluated in a multicenter medical and economic study.

Acknowledgment: We thank Valérie Macioce for her help in reading the manuscript and correcting English language.

Disclosures

The authors have no conflicts of interest to disclose.

1. Smith CR, Leon MB, Mack MJ, Miller C, Moses JW, Swensson LG, Tuzcu EM, Webb JG, Fontanna GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babalarios V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; for the PARTNER trial investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–2198.
2. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochellière R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. 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;55:1080–1090.
3. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Michev I, Lange R, Anderson WN, Wendler O. Thirty-day results of the SAPIEN aortic bioprosthesis European outcome (SOURCE) Registry; European Registry of Transcatheter Aortic Valve Implantation Using the Edwards SAPIEN Valve. *Circulation* 2010;122:62–69.
4. Vahanian A, Alfieri O, Andreotti F, Antunes M, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HS, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppel UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;33:2451–2496.
5. Mack MJ, Leon MB, Smith CR, Miller DG, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana G, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babalarios V, Pichard A, Herrmann HC, Brown DL, Williams M, Davidson MJ, Svensson LG; for the PARTNER investigators. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomized controlled trial. *Lancet* 2015;385:2477–2484.
6. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hugues GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK; for the US Corevalve Clinical investigators. Transcatheter aortic valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790–1798.
7. Babaliaros V, Devireddy C, Lerakis S, Leonardi R, Iturra SA, Mavromatis K, Leshnower BG, Guyton RA, Kanitkar M, Keegan P, Simone A, Stewart JP, Ghasemzadeh N, Block P, Thourani VH. Comparison of transfemoral transcatheter aortic valve replacement performed in the catheterization laboratory (minimalist approach) versus hybrid operating room (standard approach): outcomes and cost analysis. *JACC Cardiovasc Interv* 2014;7:898–904.
8. Durand E, Borz B, Godin M, Tron C, Litzler PY, Besson JP, Bejar K, Fraccaro C, Sanchez-Giron C, Dacher JN, Bauer F, Cribier A,

Eltchaninoff H. Transfemoral aortic valve replacement with the Edwards SAPIEN and Edwards SAPIEN XT prosthesis using exclusively local anesthesia and fluoroscopic guidance: feasibility and 30-day outcomes. *JACC Cardiovasc Interv* 2012;5:461−467.

9. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. 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.
10. Svensson LG, Blackstone EH, Rajeswaran J, Brozzi N, Leon M, Smith CR, Mack M, Miller DC, Moses JW, Tuzcu EM, Webb JG, Kapadia S, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Thourani VH, Pichard AD, Bavaria JE, Herrmann HC, Williams MR, Babalarios V, Genereux P, Akin JJ. Comprehensive analysis of mortality among patients undergoing TAVR: results of the PARTNER trial. *J Am Coll Cardiol* 2014;64:158−168.
11. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, Laskar M. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012;366:1705−1715.
12. Webb J, Gerosa G, Lefèvre T, Leipsic J, Spence M, Thomas M, Thielmann M, Treede H, Wendler O, Walther T. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. *J Am Coll Cardiol* 2014;64:2235−2243.
13. Ludman PF, Moat N, de Belder MA, Blackman DJ, Duncan A, Banya W, MacCarty PA, Cunningham D, Wendler O, Marlee D, Hildick-Smith D, Young CP, Kovac J, Uren NG, Spyt T, Triveri U, Howell J, Gray H; UK TAVI Steering Committee and the National Institute for Cardiovascular Outcomes Research. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. *Circulation* 2015;131:1181−1190.
14. Durand E, Eltchaninoff H, Canville A, Bouhzam K, Godin M, Tron C, Rodriguez C, Litzler PY, Bauer F, Cribier A. Feasibility and safety of early discharge after transfemoral transcatheter aortic valve implantation with the Edwards SAPIEN-XT prosthesis. *Am J Cardiol* 2015;115:1116−1122.
15. Noad RL, Johnston N, McKinley A, Dougherty M, Nzewi OC, Jeganathan R, Manoharan G, Spence MS. A pathway to earlier discharge following TAVI: assessment of safety and resource utilization. *Catheter Cardiovasc Interv* 2016;87:134−142.
16. Barbanti M, Capranzano P, Ohno Y, Attizzani GF, Gulino S, Imme S, Cannata S, Aruta P, Bottari V, Parane P, Tamburino C, Di Stephano D, Deste W, Giannazzo D, Gargiulo G, Caruso G, Sgroi C, Todoro D, Di Simone E, Capodanno D, Tamburino C. Early discharge after transfemoral transcatheter aortic valve implantation. *Heart* 2015;101:1485−1490.
17. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2013;34:2281−2329.
18. Hamm CW, Möllmann H, Holzhey D, Beckmann A, Veit C, Figulla HR, Cremer J, Kuck KH, Lange R, Zahn R, Sack S, Schuler G, Walther T, Beyersdorf F, Böhm M, Heusch G, Funkat AK, Meinertz T, Neumann T, Papoutsis K, Schneider S, Welz A, Mohr FW. The German Aortic Valve Registry (GARY): in-hospital outcome. *Eur Heart J* 2014;35:1588−1598.
19. Borz B, Durand E, Godin M, Tron C, Canville A, Litzler PY, Bessou JP, Cribier A, Eltchaninoff H. Incidence, predictors and impact of bleeding after transcatheter aortic valve implantation using the balloon-expandable Edwards prosthesis. *Heart* 2013;99:860−865.
20. Franzoni I, Latib A, Maisano F, Costopoulos C, Testa L, Figini F, Giannini F, Basavarajaiah S, Mussardo M, Slavich M, Taramasso M, Cioni M, Longoni M, Ferrarello S, Radinovic A, Sala S, Ajello S, Sticchi A, Giglio M, Agricola E, Chieffo A, Montorfano M, Alfieri O, Colombo A. Comparison of incidence and predictors of left bundle branch block after transcatheter aortic valve implantation using the CoreValve versus the Edwards valve. *Am J Cardiol* 2013;112:554−559.
21. Kadakia MB, Herrmann HC, Desai ND, Fox Z, Ogbara J, Anwaruddin S, Jagasia D, Bavaria JE, Szeto WY, Vallabhajosyula P, Li R, Menon R, Kobrin DM, Giri J. Factors associated with vascular complications in patients undergoing balloon-expandable transfemoral transcatheter aortic valve replacement via open versus percutaneous approaches. *Circ Cardiovasc Interv* 2014;7:570−576.
22. Leclercq F, Akodad M, Macia JC, Gandet T, Lattuca B, Schmutz L, Gervasoni R, Nogues E, Nagot N, Levy G, Maupas E, Robert G, Targoz F, Vernhet H, Cayla G, Albat B. Vascular complications and bleeding after transfemoral transcatheter aortic valve implantation performed through open surgical access. *Am J Cardiol* 2015;116:1399−1404.
23. Piazza N, Wenaweser P, Van Gameren M, Pilgrim T, Tsikas A, Otten A, Nuis R, Onuma Y, Cheng JM, Kappetein AP, Boersma E, Juni P, de Jaegere P, Windecker P, Serruys PW. Relationship between the logistic EuroSCORE and the Society of Thoracic Surgeons score predicted risk of mortality in patients implanted with the CoreValve ReValving System—a Bern-Rotterdam study. *Am Heart J* 2010;159:323−329.
24. Iung B, Laouénan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P, Fajadet J, Leprince P, Leguerrier A, Lièvre M, Prat A, Teiger E, Laskar M, Vahanian A, Gilard M; for the FRANCE 2 Investigators. Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. *Heart* 2014;100:1016−1023.
25. Bleiziffer S, Ruge H, Hörer J, Hutter A, Geisbüsch S, Brockmann G, Mazzitelli D, Bauernschmitt R, Lange R. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2010;3:524−530.
26. Mouillet G, Lellouche N, Lim P, Meguro K, Yamamoto M, Deux JF, Monin JL, Bergoend E, Dubois-Rande JL, Teiger E. Patients without prolonged QRS after TAVI with CoreValve device do not experience high-degree atrio-ventricular block. *Catheter Cardiovasc Interv* 2013;81:882−887.
27. Siontis GC, Jüni P, Pilgrim T, Stortecky S, Büllesfeld L, Meier B, Wenaweser P, Windecker S. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol* 2014;64:129−140.
28. Lange R, Bleiziffer S, Mazzitelli D, Elhmidi Y, Opitz A, Krane M, Deutsch MA, Ruge H, Brockmann G, Voss B, Schreiber C, Tassani P, Piazza N. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2012;59:280−287.
29. Szalados JE. Access to critical care: medical rationing of a public right or privilege? *Crit Care* 2004;32:1623−1624.
30. Chen R, Strait KM, Dharmarajan K, Li SX, Ranasinghe I, Martin J, Fazel R, Masoudi FA, Cooke CA, Nallamothu BK, Krumholz HM. Hospital variation in admission to intensive care units for patients with acute myocardial infarction. *Am Heart J* 2015;170:1161−1169.

Annexe 2 :

Leclercq *et al. Trials* (2017) 18:303
DOI 10.1186/s13063-017-2036-y

Trials

STUDY PROTOCOL Open Access

Prior balloon valvuloplasty versus DIRECT transcatheter Aortic Valve Implantation (DIRECTAVI): study protocol for a randomized controlled trial

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Abstract

Background: Balloon predilatation of the aortic valve has been regarded as an essential step during the transcatheter aortic valve implantation (TAVI) procedure. However, recent evidence has suggested that aortic valvuloplasty may cause complications and that high success rates may be obtained without prior dilatation of the valve. We hypothesize that TAVI performed without predilatation of the aortic valve and using new-generation balloon-expandable transcatheter heart valves is associated with a better net clinical benefit than TAVI performed with predilatation.

Methods/design: The transcatheter aortic valve implantation without prior balloon dilatation (DIRECTAVI) trial is a randomized controlled open label trial that includes 240 patients randomized to TAVI performed with prior balloon valvuloplasty (control arm) or direct implantation of the valve (test arm). All patients with an indication for TAVI will be included excepting those requiring transapical access. The trial tests the hypothesis that the strategy of direct implantation of the new-generation balloon-expandable SAPIEN 3 valve is noninferior to current medical practice using predilatation of the valve. The primary endpoint assessing efficacy and safety of the procedure consists of immediate procedural success and secondary endpoints include complications at 30-day follow-up (VARC-2 criteria). A subgroup analysis evaluates neurological ischemic events with cerebral MRI imaging (25 patients in each strategy group) performed before and between 1 and 3 days after the procedure.

Discussion: This prospective randomized study is designed to assess the efficacy and safety of TAVI performed without prior dilatation of the aortic valve using new-generation balloon-expandable transcatheter heart valves. We aim to provide robust evidence of the advantages of this strategy to allow the interventional cardiologist to use it in everyday practice.

Trial registration: ClinicalTrials.gov identifier: NCT02729519. Registered on 15 July 2016.

Keywords: Transcatheter aortic valve implantation (TAVI), Balloon aortic valvuloplasty, Procedural success, Safety, Randomized clinical trial

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Background

Transcatheter aortic valve implantation (TAVI) is now the standard of care for patients with inoperable severe symptomatic aortic stenosis and an accepted alternative to surgery for high-risk patients [1–6]. The improvement in operator experience and valve technology, combined with better screening and inclusion of lower-risk patients, have resulted in dramatically decreased in-hospital complications after TAVI procedures. However, despite a high procedure success rate (>95%), TAVI has remained associated with complications directly related to the technique (stroke, aortic regurgitation, vascular access bleeding) or to comorbidities frequently associated with aortic valve disease in older and frail patients [3–6]. Reducing periprocedural complications is thereby the key for the future use of TAVI in lower-risk patients. Balloon aortic valvuloplasty (BAV) has been considered as a mandatory step in the TAVI procedure both to facilitate the implantation of the transcatheter heart valve (THV) and to reduce the radial counterforce for optimal device expansion. However, BAV has been shown to carry specific complications and risks [7, 8]. With the development of a new generation of balloon-expandable THVs, associated with low profile and orientable delivery system, the crossing of the valve is facilitated. While both balloon dilatation and the need for post dilatation have been considered to increase the risk of cerebral embolization, avoiding BAV prior to TAVI is attractive and may simplify the procedure [9–12]. Only few non-randomized studies have shown that direct implantation of the THV is feasible [10, 13, 14], but there are currently no randomized data concerning the safety and efficacy of TAVI performed with new-generation balloon-expandable THVs without prior dilatation of the aortic valve.

DIRECTAVI is the first randomized controlled trial that will evaluate the efficacy and safety of direct implantation of a balloon-expandable new-generation prosthesis, the Edwards SAPIEN 3 THV.

Methods/design

DIRECTAVI is a prospective, randomized, monocentric, open-label trial that aims to test the hypothesis that TAVI performed without predilatation (test arm) and using the new-generation balloon-expandable Edwards SAPIEN 3 THV is associated with a better net clinical benefit in comparison to procedures performed with predilatation (control arm). The trial has an intentional noninferiority design concerning the primary endpoint. From an ethical standpoint, a sham procedure in the no-dilatation control arm could not be countenanced. The study is conducted in the academic University Hospital of Montpellier, France. The study flow chart is presented in Fig. 1.

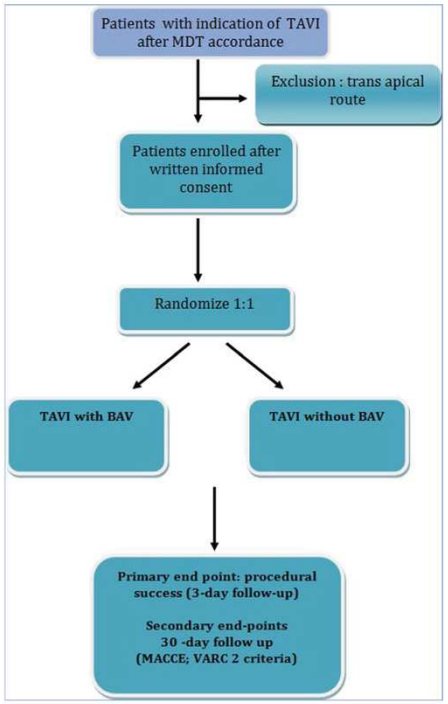


Fig. 1 Flow chart of the study. *BAV* balloon aortic valvuloplasty, *MDT* multidisciplinary heart team, *MACCE* major adverse cardiovascular and cerebral events

Patient population and procedure

The study population consists of 240 patients who will have TAVI via a transvascular or transthoracic approach. Patients should be deemed eligible for TAVI by a multidisciplinary team including at least an interventional cardiologist, a cardiothoracic surgeon and an anesthetist. All the procedures performed with the third-generation balloon-expandable Edwards SAPIEN 3 THV (Edwards Lifesciences, Irvine, CA, USA) will be considered for inclusion in the study. The SAPIEN 3 THV system is a new generation of balloon-expandable THVs which incorporates various new features to facilitate implantation and minimize vascular injury, stroke, suboptimal positioning, and paravalvular regurgitation [15]. The prosthesis size (23, 26 or 29 mm) and the access route (transfemoral, transcarotid, subclavian or transaortic) are left to the discretion of the operating team. For all patients, both vascular access and aortic valve apparatus are evaluated before the procedure with multislice computerized tomographic angiography (MSCT) of the

entire aorta using vascular windows settings. The transfemoral access is the first choice when possible.

Main procedures are done under mild sedation and local anesthesia in our center. Low-profile 14 to 16 French delivery systems are used in all patients with an almost exclusive surgical vascular access. For femoral or carotid access, we use a surgical "preclose technique" in order to avoid arterial cross-clamping and the purse-string effect [16]. For the control group, BAV will be performed with a balloon of 18, 20 or 22 mm diameter according to the THV size. All patients will receive 0.5 mg/kg heparin at the time of introducing the femoral sheath to achieve an activated clotting time of >250 s. All TAVI procedures are performed in the same site by six medical teams comprising at least one interventional cardiologist and a cardiac surgeon, assisted by one nurse for valve-crimping, a nurse who assists the anesthetist and a technician from the catheterization laboratory. A combination of clopidogrel 75 mg and aspirin 75 mg is introduced in all patients after the procedure except in those with an indication for vitamin k antagonists or direct anticoagulant therapy who had only aspirin 75 mg. The vitamin K antagonists or direct orally administered anticoagulants are always stopped at least 2 days before the procedure and usually reintroduced 1 day later.

Study design

Inclusion/exclusion criteria

According to the inclusion and exclusion criteria summarized in Table 1, the study investigators will confirm patient eligibility. All patients who are referred for TAVI in our center and who meet the inclusion criteria will be successively included and randomized. After verification of the eligibility criteria and obtaining informed consent, the patients will be randomized by an investigator to receive either BAV or direct implantation of the valve. For this purpose, the investigator will connect to the secure and dedicated CLINSIGHT website (CS Online) with his username and personal password. The random allocation sequences will be computer-generated by an

Table 1 Eligibility criteria for the transcatheter aortic valve implantation without prior balloon dilatation (DIRECTAVI) study

Criteria	Definition
Inclusion criteria	
Patients aged ≥18 years	
Severe aortic valve stenosis	Mean gradient ≥40 mmHg or aortic valve area <1 cm^2 on TTE[a]
Symptoms suggestive of severe aortic stenosis	Dyspnea, heart failure, angina, syncope
Contraindication for open heart surgery or excessive surgical risk	Decision of the multidisciplinary heart team
TAVI using the balloon-expandable SAPIEN 3 valve	
Vascular access	Transfemoral, transcarotid, transaortic or subclavian access
Exclusion criteria	
Preexisting aortic prosthesis	"Valve in valve" technique
Transapical access	
BAV[b] performed for less than 1 week	
Recent myocardial infarction	Within the last 3 months
Left ventricular or atrial thrombus	TTE evaluation
Significant mitral or tricuspid regurgitation	>grade II on TTE
Recent cerebrovascular event	Within the last 3 months
Carotid or vertebral arterial narrowing	Stenosis >80% (Doppler or CT scan)
Active internal bleeding	
Thrombocytopenia	Platelet count <50,000/mm^3
Lack of written informed consent	
Severe mental disorder, drug/alcohol addiction	Specialized evaluation
Life expectancy <1 year	
Participation in another drug or device study	Any study that would jeopardize the appropriate analysis of study endpoints
High probability of nonadherence to the follow-up	Social, psychological or medical requirement reason
Pregnancy	

[a]*TTE* transthoracic echocardiography, [b]*BAV* balloon aortic valvuloplasty. *CT* computed tomography

independent statistician using a 1:1 ratio and permuted blocks of 4 and 6.

Data collection and follow-up (see Fig. 2)

Baseline data collected from enrolled patients will include demographics, past medical history, previous cardiac investigations and current medication. Patients will undergo transthoracic echocardiography at baseline, post procedure and at 1-month follow-up. Prospective monitoring of adverse and clinical events starts at randomization and continues until 1 month. All major adverse cardiovascular and cerebrovascular events (MACCE) and other serious adverse events will be recorded in the electronic Case Record Form and reported to the coordinating center within 3 days of first identification. On receipt of notification of any adverse or clinical event, the coordinating center will request additional details, specific to the nature of the event. These episodes will be carefully monitored by the trial coordinator and will be part of the information provided at regular intervals to the Clinical Events and Data Monitoring and Ethics Committees. The Clinical Events Committee will be blinded to treatment and will consider each MACCE or adverse event reported and ratify occurrence of an endpoint according to the study definitions.

This 1-month visit is part of the routine practice after TAVI. A consultation appointment will be given to patients when they will be discharged from the hospital, and a dedicated research assistant will call the patients who did not attend on the day after their missed visit. In case of inability for the patient to come, the research assistant and/or investigator will contact the patient GP or cardiologist to obtain some clinical information on the patient. All concomitant care or interventions are permitted during the study follow-up.

Study endpoints

The primary endpoint, assessing efficacy and safety of the procedure, consists of immediate procedural success defined as the absence of immediate procedural mortality *and* correct positioning of a single prosthetic heart valve into the proper anatomical location *and* intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s), *and* no moderate or severe prosthetic valve regurgitation [17].

According to Valve Academic Research Consortium (VARC-2) criteria immediate procedural mortality is defined to capture intraprocedural events that result in immediate or consequent death ≤72 h post procedure [17].

Secondary endpoints include cardiovascular and all-cause mortality, procedure outcomes (length of procedure,

	Enrolment	Allocation	Post allocation		Close-out
TIMEPOINT**	*J-30 to J-1*	J0	*J1. J3*	*Hospital exit*	*1 month follow-up*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
TAVI		X			
ASSESSMENTS:					
baseline variables					
Echocardiography	X		X	X	X
ECG	X	X	X	X	X
Biological parameters	X	X	X	X	
Outcome variables					
Clinical data (main outcome)			X		
Clinical data (secondary outcome)					X

Fig. 2 The transcatheter aortic valve implantation without prior balloon dilatation (DIRECTAVI) trial

incidence of post dilatation, radiation exposure, contrast volume injection), and adverse events (VARC-2 criteria) at 30-day follow-up. Adverse events considered included life-threatening/major/minor bleeding, vascular access complications, acute kidney failure (RANKIN classification stage 2 or 3), pacemaker implantation, neurological events or new hospitalization for cardiac causes. We will also evaluate duration of hospital stay, echocardiography data (transvalvular gradients, aortic regurgitation quantification, left ventricular systolic and diastolic parameters). All the definitions used are in accordance with the VARC-2 guidelines [17].

Potential biases and prevention

Our study is prone to a number of biases. Since the investigator cannot be blinded during the study, the measurements of the primary outcome components will be made by an independent and blinded cardiologist as follows:

- Absence of immediate procedural mortality: death of the patient during or within 24 h of the procedure
- Correct positioning of a single prosthetic heart valve into the proper anatomical location in the aortic ring
- No prosthesis-patient mismatch (conformity between the size of the prosthesis and the size of the annulus ring) and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s), *and* no moderate or severe prosthetic valve regurgitation. This evaluation using echography and Doppler at 24 and 72 h post procedure will be made by the blinded cardiologist. A potential selection bias will be minimized by the enrollment of all consecutive patients who meet the eligibility criteria

Ancillary study

An ancillary substudy will enroll 50 patients (25 in each arm) and will be dedicated to evaluate ischemic cerebral events with diffusion-weighted magnetic resonance imaging (DW-MRI) of the brain performed before and after (within 3 days) the TAVI procedure (between days 2 and 5). All consecutive included patients will be proposed to participate in this ancillary study, and all those agreeing to participate will be enrolled until completion of the sample size. MRI will be interpreted by two experienced radiologists blinded to the timing of the imaging and the neurological status of the patient.

Ethics

The Regional Ethics Committee has approved the trial (Comité de Protection des Personnes Sud Méditerranée, Montpellier, France) and all patients will provide oral and written informed consent. The trial is conducted according to the World Medical Association Declaration of Helsinki and will conform to the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. The trial has a Steering Committee, an independent Event Adjudication Committee, and an external Independent Data Monitoring and Safety Committee (DMSC) (registered number: 2015-A01824-45). The DMSC is composed of an interventional cardiologist, a cardiac surgeon, a neurologist, and a statistician. The trial is registered at ClinicalTrials.gov (NCT02729519).

Statistical consideration

Sample size determination

No randomized trials have evaluated the efficiency and safety of direct implantation of THVs without prior BAV. The only randomized study is ongoing and concerns the self-expandable MEDTRONIC CoreValve THV [18]. According to SOURCE, FRANCE 2 AND PARTNER 2 studies [2, 3, 6], we assume a procedural success rate of 95% in the control group. Using a noninferiority threshold of 7%, a power of 80% and 5% significance level, 240 patients must be included to conclude that TAVI without predilatation is noninferior to conventional TAVI.

Statistical analysis

A detailed plan of analysis will be elaborated and finalized before the database is frozen (i.e., after completion of the data management). After verification that patients' characteristics are clinically similar between study arms, the noninferiority of the HFNC device will be assessed by the one-sided Farrington-Manning confidence limit for the risk method using the noninferiority margin of 7%. The noninferiority will be declared if the success rate of the intervention arm (no prior dilatation) will be at most 7% higher than the success rate of the control (prior dilatation) arm. The main analysis will be based on an intention-to-treat analysis whereby all patients randomized in their original arm will be included in the analysis. Given that the primary outcome will be measured during the patient hospitalization, we do not expect any loss to follow-up nor any missing data for the primary outcome. However, any such missing data will be dealt with according to standard approaches, depending on the nature of the missing data [19].

This approach is, therefore, equivalent to the per-protocol analysis recommended for noninferiority trials. Fisher, chi-square and Wilcoxon-Mann-Whitney tests will be used as appropriate to compare secondary outcomes between groups with a superiority approach.

Protocol violations will be reviewed case by case by the investigators to decide whether the patients can remain in the study and in the analyses. For the secondary outcomes, the data of patients who will withdraw or drop out from the study will be retained in the analyses until the time that they leave the study. Statistical

significance will be set at 0.05. Statistical analyses will be carried out with SAS (SAS Institute, Cary, NC, USA). The final report will follow the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines and the consort extensions for nonpharmaceutical drugs and for equivalence studies.

Study management

The DIRECTAVI study is planned to be a randomized open-label trial, conducted and sponsored by the University Hospital of Montpellier (France). Funding has been obtained from Edwards Lifesciences. An Executive Committee composed of experienced clinical investigators will provide trial leadership. A Clinical Events Committee, blinded to the assignment strategy, will adjudicate all clinical events and a DMSC in operation. The committee will comprise physicians who are provided with all the data from medical records necessary to perform optimal adjudication. The study conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidelines (see Additional file 1).

Discussion

Before deployment of the THV, current medical practice requires right ventricular rapid-burst pacing (rates >180/min) with induction of a functional cardiac arrest for up to 30 s for BAV. This step is thought to be necessary to predilate the native aortic valve and to facilitate an accurate positioning of the valve. BAV is an established palliative procedure for patients with aortic stenosis that has been shown to have numerous detrimental effects [7, 8, 20]: (1) the functional cardiac arrest induced by rapid pacing needed to stabilize the balloon during inflation leads to transient coronary, cerebral, and renal ischemia. In patients with impaired left ventricular ejection fraction, prolonged cardiac depression after rapid pacing may result in hemodynamic failure, (2) causing intraleaflet fractures within calcified nodular deposits of the valve, BAV has been identified as a potential source of embolization of thrombotic and valvular material, (3) due to the displacement of a bulky calcified native valve over a coronary ostium, BAV may increase the risk for coronary obstruction with subsequent myocardial infarction, (4) the local trauma in the left ventricular outflow tract caused by BAV may contribute to conduction disturbances and to permanent pacemaker implantation after TAVI, (5) BAV may induce massive acute aortic regurgitation inducing hemodynamic instability that may require urgent THV placement, (6) with mechanical compression of a "vulnerable area" by calcification, high-pressure BAV may induce annulus rupture, one of the most dramatic and life-threatening complication after TAVI.

A better prosthesis expansion with balloon predilatation, particularly for patients allocated to the self-expandable THV, may in theory reduce the risk of under expansion of the valve and the need for post dilatation. However, the radial force provided by the TAVI device itself is obviously sufficient to guarantee a good expansion in most cases [10, 21]. Lastly, using with contrast injection, BAV may be a help to annular sizing and to evaluate the risk of coronary occlusion in case of lower sinus height. However, with the use MSCT for detailed assessment of the native aortic valve, optimal selection of patients is usually obtained. Conversely, there are potential advantages of avoiding balloon predilatation during TAVI. Firstly, the procedure can be simpler and shorter which can carry advantages particularly in older and frail patients. The radiation dose and the contrast volume are significantly reduced [10, 13, 14]. Reduction in complications associated with BAV (embolization, annulus rupture, conductive disturbances, acute aortic regurgitation) may also be considered [10, 13].

Although recent reports have shown that direct implantation of the valve without balloon predilatation is feasible and yields high success rates, such studies were nonrandomized, registry-type and with relatively small sample sizes [10, 13, 14]. A pilot study was for the first time reported in 2011 by Grübe et al., evaluating the feasibility and safety of TAVI without balloon predilatation in 60 consecutive patients using the self-expanding Medtronic CoreValve prosthesis. The patients were prospectively enrolled in 13 international centers. Technical success rate was 96.7% and post dilatation was required in 16.7% of the patients. In-hospital major events were similar as with the current standard reported approach of TAVI with predilatation. There was no valve embolization. New permanent pacing was needed in 11.7% (7 of 60) of patients [10]. In a monocentric study, Fiorina et al. evaluated 55 consecutive TAVIs performed without predilatation using the self-expandable CoreValve THV. Compared to 45 TAVIs with predilatation performed the previous year, direct TAVI appears feasible and safe regardless of the presence of a bulky calcified aortic valve or the valve size implanted. Device success was higher in direct TAVI, mostly driven by a lower incidence of paravalvular leak [13]. In a retrospective study, Mollmann et al. evaluated 26 consecutive patients undergoing transfemoral TAVI with the Edwards SAPIEN XT prosthesis without predilatation and compared with 30 patients treated previously with predilatation. The procedure was successfully performed in all 26 patients, irrespective of the valve area and the extent of calcification. Post dilatation was required in three patients due to aortic regurgitation >grade 2, and can reduced regurgitation < grade 2 in all cases. Radiation dose and amount of contrast dye were significantly

reduced in comparison with the predilatation group. No periprocedural neurological adverse events occurred. Mortality at 30 days was 0% [14]. The procedure appears safe and feasible even with self-expanding THVs which are able to "dilate" the stenotic aortic valve through the radial forces of the self-expanding nitinol frame. Post dilatation is, however, frequently required with this device [13, 21]. Chan et al. reported two cases in which balloon predilatation was not performed initially during TAVI but eventually required to facilitate device crossing and implantation. They illustrated the importance of case selection and drew attention to the potential limitation in performing TAVI without balloon predilatation which is not always feasible [22]. More recently, a meta-analysis of 18 studies incorporating 2443 patients showed that no balloon predilatation prior to TAVI was safe and feasible and associated with fewer complications and short-term mortality in selected patients, especially using the self-expandable valve [23].

Direct comparative studies of patients receiving TAVI, with or without prior BAV, with new-generation devices are lacking. In a recent nonrandomized study, Bijuklic et al. reported a significantly higher volume of cerebral ischemic lesions on cerebral magnetic resonance imaging (MRI) after implantation of a balloon-expandable aortic valve without prior BAV. The authors speculated that predilatation leads to plaque fragmentation which can reduce the risk of embolization and the size of pieces that embolize during stent implantation. In that study, however, most patients undergoing TAVI with the Edwards SAPIEN 3 THV had no BAV and they were compared with a historical control group of patients who received either an Edwards SAPIEN XT or an Edwards SAPIEN 3 [18]. No difference in MACCE was also reported by Pagnesi et al. in a cohort of 517 patients undergoing transfemoral TAVI with various generation devices with or without pre-BAV but the rate of post dilatation was increased in the group without prior valvuloplasty [24]. We recently presented in a pilot study the rate of embolic stroke evaluated with MRI in 46 consecutive patients undergoing TAVI with the balloon-expandable EDWARDS SAPIEN 3 THV with or without balloon predilatation. Our results did not show significant differences in cerebral ischemic lesions between the two groups and the new lesions were mainly lacunar [25].

The ongoing SIMPLIFy study randomizes 110 patients with LVEF ≤35% to TAVI without BAV (experimental group) or TAVI with BAV (control group) with the safe expandable Medtronic Corevalve THV [26]. The primary composite efficacy endpoint will include all-cause mortality, stroke, nonfatal myocardial infarction, acute kidney injury, or pacemaker implantation at 30-day follow-up.

Although this study will be implemented in a single hospital, which may limit the generalization of the findings, the design of the DIRECTAVI trial is unique in that no randomized comparisons have been made between TAVI performed with or without predilatation of the aortic valve using the third-generation SAPIEN 3 THV. While direct implantation of the THV is probably associated with reduction of procedure duration and radiation exposure, we do not know if this technique will be associated with net clinical benefits. Of particular concern is the possible increase of risk of stroke associated with direct implantation of the THV [18, 24]. Feasibility of the technique (noninferiority study) has also to be demonstrated. Simplifying the procedure and reducing complications of TAVI is challenging considering the future extension of the procedure to intermediate and low-risk patients [27]. Finally, the findings of DIRECTAVI will help to define the optimum strategy of the TAVI procedure and will facilitate evidence-based guidelines on the controversial issue of whether to predilate or not predilate the valve before implanting the THV.

Trial status

This study has been recruiting patients since May 2016.

Additional file

Additional file 1: SPIRIT 2013 Check list. (DOCX 22 kb)

Abbreviations

BAV: Balloon aortic valvuloplasty; DIRECTAVI: Direct transcatheter aortic valve implantation; DMSC: Data Monitoring and Safety Committee; DW-MRI: Diffusion-weighted magnetic nuclear imaging; MACCE: Major adverse cardiaovascular and cerebral events; MSCT: Multislice computed tomography; TAVI: Transcatheter aortic valve implantation; THV: Transcatheter heart valve; VARC: Valve Academic Research Consortium

Acknowledgements

We thank Valérie Macioce for her help in reading the manuscript, and help with the English language translation and Claire Chauveton for her assistance in setting up the study protocol. We thank also Marine Chettouh for her help in selecting clinical data.

Funding

This study is funded by the University Hospital of Montpellier, avenue du doyen Giraud, 34295 Montpellier (France) and grants from Edwards Lifesciences, docteur Jean Luc Lemercier, route de l'Etraz 70, 1260 Nyon (Switzerland). The funder will not be implicated in collection, management, analysis, interpretation of data or writing the report of the study.

Availability of data and materials

Data and material are available in the University Center of Montpellier, at the medical research office, avenue du doyen Giraud, 24295 Montpellier, France.

Authors' contributions

FL and GC conceived the study. FL, PR, JL, BL, BA and GC participated in the study design. FL, GC, PR, MA, BL, JCM, RG, FR, TG and LS will recruit, select and collect clinical data of the patients. EN and NN will perform statistical analysis. FL is the principal investigator. FL, EN, NN and GC drafted the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
All authors and sponsor have consent for publication.

Ethics approval and consent to participate
The Regional Ethics Committee has approved the trial (Comité de Protection des Personnes Sud Méditerranée, Montpellier, France) and all patients will provide oral and written informed consent. The trial is conducted according to the World Medical Association Declaration of Helsinki and will be conformed to the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. The trial has a Steering Committee, an independent Event Adjudication Committee, and an external independent Data Monitoring and Safety Committee (DMSC) (registered number: 2015-A01824-45).

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Received: 18 October 2016 Accepted: 1 June 2017
Published online: 04 July 2017

References

1. Vahanian A, Alfieri O, Andreotti F, Antunes M, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HS, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppel UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2012;42:S1–44.
2. Smith CR, Leon MB, Mack MJ, Miller C, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontanna GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babalarios V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, for the PARTNER trial investigators. Transcatheter versus surgical aortic valve replacement in high-risk patients. N Engl J Med. 2011;364:2187–98.
3. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, Laskar M. Registry of transcatheter aortic valve implantation in high-risk patients. N Engl J Med. 2012;366:1705–15.
4. Eltchaninoff H, Prat A, Gilard M, Leguerrier A, Blanchard D, Fournial G, Iung B, Donzeau-Gouge P, Tribouilloy C, Debrux JL, Pavie A, Gueret P. Transcatheter aortic valve implantation: early results of the FRANCE (FRenchAortic National CoreValve and Edwards) Registry. Eur Heart J. 2011;32:191–7.
5. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochellière R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. 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.
6. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Michev I, Lange R, Anderson WN, Wendler O. 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.
7. Eltchaninoff H, Cribier A, Tron C, Anselme F, Koning R, Soyer R, Letac B. Balloon aortic valvuloplasty in elderly patients at high risk for surgery, or inoperable: immediate and mid-term results. Eur Heart J. 1995;16:1079–84.
8. Sack S, Kahlert P, Khandanpour S, Naber C, Philipp S, Möhlenkamp S, Sievers B, Kälsch H, Erbel R. Revival of an old method with new techniques: balloon aortic valvuloplasty of the calcified aortic stenosis in the elderly. Clin Res Cardiol. 2008;97:288–97.
9. Kahlert P, Al-Rashid F, Döttger P, Mori C, Plicht B, Wendt D, Bergmann L, Kottenberg E, Schlamann M, Mummel P, Holle D, Thielmann M, Jakob HG, Konorza T, Heusch G, Erbel R, Eggebrecht H. Cerebral embolization during transcatheter aortic valve implantation: a transcranial Doppler study. Circulation. 2012;126:1245–55.
10. Grube E, Naber C, Abizaid A, Sousa E, Mendiz O, Lemos P, Kalil Filho R, Mangione J, Buellesfeld L. Feasibility of transcatheter aortic valve implantation without balloon pre-dilation. A pilot study. J Am Coll Cardiol Intv. 2011;4:751–7.
11. Nombela-Franco L, Webb J, de Jaegere PP, Toggweiler S, Nuis RJ, Dager AE, Amat-Santos IJ, Cheung A, Ye J, Binder RK, Van der Boon RM, Van Mieghem N, Benitez LM, Perez S, Lopez J, San Roman JA, Doyle D, DeLarochellière R, Urena M, Leipsic J, Dumont E, Rodes-Cabau J. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. Circulation. 2012;126:3041–53.
12. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. Circulation. 2010;121:870–8.
13. Fiorina C, Maffeo D, Curello S, Lipartiti F, D'Aloia GCA, Adamo M, Mastropierro R, Gavazzi E, Chiari CCE, Ettori F. Direct transcatheter aortic valve implantation with self-expandable bioprosthesis: feasibility and safety. Cardiovasc Revasc Med. 2014;15:200–3.
14. Möllmann H, Kim WK, Kempfert J, Blumenstein J, Liebetrau C, Nef H, Van Linden A, Walther T, Hamm C. Transfemoral aortic valve implantation of Edwards SAPIEN XT without predilatation is feasible. Clin Cardiol. 2014;37:667–71.
15. Binder R, Rodés-Cabau J, Wood DA, Mok M, Leipsic J, De Larochellière R, Toggweiler S, Dumont E, Freeman M, Willson AB, Webb JG. Transcatheter aortic valve replacement with the SAPIEN 3: a new balloon-expandable transcatheter heart valve. J Am Coll Cardiol Intv. 2013;6:293–300.
16. Leclercq F, Akodad M, Macia JC, Gandet T, Lattuca B, Schmutz L, Gervasoni R, Nogues E, Nagot N, Levy G, Maupas E, Robert G, Targoz F, Vernhet H, Cayla G, Albat B. Vascular complications and bleeding after transfemoral transcatheter aortic valve implantation performed through open surgical access. Am J Cardiol. 2015;116:1399–404.
17. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. 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.
18. Bijuklic K, Haselbach T, Witt J, Krause K, Hansen L, Gehrckens R, Rieß FC, Schofer J. Increased risk of cerebral embolization after implantation of a balloon-expandable aortic valve without prior balloon valvuloplasty. J Am Coll Cardiol Intv. 2015;8:1608–13.
19. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, Frangakis C, Hogan JW, Molenberghs G, Murphy SA, Neaton JD, Rotnitzky A, Scharfstein D, Shih WJ, Siegel JP, Stern H. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012;367:1355–60.
20. Bashore T, Berman AD, Davidson CJ, Mickel MC, Kennedy JW, Davis K. The NHLBI balloon valvuloplasty registry participants. Percutaneous balloon aortic valvuloplasty. Acute and 30-day follow-up results in 674 patients from the NHLBI Balloon Valvuloplasty Registry. Circulation. 1991;84:2383–9.
21. Grube E, Buellesfeld L, Mueller R, Sauren B, Zickmann B, Nair D, Beucher H, Felderhoff T, Iversen S, Gerckens U. 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.
22. Chan PH, Mario CD, Moat N. Transcatheter aortic valve implantation without balloon predilatation: not always feasible. Catheter Cardiovasc Interv. 2013;82:328–32.

23. Liao YB, Meng Y, Zhao ZG, Zuo ZL, Li YJ, Xiong TY, Cao JY, Xu YN, Feng Y, Chen M. Meta-analysis of the effectiveness and safety of transcatheter aortic valve implantation without balloon predilation. doi:10.1016/j.amjcard.2016.02.036.
24. Pagnesi M, Jabbour RJ, Latib A, Kawamoto H, Tanaka A, Regazzoli D, Mangieri A, Montalto C, Ancona M, Giannini F, Chieffo A, Montorfano M, Monaco F, Castiglioni A, Alfieri O, Colombo A. Usefulness of predilatation prior to transcatheter aortic valve implantation. doi:10.1016/j.amjcard.2016.04.018.
25. Leclercq F, Labour J, de Champfleur N, Lattuca B, Gandet T, Macia JC, Agullo A, Schmutz L, Gervasoni R, Vernhet H, Albat B, Cayla G. Periprocedural cerebral ischemic events with TAVI performed without prior balloon dilatation of the aortic valve: a pilot prospective study. Circulation. 2015;132:A 11735.
26. Transcatheter aortic valve implantation without predilation (SIMPLIFy TAVI): ClinicalTrials.gov Identifier:NCT01539746.
27. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, for the PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. doi:10.1056/NEJMoa1514616.

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Annexe 3 :

frontiers in Cardiovascular Medicine

REVIEW
published: 18 July 2018
doi: 10.3389/fcvm.2018.00096

TAVI: Simplification Is the Ultimate Sophistication

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Since its introduction in 2002, TAVI has evolved dramatically and is now standard of care for intermediate risk patients when the femoral approach can be implemented safely. The development of innovative transcatheter heart valves (THVs) and refinement of technical skills have contributed to the decrease in complication rates associated with TAVI[4]. Increased experience, smaller sheaths, rigorous pre-procedural planning and improved vascular closing techniques have resulted in markedly lower rates of vascular complications. The next step is the simplification of the procedure, which should contribute to a further decrease in complications, and also reduce procedural time, hospital stay as well as staff workload and costs. Moving to conscious sedation, no predilatation, no temporary pace maker and use of the radial approach as the contralateral approach are all instrumental in achieving this ultimate refinement.

Keywords: TAVI, simplification, minimalist, vascular complications, temporary pace maker, hospital stay duration

OPEN ACCESS

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Specialty section:
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *10 March 2018*
Accepted: *29 June 2018*
Published: *18 July 2018*

Citation:
Akodad M and Lefèvre T (2018) TAVI: Simplification Is the Ultimate Sophistication. Front. Cardiovasc. Med. 5:96. doi: 10.3389/fcvm.2018.00096

INTRODUCTION

Since the first successful procedure was carried out in 2002 (1), transcatheter aortic valve implantation (TAVI) has gradually been established as an alternative to conventional surgery in patients with severe aortic stenosis contra-indicated to surgery or at high surgical risk (2). In 2017, during the last ESC meeting, TAVI indications were extended to intermediate risk patients when the transfemoral approach (TFA) is feasible (3).

Improvements in technique, devices, operator's experience, and patient selection have contributed to a dramatic decrease in procedural complications, thus allowing further technical simplification at every step of the procedure (4–9). In this paper, our aim is to describe how to simplify the technique at each stage of the procedure in order to turn it into a "PCI-like" procedure and to discuss how this may improve TAVI outcomes.

PRE-PROCEDURAL EVALUATION AND PROCEDURAL SETTING

Patient clinical and anatomical criteria may influence per- and post- procedural outcomes. Therefore, a truly minimalist approach should be considered only when femoral access is possible. Recently, Barbalios et al. compared minimalist TAVI performed in the catheterization laboratory to standard TAVI performed in the hybrid room demonstrating shorter procedure and intensive care unit time, as well as reduced hospitalization duration and costs in the minimalist approach group without differences in terms of short- and long-term survival (10).

Multislice CT (MSCT) is instrumental in procedural simplification. Image quality and optimal analysis are therefore crucial for anticipating the potential difficulty of the procedure as well as for optimal valve selection and working view. The role of MSCT has also been central in allowing a shift from general anesthesia to conscious sedation by obviating the need for transesophageal echocardiography (TOE) during the procedure. MSCT became the gold standard for evaluation of the aortic root in our center in 2009.

The use of the TRA for preprocedural evaluation of the coronary arteries is also part of the simplification process. It helps not only to reduce the risk of vascular complications related to the screening phase, but also to assess femoral access by performing a selective bilateral iliac injection using a long multipurpose catheter. Recently, screening of coronary artery disease and ad hoc percutaneous coronary intervention (PCI) during TAVI has been described by Barbanti et al. showing to be feasible without increased periprocedural complications (11).

A minimalist approach can be performed in routine practice with two operators, two nurses and an anesthesiologist (**Figure 1**). A cardiac surgeon and an echocardiographist are not mandatory in the room but should be available.

FROM GENERAL ANESTHESIA TO CONSCIOUS SEDATION

Although the first in-man TAVI cases in Rouen were initially performed on conscious sedation (1), the procedure was commonly carried out under general anesthesia between 2002 and 2008 in Europe. It remains standard practice in the majority of cases in North America (12). However, it was Alain Cribier's idea that TAVI should be a "PCI- like" procedure. Potential advantages of general anesthesia are patient's procedural comfort, possibility of using TOE and rapid conversion to surgery when complications occur (13–15). Conversely, many issues are related to general anesthesia such as hemodynamic instability, higher need for inotropic drugs, higher risk of bleeding, increased risk of pulmonary infection, extubation difficulty or delay in patients with chronic pulmonary disease, late complication identification such as stroke or aortic complications and finally, longer procedural duration, hospital stay, higher staff workload, and global costs (16–18). In the France 2 and the France TAVI registries, the adoption of local anesthesia with conscious sedation has progressively increased from 30% in 2010 to 70% in 2017 (15, 19). In a recent meta-analysis, outcomes of both approaches were similar with respect to in-hospital mortality, conversion to open-heart surgery, major vascular complications, acute kidney failure and stroke (17). Cross-over to general anesthesia was observed in only 6%. Conversely, catecholamine requirement and transfusion were less frequent in patients on conscious sedation, and duration of intensive care unit and global hospital stay was also shorter (17, 20, 21). No difference concerning neurocognitive outcomes was highlighted between both approaches (21).

Data from registries demonstrated the feasibility, safety, and cost-effectiveness of local anesthesia with conscious sedation in comparison to general anesthesia, with potential advantages in terms of bleeding and hospitalization length. It has been adopted as the default approach in our center since April 2009.

FROM SURGICAL CUT DOWN TO PERCUTANEOUS ACCESS

Initially, TAVI procedures were performed exclusively via surgical cut down (1). Over the past decade, sheath diameter has been gradually reduced to 14–16 French with the last generation percutaneous heart valves (**Figure 2**). TFA is currently the default access route, with superior outcomes than transapical route and other transvascular approaches as carotid, aortic, axillary, and caval-aortic. Alternative transvascular routes may be considered anly in case of unsuitable femoral access (22).

Percutaneous closure has been progressively adopted in routine practice in most centers for TF TAVI procedures (23). Indeed, even though the surgical approach has been reported to be associated with a low rate of vascular complications and to provide a more direct control of haemostasis (24), percutaneous closure is a less invasive technique and may result in shorter hospital stay (25). With the refinement of the TAVI procedure, better patient preprocedural screening, increased operator experience, and device improvement, the percutaneous approach has become more simple, less time consuming, thus allowing a reduction in staff workload. The Prostar technique was introduced in our center in 2009 and we moved progressively to Proglide (Abbott Vascular Devices, Redwood City, CA, United States) preclosing in 2015-2016 (26) because this technique was simpler and less costly. In 2016, a lower risk of vascular complications was reported with the use of 2 Proglide devices in comparison with Prostar (27). New collagen-based closure devices were recently described in TAVI procedure as the MANTA closure device with similar results than suture based closure devices (28).

In addition to the selection of the most appropriate percutaneous device, the percutaneous technique should be rigorous in order to limit access site complications. Indeed, the common femoral artery puncture site should be carefully selected on the CT-scan or angiography before the procedure. During the procedure, puncture should be performed under angiographic or ultra-sound guidance at the center of the anterior arterial wall (29). Percutaneous closure devices should be subsequently deployed as previously described (30).

Thus, percutaneous transfemoral access is as safe as the surgical approach and feasible in the majority of cases with a very high rate of success after the learning phase. Most vascular complications can be managed percutaneously. It is an essential component of TAVI's simplification process allowing early discharge.

Abbreviations: BAV, balloon aortic valvuloplasty; CCU, conventional cardiology unit; ICU, intensive care unit; LV, left ventricle; MP, multipurpose; MSCT, multislice CT; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; TFA, transfemoral approach; TOE, transesophagal echocardiography; TRA, transradial approach.

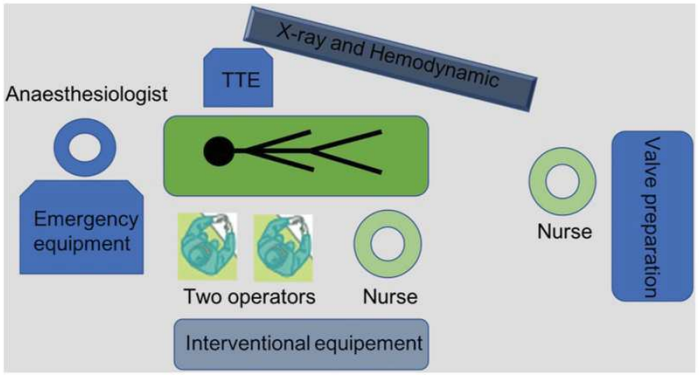


FIGURE 1 | Equipment and procedural set-up for a "minimalist" TAVI procedure.

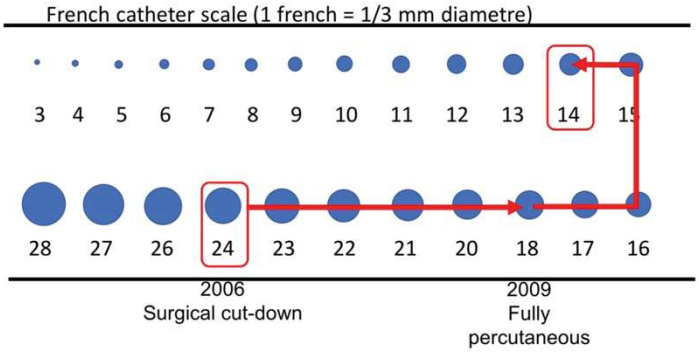


FIGURE 2 | Sheath size from first to last generation devices.

FROM CONTRALATERAL FEMORAL ACCESS TO RADIAL ACCESS

Although vascular complications dramatically decreased in parallel with enhanced operator experience, availability of low profile sheaths and better patient selection, 25–30% of these complications occurred at the contralateral femoral access site, (9). Therefore, using the TRA as a secondary access appears to be very promising (29–31). We have been using this approach since 2016 and have observed a 50% reduction in vascular complications. The radial artery (right or left) is punctured and a 40 cm 6 Fr hydrophilic sheath with a side port for blood pressure measurement is subsequently inserted through the radial artery. A 125 4 or 5 Fr multipurpose (MP) catheter is advanced over a standard 0.35 guide wire to the common iliac artery in order to obtain a reference image and guide the puncture. After the puncture, the MP catheter is retrieved and a pig-tail is advanced in the ascending aorta via the 0.35 guide wire to perform aortography before and after TAVI. At the end of the procedure, prior to access closure, the MP catheter is re-advanced to the common femoral artery in order to check the final result of the closure (29). In cases of vascular complication, a long 120 cm 5 Fr catheter (Optimed, Germany) can be positioned in the common femoral artery to perform femoral artery balloon inflation or stent implantation. In rare cases where a covered stent is needed, a larger balloon can be used through the Optimed catheter in order to close temporarily the iliac or femoral artery, while a cross-over femoral approach is implemented (29). Indeed, in our practice, even if the radial secondary access is our default approach, the controlateral femoral access should be available immediately in case of failure or emergent need of cross-over.

Therefore, by reducing contralateral vascular complications and simplifying the procedure, TRA will probably follow the predominant tendency observed in other interventional

cardiology settings and become the gold standard contralateral approach for TAVI.

FROM VENOUS STIMULATION TO LV GUIDE WIRE PACING

During balloon valvuloplasty (BAV) or balloon expandable TAVI procedures, rapid ventricular pacing is mandatory. Traditionally, rapid pacing is performed through a venous access with temporary pacemaker implantation (1). However, this technique may be challenging in anatomic variations and may lead to increased X-ray exposure and complications (32) such as hematoma, arterio-venous fistula, thrombosis or right ventricle perforation. Recently, rapid ventricular pacing through the left ventricle guide wire has been described as a way of simplifying the procedure by eliminating the need for additional vascular access during TAVI (33). This approach was adopted in 2016 in our center. Briefly, a 22 G needle is inserted subcutaneously near the femoral sheath. Alligator clips are then connected to the left ventricle guide wire (negative clip) and to the needle (positive clip) following insertion of the delivery system close to the aortic valve. The rapid pacing is then tested using maximal output and minimal sensitivity (**Figure 3**). Valve implantation is then carried out under rapid pacing. In the presence of high-degree conduction disturbance, stimulation can be performed with this technique while a temporary pacemaker is inserted through a venous access, more frequently through brachial vein access to limit femoral vascular complications.

This new technique has been shown to be feasible and safe, allowing stable stimulation with a low rate of complications and a potential reduction in procedural time. A randomized trial comparing left ventricle guide wire rapid pacing to conventional pacing (Easy TAVI) is ongoing in France (NCT02781896).

VALVE IMPLANTATION WITHOUT PREDILATION

In the early days of TAVI, BAV was considered a mandatory step. However BAV have been shown to be associated with a higher risk of cerebral embolization, and severe acute aortic regurgitation may occur after predilatation in up to 3% of cases. TAVI without BAV was evaluated for the first time in 2011 by Grübe et al. (34) and was shown to be feasible in non-randomized studies (35, 36). Currently, improvements in new generation devices including paravalvular skirts, the ability of repositioning of the valve, lower profile of delivery system, and of the prosthesis provide more favorable outcomes (22). Therefore, BAV seems no longer essential during TAVI procedures, and consequently, TAVI without predilation is routinely implemented in many centers.

We moved progressively to this approach between 2012 and 2015 in our center. Today, more than 90% of cases are performed without predilatation. Only very complex anatomies or highly calcified valves are predilated before valve deployment (5–10%). Post dilatation is performed mainly after self-expandable valve deployment in the presence of significant paravalvular leak or transvalvular gradient (10–15%).

Thus, avoiding balloon predilatation may reduce complication rates, decrease the need for permanent pacemaker and reduce procedural time. A large randomized trial (37) with the Sapien 3 valve is on-going in France (NCT02729519).

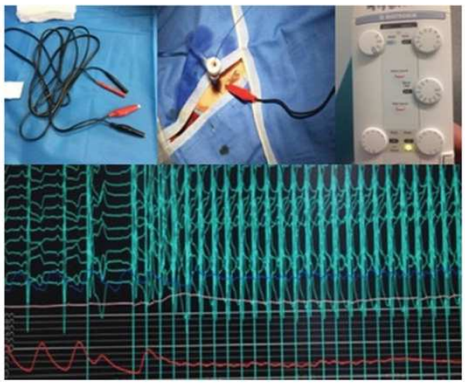


FIGURE 3 | From left to right and up to down: Alligator clips with negative clip (black) and positive clip (red). After insertion of Sheath, a 22G needle is inserted subcutaneously through the skin, close to the femoral sheath and the positive clip is connected to the needle while the negative clip is connected to the guidewire. Setting of the temporary pacemaker with maximal output and minimal sensitivity. Pacing efficacy at 180 beats per minute with the LV wire and drop in blood pressure.

TABLE 1 | Current outcomes of early discharge after TAVI.

Study	Patients	Early discharge, n (%)	Timing of early discharge	30-days mortality, n (%)	Rehospitalization within 30-days, n (%)
Durand et al. (40)	337	121 (36)	Within 3 days	0 (0)	4 (3.3)
Noad et al. (41)	120	26 (21.7)	Same/next day	0 (0)	1 (3.84)
Serletis-Bizios et al. (42)	130	76 (59)	Within 3 days	1 (1.3)	3 (3.94)
Lauck et al. (43)	393	150 (38.2)	Within 2 days	1 (0.7)	12 (8)

POST-PROCEDURE MANAGEMENT:

From Intensive Care Unit (ICU) to Conventional Cardiology Unit (CCU)

After TAVI, systematic close monitoring with special attention to hemodynamic and cardiac rhythm is mandatory to allow early detection of periprocedural complications. In many centers, monitoring is performed for at least 12 to 24 h in the ICU before transferring the patient to a CCU after clinical and paraclinical status re-assessment. Recently, TAVI without subsequent ICU admission has been evaluated and has been shown to be feasible and safe in selected patients after rigorous preprocedural and postprocedural evaluation (38). Indeed, this new strategy adopted in our center in 2017 may obviate ICU admission in up to one third of cases and should be considered a part of the "minimalist" approach.

Short Hospitalization

Early discharge was evaluated in the literature demonstrating safety in patients with hospitalization duration shorter than 48 h (39). Indeed, the median length of hospitalization was 1 day in the early discharge group with no differences between early discharge and discharge after 48 h in terms of 1-month mortality, stroke and readmission. A "minimalistic" TAVI procedure with local anesthesia, no predilatation, urinary catheter avoidance and early removal of temporary pacemaker was predictive of early discharge in this study. Current outcomes of early discharge after TAVI are summarized in **Table 1.** Shortening hospital stay is also an essential component of the TAVI simplification process with a potential reduction in procedural costs and need for rehabilitation but may be studied in large studies to ensure safety without increased risk of outcomes or readmission.

CONCLUSION

TAVI simplification has already been adopted in routine practice in experienced centers, resulting in a low rate of complications, shorter procedural time, improved patient comfort, as well as decreased costs and staff workload. However, rigorous patient selection, and risk stratification are key factors in ensuring successful "PCI-like" procedures. On-going randomized trials may confirm preliminary results, thus leading to a "simple" but not "simpler" procedure in the near future with lower profile devices.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* (2002) 106:3006–8. doi: 10.1161/01.CIR.0000047200.36165.B8
2. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* (2012) 42:S1–44. doi: 10.1093/ejcts/ezs455
3. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. ESC Scientific Document Group, ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* (2017) 38:2739–91. doi: 10.1093/eurheartj/ehx391
4. Auffret V, Lefèvre T, Van Belle E, Eltchaninoff H, Iung B, Koning R, et al. Temporal trends in transcatheter aortic valve replacement in France: FRANCE 2 to FRANCE TAVI. *JACC* 70:42–55. doi: 10.1016/j.jacc.2017.04.053
5. Durand E, Borz B, Godin M, Tron C, Litzler PY, Bessou JP, et al. Transfemoral aortic valve replacement with the Edwards SAPIEN and Edwards SAPIEN XT prosthesis using exclusively local anesthesia and fluoroscopic guidance: feasibility and 30-day outcomes. *JACC Cardiovasc Interv.* (2012) 5:461–7. doi: 10.1016/j.jcin.2012.01.018
6. Landes U, Barsheshet A, Finkelstein A, Guetta V, Assali A, Halkin A, et al. Temporal trends in transcatheter aortic valve implantation, 2008-2014: patient characteristics, procedural issues, and clinical outcome. *Clin Cardiol.* (2017) 40:82–8. doi: 10.1002/clc.22632
7. Vahl TP, Kodali SK, Leon MB. Transcatheter aortic valve replacement 2016: a modern-day "Through the Looking-Glass" Adventure. *JACC* (2016) 67:1472–87. doi: 10.1016/j.jacc.2015.12.059
8. Kodali S, Thourani VH, White J, Malaisrie SC, Lim S, Greason KL, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J.* (2016) 37:2252–62. doi: 10.1093/eurheartj/ehw112
9. Allende R, Urena M, Cordoba JG, Ribeiro HB, Amat-Santos I, DeLarochellière R, et al. Impact of the use of transradial versus transfemoral approach as secondary access in transcatheter aortic valve implantation procedures. *Am J Cardiol.* (2014) 114:1729–34. doi: 10.1016/j.amjcard.2014.09.009
10. Babaliaros V, Devireddy C, Lerakis S, Leonardi R, Iturra SA, Mavromatis K, et al. Comparison of transfemoral transcatheter aortic valve replacement performed in the catheterization laboratory (minimalist approach) versus hybrid operating room (standard approach): outcomes and cost analysis. *JACC Cardiovasc Interv.* (2014) 7:898–904. doi: 10.1016/j.jcin.2014.04.005
11. Barbanti M, Todaro D, Costa G, Pilato G, Picci A, Gulino S, et al. Optimized screening of coronary artery disease with invasive coronary angiography and Ad Hoc percutaneous coronary intervention during transcatheter aortic valve replacement. *Circ Cardiovasc Interv.* (2017) 10:e005234. doi: 10.1161/CIRCINTERVENTIONS.117.005234
12. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, 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. *JACC* (2010) 55:1080–90. doi: 10.1016/j.jacc.2009.12.014
13. Villablanca PA, Mohananey D, Nikolic K, Bangalore S, Slovut DP, Mathew V, et al. Comparison of local versus general anesthesia in patients undergoing transcatheter aortic valve replacement: a meta-analysis. *Catheter Cardiovasc Interv.* (2018) 91:330–42 doi: 10.1002/ccd.27207
14. Maas EHA, Pieters BMA, Van de Velde M, Rex S. General or local anesthesia for TAVI? a systematic review of the literature and meta-analysis. *Curr Pharm Des.* (2016) 22:1868–78. doi: 10.2174/1381612822666151208121825
15. Oguri A, Yamamoto M, Mouillet G, Gilard M, Laskar M, Eltchaninoff H, et al. FRANCE 2 Registry Investigators, Clinical outcomes and safety of transfemoral aortic valve implantation under general versus local anesthesia: subanalysis of the French Aortic National CoreValve and Edwards 2 registry. *Circ Cardiovasc Interv.* (2014) 7:602–10. doi: 10.1161/CIRCINTERVENTIONS.113.000403

16. Fröhlich GM, Lansky AJ, Webb J, Roffi M, Toggweiler S, Reinthaler M, et al. Local versus general anesthesia for transcatheter aortic valve implantation (TAVR) – systematic review and meta-analysis. *BMC Med.* (2014) 12: 41. doi: 10.1186/1741-7015-12-41
17. Ehret C, Rossaint R, Foldenauer AC, Stoppe C, Stevanovic A, Dohms K, et al. Is local anaesthesia a favourable approach for transcatheter aortic valve implantation? A systematic review and meta-analysis comparing local and general anaesthesia. *BMJ Open* (2017) 7:e016321. doi: 10.1136/bmjopen-2017-016321
18. Hosoba S, Yamamoto M, Shioda K, Sago M, Koyama Y, Shimura T, et al. Safety and efficacy of minimalist approach in transfemoral transcatheter aortic valve replacement: insights from the Optimized transCathEter vAlvular interventioN-Transcatheter Aortic Valve Implantation (OCEAN-TAVI) registry. *Interact Cardiovasc Thorac Surg.* (2017) 26:420–4. doi: 10.1093/icvts/ivx355
19. Auffret V, Bedossa M, Boulmier D, Verhoye JP, Ruggieri VG, Koning R, 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. doi: 10.1016/j.lpm.2015.05.004
20. Yamamoto M, Meguro K, Mouillet G, Bergoend E, Monin JL, Lim P, et al. Effect of local anesthetic management with conscious sedation in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol.* (2013) 111:94–9. doi: 10.1016/j.amjcard.2012.08.053
21. Mayr NP, Hapfelmeier A, Martin K, Kurz A, van der Starre P, Babik B, et al. Comparison of sedation and general anaesthesia for transcatheter aortic valve implantation on cerebral oxygen saturation and neurocognitive outcome†. *Br J Anaesth.* (2016) 116:90–9. doi: 10.1093/bja/aev294
22. Figulla HR, Webb JG, Lauten A, Feldman T. The transcatheter valve technology pipeline for treatment of adult valvular heart disease. *Eur Heart J.* (2016) 37:2226–39. doi: 10.1093/eurheartj/ehw153
23. Webb J, Gerosa G, Lefèvre T, Leipsic J, Spence M, Thomas M, et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. *JACC* (2014) 64:2235–43. doi: 10.1016/j.jacc.2014.09.026
24. Leclercq F, Akodad M, Macia JC, Gandet T, Lattuca B, Schmutz L, et al. Vascular complications and bleeding after transfemoral transcatheter aortic valve implantation performed through open surgical access. *Am J Cardiol.* (2015) 116:1399–404. doi: 10.1016/j.amjcard.2015.08.003
25. Kadakia MB, Herrmann HC, Desai ND, Fox Z, Ogbara J, Anwaruddin S, et al. Factors associated with vascular complications in patients undergoing balloon-expandable transfemoral transcatheter aortic valve replacement via open versus percutaneous approaches. *Circ Cardiovasc Interv.* (2014) 7:570–6. doi: 10.1161/CIRCINTERVENTIONS.113.001030
26. Barbash IM, Barbanti M, Webb J, Molina-Martin De Nicolas J, Abramowitz Y, et al. Comparison of vascular closure devices for access site closure after transfemoral aortic valve implantation. *Eur Heart J.* (2015) 36:3370–9. doi: 10.1093/eurheartj/ehv417
27. Julinda M, David J, Mohamed AW, D RK, Hans T, Nina S, et al. One-year outcomes with two suture-mediated closure devices to achieve access-site haemostasis following transfemoral transcatheter aortic valve implantation. *EuroIntervention* (2016) 12:1298–304. doi: 10.4244/EIJV12I10A213
28. De Palma R, Settergren M, Rück A, Linder R, Saleh N. Impact of percutaneous femoral arteriotomy closure using the MANTATM device on vascular and bleeding complications after transcatheter aortic valve replacement. *Catheter Cardiovasc Interv.* (2018). doi: 10.1002/ccd.27595. [Epub ahead of print].
29. Sawaya FJ, Lefèvre T, Spaziano M, Roy A, Fernandez L, Garot P, et al. Transfemoral transcatheter aortic valve implantation: how minimalistic can we become? *J Interv Cardiol.* (2016) 29:628–31. doi: 10.1111/joic.12348
30. Dato I, Burzotta F, Trani C, Crea F, Ussia GP. Percutaneous management of vascular access in transfemoral transcatheter aortic valve implantation. *World J Cardiol.* (2014) 6:836–46. doi: 10.4330/wjc.v6.i8.836
31. Curran H, Chieffo A, Buchanan GL, Bernelli C, Montorfano M, Maisano F, et al. A comparison of the femoral and radial crossover techniques for vascular access management in transcatheter aortic valve implantation: the Milan experience. *Catheter Cardiovasc Interv.* (2014) 83:156–61. doi: 10.1002/ccd.24913
32. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J.* (2009) 157:132–40. doi: 10.1016/j.ahj.2008.08.023
33. Faurie B, Abdellaoui M, Wautot F, Staat P, Champagnac D, Wintzer-Wehekind J, et al. Rapid pacing using the left ventricular guidewire: reviving an old technique to simplify BAV and TAVI procedures. *Cathet Cardiovasc Intervent.* (2016) 88:988–93. doi: 10.1002/ccd.26666
34. Grube E, Naber C, Abizaid A, Sousa E, Mendiz O, Lemos P, et al. Feasibility of transcatheter aortic valve implantation without balloon pre-dilation: a pilot study. *JACC Cardiovasc Interv.* (2011) 4:751–7. doi: 10.1016/j.jcin.2011.03.015
35. Fiorina C, Maffeo D, Curello S, Lipartiti F, Chizzola G, D'Aloia A, et al. Direct transcatheter aortic valve implantation with self-expandable bioprosthesis: feasibility and safety. *Cardiovasc Revasc Med* (2014) 15:200–3. doi: 10.1016/j.carrev.2014.03.005
36. Spaziano M, Sawaya F, Chevalier B, Roy A, Neylon A, Garot P, et al. Comparison of systematic predilation, selective predilation, and direct transcatheter aortic valve implantation with the SAPIEN S3 Valve. *Can J Cardiol.* (2017) 33:260–8. doi: 10.1016/j.cjca.2016.09.007
37. Leclercq F, Robert P, Labour J, Lattuca B, Akodad M, Macia JC, et al. Prior balloon valvuloplasty versus DIRECT transcatheter Aortic Valve Implantation (DIRECTAVI): study protocol for a randomized controlled trial. *Trials* (2017) 18:303. doi: 10.1186/s13063-017-2036-y
38. Leclercq F, Iemmi A, Lattuca B, Macia JC, Gervasoni R, Roubille F, et al. Feasibility and safety of transcatheter aortic valve implantation performed without intensive care unit admission. *Am J Cardiol.* (2016) 118:99–106. doi: 10.1016/j.amjcard.2016.04.019
39. Mallikethi-Reddy S, Akintoye E, Telila T, Sudhakar R, Jagadeesh K, Briasoulis A, et al. Transcatheter aortic valve implantation in the United States: Predictors of early hospital discharge. *J Interv Cardiol.* (2017) 30:149–55. doi: 10.1111/joic.12373
40. Durand E, Eltchaninoff H, Canville A, Bouhzam N, Godin M, Tron C, et al. Feasibility and safety of early discharge after transfemoral transcatheter aortic valve implantation with the Edwards SAPIEN-XT prosthesis. *Am J Cardiol.* (2015) 115:1116–22. doi: 10.1016/j.amjcard.2015.01.546
41. Noad RL, Johnston N, McKinley A, Dougherty M, Nzewi OC, Jeganathan R, et al. A pathway to earlier discharge following TAVI: assessment of safety and resource utilization. *Catheter Cardiovasc Interv.* (2016) 87:134–42. doi: 10.1002/ccd.26005
42. Serletis-Bizios A, Durand E, Cellier G, Tron C, Bauer F, Glinel B, et al. A prospective analysis of early discharge after transfemoral transcatheter aortic valve implantation. *Am J Cardiol.* (2016) 118:866–72. doi: 10.1016/j.amjcard.2016.06.035
43. Lauck SB, Wood DA, Baumbusch J, Kwon JY, Stub D, Achtem L, et al. Vancouver transcatheter aortic valve replacement clinical pathway: minimalist approach, standardized care, and discharge criteria to reduce length of stay. *Circ Cardiovasc Qual Outcomes* (2016) 9:312–21. doi: 10.1161/CIRCOUTCOMES.115.002541

Conflict of Interest Statement: TL is proctor for edwards and Abbott vascular MA received research grants from Edwards Lifescience and Medtronic.

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BIBLIOGRAPHIE

1. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003 Jul;24(13):1231–43.
2. Lindman BR, Clavel M-A, Mathieu P, Iung B, Lancellotti P, Otto CM, et al. Calcific aortic stenosis. Nat Rev Dis Primers. 2016 03;2:16006.
3. Carabello BA, Paulus WJ. Aortic stenosis. Lancet. 2009 Mar 14;373(9667):956–66.
4. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep 21;38(36):2739–91.
5. Bohbot Y, Rusinaru D, Tribouilloy C. Rétrécissement aortique calcifié : aspects cliniques, exploration échocardiographique et prise en charge thérapeutique. Revue Francophone des Laboratoires. 2017 Jun 1;2017(493):33–9.
6. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002 Dec 10;106(24):3006
7. Nguyen V, Michel M, Eltchaninoff H, Gilard M, Dindorf C, Iung B, et al. Implementation of Transcatheter Aortic Valve Replacement in France. J Am Coll Cardiol. 2018 17;71(15):1614–27.
8. Benamer H, Auffret V, Cayla G, Chevalier B, Dupouy P, Eltchaninoff H, et al. Position paper of French Interventional Group (GACI) for TAVI in France in 2018. Ann Cardiol Angeiol (Paris). 2018 Dec;67(6):455–65.
9. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Thorac Cardiovasc Surg. 2013 Jan;145(1):6–23.
10. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. New England Journal of Medicine. 2011 Jun 9;364(23):2187–98.

11. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. New England Journal of Medicine. 2016 Apr 28;374(17):1609–20.

12. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2017 06;376(14):1321–31.

13. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019 02;380(18):1695–705.

14. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. New England Journal of Medicine. 2019 May 2;380(18):1706–15.

15. Puri R, Iung B, Cohen DJ, Rodés-Cabau J. TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. Eur Heart J. 2016 Jul 21;37(28):2217–25

16. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2019 Mar 14;40(11):902–10.

17. Darden D, Nishimura M, Sharim J, Maisel A. An update on the use and discovery of prognostic biomarkers in acute decompensated heart failure. Expert Rev Mol Diagn. 2019 Sep 27;1–11.

18. Chopra V, Eagle KA. Cardiac biomarkers in the diagnosis, prognosis and management of coronary artery disease: a primer for internists. Indian J Med Sci. 2010 Dec;64(12):561–73.

19. Toutouzas K, Stathogiannis K, Latsios G, Synetos A, Drakopoulou M, Penesopoulou V, et al. Biomarkers in Aortic Valve Stenosis and their Clinical Significance in Transcatheter Aortic Valve Implantation. Curr Med Chem. 2019;26(5):864–72.

20. Small A, Kiss D, Giri J, Anwaruddin S, Siddiqi H, Guerraty M, et al. Biomarkers of Calcific Aortic Valve Disease. Arterioscler Thromb Vasc Biol. 2017 Apr;37(4):623–32.

21. Yalta K, Palabiyik O, Gurdogan M, Gurlertop Y. Serum copeptin might improve risk stratification and management of aortic valve stenosis: a review of pathophysiological insights and practical implications. Ther Adv Cardiovasc Dis [Internet]. 2019 Feb 8 [cited 2019 Sep 30];13.

22. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, 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 Mar 16;55(11):1080–90.

23. Villablanca PA, Mohananey D, Nikolic K, Bangalore S, Slovut DP, Mathew V, et al. Comparison of local versus general anesthesia in patients undergoing transcatheter aortic valve replacement: A meta-analysis. Catheter Cardiovasc Interv. 2017 Jul 24;

24. Maas EHA, Pieters BMA, Van de Velde M, Rex S. General or Local Anesthesia for TAVI? A Systematic Review of the Literature and Meta-Analysis. Curr Pharm Des. 2016;22(13):1868–78.

25. Oguri A, Yamamoto M, Mouillet G, Gilard M, Laskar M, Eltchaninoff H, et al. Clinical outcomes and safety of transfemoral aortic valve implantation under general versus local anesthesia: subanalysis of the French Aortic National CoreValve and Edwards 2 registry. Circ Cardiovasc Interv. 2014 Aug;7(4):602–10.

26. Ehret C, Rossaint R, Foldenauer AC, Stoppe C, Stevanovic A, Dohms K, et al. Is local anaesthesia a favourable approach for transcatheter aortic valve implantation? A systematic review and meta-analysis comparing local and general anaesthesia. BMJ Open. 2017 Sep 25;7(9):e016321.

27. Auffret V, Lefevre T, Van Belle E, Eltchaninoff H, Iung B, Koning R, et al. Temporal Trends in Transcatheter Aortic Valve Replacement in France: FRANCE 2 to FRANCE TAVI. J Am Coll Cardiol. 2017 Jul 4;70(1):42–55.

28. Yamamoto M, Meguro K, Mouillet G, Bergoend E, Monin J-L, Lim P, et al. Effect of local anesthetic management with conscious sedation in patients undergoing transcatheter aortic valve implantation. Am J Cardiol. 2013 Jan 1;111(1):94–9.

29. Mayr NP, Hapfelmeier A, Martin K, Kurz A, van der Starre P, Babik B, et al. Comparison of sedation and general anaesthesia for transcatheter aortic valve

implantation on cerebral oxygen saturation and neurocognitive outcome†. Br J Anaesth. 2016 Jan;116(1):90–9.

30. Kadakia MB, Herrmann HC, Desai ND, Fox Z, Ogbara J, Anwaruddin S, et al. Factors associated with vascular complications in patients undergoing balloon-expandable transfemoral transcatheter aortic valve replacement via open versus percutaneous approaches. Circ Cardiovasc Interv. 2014 Aug;7(4):570–6.

31. Barbash IM, Barbanti M, Webb J, Molina-Martin De Nicolas J, Abramowitz Y, Latib A, et al. Comparison of vascular closure devices for access site closure after transfemoral aortic valve implantation. Eur Heart J. 2015 Dec 14;36(47):3370–9.

32. Leclercq F, Akodad M, Macia J-C, Gandet T, Lattuca B, Schmutz L, et al. Vascular Complications and Bleeding After Transfemoral Transcatheter Aortic Valve Implantation Performed Through Open Surgical Access. Am J Cardiol. 2015 Nov 1;116(9):1399–404.

33. Toggweiler S, Gurvitch R, Leipsic J, Wood DA, Willson AB, Binder RK, et al. Percutaneous aortic valve replacement: vascular outcomes with a fully percutaneous procedure. J Am Coll Cardiol. 2012 Jan 10;59(2):113–8.

34. Webb J, Gerosa G, Lefèvre T, Leipsic J, Spence M, Thomas M, et al. Multicenter Evaluation of a Next-Generation Balloon-Expandable Transcatheter Aortic Valve. Journal of the American College of Cardiology. 2014 Dec 2;64(21):2235–43.

35. Sawaya FJ, Lefèvre T, Spaziano M, Roy A, Fernandez L, Garot P, et al. Transfemoral Transcatheter Aortic Valve Implantation: How Minimalistic Can We Become? J Interv Cardiol. 2016 Dec;29(6):628–31.

36. Akodad M, Lefèvre T. TAVI: Simplification Is the Ultimate Sophistication. Front Cardiovasc Med. 2018;5:96.

37. Allende R, Urena M, Cordoba JG, Ribeiro HB, Amat-Santos I, DeLarochellière R, et al. Impact of the use of transradial versus transfemoral approach as secondary access in transcatheter aortic valve implantation procedures. Am J Cardiol. 2014 Dec 1;114(11):1729–34.

38. Dato I, Burzotta F, Trani C, Crea F, Ussia GP. Percutaneous management of vascular access in transfemoral transcatheter aortic valve implantation. World J Cardiol. 2014 Aug 26;6(8):836–46.

39. Curran H, Chieffo A, Buchanan GL, Bernelli C, Montorfano M, Maisano F, et al. A comparison of the femoral and radial crossover techniques for vascular access management in transcatheter aortic valve implantation: the Milan experience. Catheter Cardiovasc Interv. 2014 Jan 1;83(1):156–61.

40. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. Am Heart J. 2009 Jan;157(1):132–40.

41. Faurie B, Abdellaoui M, Wautot F, Staat P, Champagnac D, Wintzer-Wehekind J, et al. Rapid pacing using the left ventricular guidewire: Reviving an old technique to simplify BAV and TAVI procedures. Cathet Cardiovasc Intervent. 2016 Nov 15;88(6):988–93.

42. Grube E, Naber C, Abizaid A, Sousa E, Mendiz O, Lemos P, et al. Feasibility of transcatheter aortic valve implantation without balloon pre-dilation: a pilot study. JACC Cardiovasc Interv. 2011 Jul;4(7):751–7.

43. Fiorina C, Maffeo D, Curello S, Lipartiti F, Chizzola G, D'Aloia A, et al. Direct transcatheter aortic valve implantation with self-expandable bioprosthesis: feasibility and safety. Cardiovasc Revasc Med. 2014 Jun;15(4):200–3.

44. Spaziano M, Sawaya F, Chevalier B, Roy A, Neylon A, Garot P, et al. Comparison of Systematic Predilation, Selective Predilation, and Direct Transcatheter Aortic Valve Implantation With the SAPIEN S3 Valve. Can J Cardiol. 2017 Feb;33(2):260–8.

45. Deharo P, Jaussaud N, Grisoli D, Camus O, Resseguier N, Le Breton H, et al. Impact of Direct Transcatheter Aortic Valve Replacement Without Balloon Aortic Valvuloplasty on Procedural and Clinical Outcomes: Insights From the FRANCE TAVI Registry. JACC Cardiovasc Interv. 2018 Oct 8;11(19):1956–65.

46. Vahanian A, Himbert D. Transcatheter aortic valve implantation: could it be done without prior balloon valvuloplasty? JACC Cardiovasc Interv. 2011 Jul;4(7):758–9.

47. Eltchaninoff H, Cribier A, Tron C, Anselme F, Koning R, Soyer R, et al. Balloon aortic valvuloplasty in elderly patients at high risk for surgery, or inoperable. Immediate and mid-term results. Eur Heart J. 1995 Aug;16(8):1079–84.

48. Kahlert P, Al-Rashid F, Döttger P, Mori K, Plicht B, Wendt D, et al. Cerebral embolization during transcatheter aortic valve implantation: a transcranial Doppler study. Circulation. 2012 Sep 4;126(10):1245–55.

49. Nombela-Franco L, Webb JG, de Jaegere PP, Toggweiler S, Nuis R-J, Dager AE, et al. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. Circulation. 2012 Dec 18;126(25):3041–53.

50. Toutouzas K, Benetos G, Voudris V, Drakopoulou M, Stathogiannis K, Latsios G, et al. Pre-Dilatation Versus No Pre-Dilatation for Implantation of a Self-Expanding Valve in All Comers Undergoing TAVR: The DIRECT Trial. JACC Cardiovasc Interv. 2019 Apr 22;12(8):767–77.

51. Leclercq F, Robert P, Labour J, Lattuca B, Akodad M, Macia J-C, et al. Prior balloon valvuloplasty versus DIRECT transcatheter Aortic Valve Implantation (DIRECTAVI): study protocol for a randomized controlled trial. Trials 2017 Jul 4

52. Leclercq F, Iemmi A, Lattuca B, Macia J-C, Gervasoni R, Roubille F, et al. Feasibility and Safety of Transcatheter Aortic Valve Implantation Performed Without Intensive Care Unit Admission. Am J Cardiol. 2016 Jul 1;118(1):99–106.

53. Toggweiler S, Stortecky S, Holy E, Zuk K, Cuculi F, Nietlispach F, et al. The Electrocardiogram After Transcatheter Aortic Valve Replacement Determines the Risk for Post-Procedural High-Degree AV Block and the Need for Telemetry Monitoring. JACC Cardiovasc Interv. 2016 27;9(12):1269–76.

54. Barbanti M, Capranzano P, Ohno Y, Attizzani GF, Gulino S, Immè S, et al. Early discharge after transfemoral transcatheter aortic valve implantation. Heart. 2015 Sep;101(18):1485–90.

55. Barbanti M, Baan J, Spence MS, Iacovelli F, Martinelli GL, Saia F, et al. Feasibility and safety of early discharge after transfemoral transcatheter aortic valve implantation - rationale and design of the FAST-TAVI registry. BMC Cardiovasc Disord. 2017 Oct 10;17(1):259.

56. Barbanti M, van Mourik MS, Spence MS, Icovelli F, Martinelli GL, Muir DF, et al. Optimising patient discharge management after transfemoral transcatheter aortic valve implantation: the multicentre European FAST-TAVI trial. EuroIntervention. 2019 Jun 20;15(2):147–54.

57. Durand E, Eltchaninoff H, Canville A, Bouhzam N, Godin M, Tron C, et al. Feasibility and safety of early discharge after transfemoral transcatheter aortic valve implantation with the Edwards SAPIEN-XT prosthesis. Am J Cardiol. 2015 Apr 15;115(8):1116–22.

58. Wood DA, Lauck SB, Cairns JA, Humphries KH, Cook R, Welsh R, et al. The Vancouver 3M (Multidisciplinary, Multimodality, But Minimalist) Clinical Pathway Facilitates Safe Next-Day Discharge Home at Low-, Medium-, and High-Volume Transfemoral Transcatheter Aortic Valve Replacement Centers: The 3M TAVR Study. JACC Cardiovasc Interv. 2019 Mar 11;12(5):459–69.

59. Mok M, Nombela-Franco L, Dumont E, Urena M, DeLarochellière R, Doyle D, et al. Chronic obstructive pulmonary disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes, prognostic markers, and functional status changes. JACC Cardiovasc Interv. 2013 Oct;6(10):1072–84.

60. Yamamoto M, Hayashida K, Mouillet G, Hovasse T, Chevalier B, Oguri A, et al. Prognostic value of chronic kidney disease after transcatheter aortic valve implantation. J Am Coll Cardiol. 2013 Sep 3;62(10):869–77.

61. Ludman PF, Moat N, de Belder MA, Blackman DJ, Duncan A, Banya W, et al. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. Circulation. 2015 Mar 31;131(13):1181–90.

62. Chen C, Zhao Z-G, Liao Y-B, Peng Y, Meng Q-T, Chai H, et al. Impact of renal dysfunction on mid-term outcome after transcatheter aortic valve implantation: a systematic review and meta-analysis. PLoS ONE. 2015;10(3):e0119817.

63. Allende R, Webb JG, Munoz-Garcia AJ, de Jaegere P, Tamburino C, Dager AE, et al. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. Eur Heart J. 2014 Oct 7;35(38):2685–96.

64. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001 Mar;56(3):M146-156.

65. Schoenenberger AW, Stortecky S, Neumann S, Moser A, Jüni P, Carrel T, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). Eur Heart J. 2013 Mar;34(9):684–92.

66. Puls M, Sobisiak B, Bleckmann A, Jacobshagen C, Danner BC, Hünlich M, et al. Impact of frailty on short- and long-term morbidity and mortality after transcatheter aortic valve implantation: risk assessment by Katz Index of activities of daily living. EuroIntervention. 2014 Sep;10(5):609–19.

67. Green P, Arnold SV, Cohen DJ, Kirtane AJ, Kodali SK, Brown DL, et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER trial). Am J Cardiol. 2015 Jul 15;116(2):264–9.

68. Afilalo J, Lauck S, Kim DH, Lefèvre T, Piazza N, Lachapelle K, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. J Am Coll Cardiol. 2017 Aug 8;70(6):689–700.

69. González-Ferreiro R, Muñoz-García AJ, López-Otero D, Avanzas P, Pascual I, Alonso-Briales JH, et al. Prognostic value of body mass index in transcatheter aortic valve implantation: A “J”-shaped curve. International Journal of Cardiology. 2017 Apr 1;232:342–7.

70. Takagi H, Hari Y, Kawai N, Kuno T, Ando T, ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Meta-analysis of impact of liver disease on mortality after transcatheter aortic valve implantation. J Cardiovasc Med (Hagerstown). 2019 Apr;20(4):237–44.

71. Seiffert M, Conradi L, Gutwein A, Schön G, Deuschl F, Schofer N, et al. Baseline anemia and its impact on midterm outcome after transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 2017 Jan;89(1):E44–52.

72. Yamamoto M, Shimura T, Kano S, Kagase A, Kodama A, Sago M, et al. Prognostic Value of Hypoalbuminemia After Transcatheter Aortic Valve Implantation (from the Japanese Multicenter OCEAN-TAVI Registry). Am J Cardiol. 2017 Mar 1;119(5):770–7.

73. Hall C. NT-ProBNP: The Mechanism Behind the Marker. Journal of Cardiac Failure. 2005;11(5):S81–3.

74. Santaguida PL, Don-Wauchope AC, Oremus M, McKelvie R, Ali U, Hill SA, et al. BNP and NT-proBNP as prognostic markers in persons with acute decompensated heart failure: a systematic review. Heart Fail Rev. 2014 Aug;19(4):453–70.

75. Chin CWL, Djohan AH, Lang CC. The role of cardiac biochemical markers in aortic stenosis. Biomarkers. 2016;21(4):316–27.

76. Endicott KM, Amdur RL, Greenberg MD, Trachiotis GD. B-type Natriuretic Peptide Predicts Morbidity and Long-Term Mortality in Coronary Artery Bypass Grafting and Valve Surgery. Innovations (Phila). 2016 Dec;11(6):439–43.

77. Kefer J, Beauloye C, Astarci P, Renkin J, Glineur D, Dekleermaeker A, et al. Usefulness of B-type natriuretic peptide to predict outcome of patients treated by transcatheter aortic valve implantation. Am J Cardiol. 2010 Dec 15;106(12):1782–6.

78. Gotzmann M, Czauderna A, Aweimer A, Hehnen T, Bösche L, Lind A, et al. B-type natriuretic peptide is a strong independent predictor of long-term outcome after transcatheter aortic valve implantation. J Heart Valve Dis. 2014 Sep;23(5):537–44.

79. Koskinas KC, O'Sullivan CJ, Heg D, Praz F, Stortecky S, Pilgrim T, et al. Effect of B-type natriuretic peptides on long-term outcomes after transcatheter aortic valve implantation. Am J Cardiol. 2015 Nov 15;116(10):1560–5.

80. Himbert D, Vahanian A. Transcatheter aortic valve replacement for patients with heart failure. Heart Fail Clin. 2015 Apr;11(2):231–42.

81. Urena M, Webb JG, Eltchaninoff H, Muñoz-García AJ, Bouleti C, Tamburino C, et al. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. J Am Coll Cardiol. 2015 Feb 10;65(5):437–48.

82. Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. Circulation. 2013 Jun 11;127(23):2316–26.

83. Ribeiro HB, Lerakis S, Gilard M, Cavalcante JL, Makkar R, Herrmann HC, et al. Transcatheter Aortic Valve Replacement in Patients With Low-Flow, Low-Gradient Aortic Stenosis: The TOPAS-TAVI Registry. J Am Coll Cardiol. 2018 27;71(12):1297–308.

84. Barbash IM, Escarcega RO, Minha S, Ben-Dor I, Torguson R, Goldstein SA, et al. Prevalence and impact of pulmonary hypertension on patients with aortic stenosis who underwent transcatheter aortic valve replacement. Am J Cardiol. 2015 May 15;115(10):1435–42.

85. O'Sullivan CJ, Wenaweser P, Ceylan O, Rat-Wirtzler J, Stortecky S, Heg D, et al. Effect of Pulmonary Hypertension Hemodynamic Presentation on Clinical Outcomes in Patients With Severe Symptomatic Aortic Valve Stenosis Undergoing Transcatheter Aortic Valve Implantation: Insights From the New Proposed Pulmonary Hypertension Classification. Circ Cardiovasc Interv. 2015 Jul;8(7):e002358.

86. Bedogni F, Latib A, De Marco F, Agnifili M, Oreglia J, Pizzocri S, et al. Interplay between mitral regurgitation and transcatheter aortic valve replacement with the CoreValve Revalving System: a multicenter registry. Circulation. 2013 Nov 5;128(19):2145–53.

87. Barbanti M, Webb JG, Hahn RT, Feldman T, Boone RH, Smith CR, et al. Impact of preoperative moderate/severe mitral regurgitation on 2-year outcome after transcatheter and surgical aortic valve replacement: insight from the Placement of Aortic Transcatheter Valve (PARTNER) Trial Cohort A. Circulation. 2013 Dec 24;128(25):2776–84.

88. Harbaoui B, Montoy M, Charles P, Boussel L, Liebgott H, Girerd N, et al. Aorta calcification burden: Towards an integrative predictor of cardiac outcome after transcatheter aortic valve implantation. Atherosclerosis. 2016 Mar;246:161–8.

89. Rosa VEE, Lopes AS de SA, Accorsi TAD, Fernandes JRC, Spina GS, Sampaio RO, et al. EuroSCORE II and STS as mortality predictors in patients undergoing TAVI. Rev Assoc Med Bras (1992). 2016 Feb;62(1):32–7.

90. Arangalage D, Cimadevilla C, Alkhoder S, Chiampan A, Himbert D, Brochet E, et al. Agreement between the new EuroSCORE II, the Logistic EuroSCORE and the Society of Thoracic Surgeons score: implications for transcatheter aortic valve implantation. Arch Cardiovasc Dis. 2014 Jul;107(6–7):353–60.

91. Iung B, Laouénan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P, et al. Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. Heart. 2014 Jul;100(13):1016–23.

92. Seiffert M, Sinning J-M, Meyer A, Wilde S, Conradi L, Vasa-Nicotera M, et al. Development of a risk score for outcome after transcatheter aortic valve implantation. Clin Res Cardiol. 2014 Aug;103(8):631–40.

93. Lantelme P, Eltchaninoff H, Rabilloud M, Souteyrand G, Dupré M, Spaziano M, et al. Development of a Risk Score Based on Aortic Calcification to Predict 1-Year Mortality After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Imaging. 2019 Jan;12(1):123–32.

94. Ebashi S, Ebashi F, Kodama A. Troponin as the Ca++-receptive protein in the contractile system. J Biochem. 1967 Jul;62(1):137–8.

95. Ebashi S, Kodama A, Ebashi F. Troponin. I. Preparation and physiological function. J Biochem. 1968 Oct;64(4):465–77.

96. Katrukha IA. Human cardiac troponin complex. Structure and functions. Biochemistry Mosc. 2013 Dec;78(13):1447–65.

97. Adamcova M, Popelova-Lencova O, Jirkovsky E, Simko F, Gersl V, Sterba M. Cardiac troponins--Translational biomarkers in cardiology: Theory and practice of cardiac troponin high-sensitivity assays. Biofactors. 2016 Apr;42(2):133–48.

98. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 2000 Sep;36(3):959–69.

99. Hamm CW, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med. 1997 Dec 4;337(23):1648–53.

100. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016 Jan 14;37(3):267–315.

101. Garg P, Morris P, Fazlanie AL, Vijayan S, Dancso B, Dastidar AG, et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. Intern Emerg Med. 2017 Mar;12(2):147–55.

102. Chenevier-Gobeaux C, Bonnefoy-Cudraz É, Charpentier S, Dehoux M, Lefevre G, Meune C, et al. High-sensitivity cardiac troponin assays: answers to frequently asked questions. Arch Cardiovasc Dis. 2015 Feb;108(2):132–49.

103. Willeit P, Welsh P, Evans JDW, Tschiderer L, Boachie C, Jukema JW, et al. High-Sensitivity Cardiac Troponin Concentration and Risk of First-Ever Cardiovascular Outcomes in 154,052 Participants. J Am Coll Cardiol. 2017 Aug 1;70(5):558–68.

104. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA. 2010 Dec 8;304(22):2494–502.

105. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA. 2010 Dec 8;304(22):2503–12.

106. Melki D, Lugnegård J, Alfredsson J, Lind S, Eggers KM, Lindahl B, et al. Implications of Introducing High-Sensitivity Cardiac Troponin T Into Clinical Practice: Data From the SWEDEHEART Registry. J Am Coll Cardiol. 2015 Apr 28;65(16):1655–64.

107. Chin CWL, Shah ASV, McAllister DA, Joanna Cowell S, Alam S, Langrish JP, et al. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. Eur Heart J. 2014 Sep 7;35(34):2312–21.

108. Røsjø H, Andreassen J, Edvardsen T, Omland T. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. Am J Cardiol. 2011 Jul 1;108(1):88–91.

109. Saito T, Hojo Y, Hirose M, Ikemoto T, Katsuki T, Kario K. High-sensitivity troponin T is a prognostic marker for patients with aortic stenosis after valve replacement surgery. J Cardiol. 2013 May;61(5):342–7.

110. Paparella D, Guida P, Caparrotti S, Fanelli V, Martinelli G, Mazzei V, et al. Myocardial damage influences short- and mid-term survival after valve surgery: a prospective multicenter study. J Thorac Cardiovasc Surg. 2014 Nov;148(5):2373-2379.e1.

111. Frank D, Stark S, Lutz M, Weissbrodt A, Freitag-Wolf S, Petzina R, et al. Preprocedural high-sensitive troponin predicts survival after transcatheter aortic valve implantation (TAVI). Int J Cardiol. 2013 Nov 5;169(3):e38-39.

112. Köhler WM, Freitag-Wolf S, Lambers M, Lutz M, Niemann PM, Petzina R, et al. Preprocedural but not periprocedural high-sensitive Troponin T (hsTNT) levels predict outcome in patients undergoing transcatheter aortic valve implantation (TAVI). Cardiovasc Ther. 2016 Jul 6;

113. Rodés-Cabau J, Gutiérrez M, Bagur R, De Larochellière R, Doyle D, Côté M, et al. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. J Am Coll Cardiol. 2011 May 17;57(20):1988–99.

114. Yong ZY, Wiegerinck EMA, Boerlage-van Dijk K, Koch KT, Vis MM, Bouma BJ, et al. Predictors and prognostic value of myocardial injury during transcatheter aortic valve implantation. Circ Cardiovasc Interv. 2012 Jun;5(3):415–23.

115. Stundl A, Schulte R, Lucht H, Weber M, Sedaghat A, Shamekhi J, et al. Periprocedural Myocardial Injury Depends on Transcatheter Heart Valve Type But Does Not Predict Mortality in Patients After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2017 Aug 14;10(15):1550–60.

116. Nugroho J, Widorini W. Correlation between Osteoprotegerin Serum Level and Coronary Calcification Using Coronary Artery Calcium Score in Patient with Moderate-Severe Cardiovascular Risk Factor. Int J Angiol. 2017 Dec;26(4):234–7.

117. Adamczyk T, Mizia-Stec K, Mizia M, Haberka M, Chmiel A, Chudek J, et al. Biomarkers of calcification and atherosclerosis in patients with degenerative aortic stenosis in relation to concomitant coronary artery disease. Pol Arch Med Wewn. 2012;122(1–2):14–21.

118. Lancellotti P, Dulgheru R, Magne J, Henri C, Servais L, Bouznad N, et al. Elevated Plasma Soluble ST2 Is Associated with Heart Failure Symptoms and Outcome in Aortic Stenosis. PLoS One [Internet]. 2015 Sep 21 [cited 2019 Sep 18];10(9).

119. Stundl A, Lünstedt N-S, Courtz F, Freitag-Wolf S, Frey N, Holdenrieder S, et al. Soluble ST2 for Risk Stratification and the Prediction of Mortality in Patients

Undergoing Transcatheter Aortic Valve Implantation. Am J Cardiol. 2017 Sep 15;120(6):986–93.

120. Schmid J, Stojakovic T, Zweiker D, Scharnagl H, Maderthaner RD, Scherr D, et al. ST2 predicts survival in patients undergoing transcatheter aortic valve implantation. Int J Cardiol. 2017 Oct 1;244:87–92.

121. Wernly B, Lichtenauer M, Jirak P, Eder S, Reiter C, Kammler J, et al. Soluble ST2 predicts 1-year outcome in patients undergoing transcatheter aortic valve implantation. Eur J Clin Invest. 2017 Feb;47(2):149–57.

122. Sádaba JR, Martínez-Martínez E, Arrieta V, Álvarez V, Fernández-Celis A, Ibarrola J, et al. Role for Galectin-3 in Calcific Aortic Valve Stenosis. J Am Heart Assoc. 2016 04;5(11).

123. Baldenhofer G, Zhang K, Spethmann S, Laule M, Eilers B, Leonhardt F, et al. Galectin-3 predicts short- and long-term outcome in patients undergoing transcatheter aortic valve implantation (TAVI). Int J Cardiol. 2014 Dec 20;177(3):912–7.

124. Rheude T, Pellegrini C, Núñez J, Joner M, Trenkwalder T, Mayr NP, et al. Differential Prognostic Value of Galectin-3 According to Carbohydrate Antigen 125 Levels in Transcatheter Aortic Valve Implantation. Rev Esp Cardiol (Engl Ed). 2018 Oct 25;

125. Sinning J-M, Wollert KC, Sedaghat A, Widera C, Radermacher M-C, Descoups C, et al. Risk scores and biomarkers for the prediction of 1-year outcome after transcatheter aortic valve replacement. Am Heart J. 2015 Oct;170(4):821–9.

126. D'Aloia A, Faggiano P, Aurigemma G, Bontempi L, Ruggeri G, Metra M, et al. Serum levels of carbohydrate antigen 125 in patients with chronic heart failure: Relation to clinical severity, hemodynamic and Doppler echocardiographic abnormalities, and short-term prognosis. Journal of the American College of Cardiology. 2003 May 21;41(10):1805–11.

127. Husser O, Núñez J, Núñez E, Holzamer A, Camboni D, Luchner A, et al. Tumor marker carbohydrate antigen 125 predicts adverse outcome after transcatheter aortic valve implantation. JACC Cardiovasc Interv. 2013 May;6(5):487–96.

128. Ayhan H, Kasapkara HA, Durmaz T, Keleş T, Sarı C, Baştuğ S, et al. Evaluation of CA125 and NT-proBNP values in patients undergoing transcatheter aortic valve implantation. J Geriatr Cardiol. 2015 Mar;12(2):100–6.

129. Kim JB, Kobayashi Y, Moneghetti KJ, Brenner DA, O'Malley R, Schnittger I, et al. GDF-15 (Growth Differentiation Factor 15) Is Associated With Lack of Ventricular Recovery and Mortality After Transcatheter Aortic Valve Replacement. Circ Cardiovasc Interv. 2017 Dec;10(12).

130. Oury C, Nchimi A, Lancellotti P, Bergler-Klein J. Can Blood Biomarkers Help Predicting Outcome in Transcatheter Aortic Valve Implantation? Front Cardiovasc Med. 2018;5:31.

131. Rouzaud-Laborde C, Delmas C, Pizzinat N, Tortosa F, Garcia C, Mialet-Perez J, et al. Platelet activation and arterial peripheral serotonin turnover in cardiac remodeling associated to aortic stenosis. Am J Hematol. 2015 Jan;90(1):15–9.

132. Van Belle E, Rauch A, Vincent F, Robin E, Kibler M, Labreuche J, et al. Von Willebrand Factor Multimers during Transcatheter Aortic-Valve Replacement. N Engl J Med. 2016 Jul 28;375(4):335–44.

133. Mohler ER, Gannon F, Reynolds C, Zimmerman R, Keane MG, Kaplan FS. Bone formation and inflammation in cardiac valves. Circulation. 2001 Mar 20;103(11):1522–8.

134. Aikawa E, Nahrendorf M, Sosnovik D, Lok VM, Jaffer FA, Aikawa M, et al. Multimodality molecular imaging identifies proteolytic and osteogenic activities in early aortic valve disease. Circulation. 2007 Jan 23;115(3):377–86.

135. Rajamannan NM, Nealis TB, Subramaniam M, Pandya S, Stock SR, Ignatiev CI, et al. Calcified rheumatic valve neoangiogenesis is associated with vascular endothelial growth factor expression and osteoblast-like bone formation. Circulation. 2005 Jun 21;111(24):3296–301.

136. Miller JD, Weiss RM, Serrano KM, Brooks RM, Berry CJ, Zimmerman K, et al. Lowering plasma cholesterol levels halts progression of aortic valve disease in mice. Circulation. 2009 May 26;119(20):2693–701.

137. Miller JD, Weiss RM, Serrano KM, Castaneda LE, Brooks RM, Zimmerman K, et al. Evidence for active regulation of pro-osteogenic signaling in advanced aortic valve disease. Arterioscler Thromb Vasc Biol. 2010 Dec;30(12):2482–6.

138. Capoulade R, Clavel M-A, Mathieu P, Côté N, Dumesnil JG, Arsenault M, et al. Impact of hypertension and renin-angiotensin system inhibitors in aortic stenosis. Eur J Clin Invest. 2013 Dec;43(12):1262–72.

139. Cueff C, Serfaty J-M, Cimadevilla C, Laissy J-P, Himbert D, Tubach F, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart. 2011 May;97(9):721–6

140. Clavel M-A, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. J Am Coll Cardiol. 2013 Dec 17;62(24):2329–38.

141. Feuchtner G, Plank F, Bartel T, Mueller S, Leipsic J, Schachner T, et al. Prediction of paravalvular regurgitation after transcatheter aortic valve implantation by computed tomography: value of aortic valve and annular calcification. Ann Thorac Surg. 2013 Nov;96(5):1574–80.

142. Hayashida K, Bouvier E, Lefèvre T, Hovasse T, Morice M-C, Chevalier B, et al. Potential mechanism of annulus rupture during transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 2013 Nov 1;82(5):E742-746.

143. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990 Mar 15;15(4):827–32.

144. Kizer JR, Gefter WB, deLemos AS, Scoll BJ, Wolfe ML, Mohler ER. Electron beam computed tomography for the quantification of aortic valvular calcification. J Heart Valve Dis. 2001 May;10(3):361–6.

145. Messika-Zeitoun D, Aubry M-C, Detaint D, Bielak LF, Peyser PA, Sheedy PF, et al. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. Circulation. 2004 Jul 20;110(3):356–62.

146. Pawade T, Sheth T, Guzzetti E, Dweck MR, Clavel M-A. Why and How to Measure Aortic Valve Calcification in Patients With Aortic Stenosis. JACC Cardiovasc Imaging. 2019 Sep;12(9):1835–48.

147. Pollari F, Großmann I, Vogt F, Kalisnik JM, Cuomo M, Schwab J, et al. Risk factors for atrioventricular block after transcatheter aortic valve implantation: a

single-centre analysis including assessment of aortic calcifications and follow-up. Europace. 2019 May 1;21(5):787–95.

148. Latsios G, Gerckens U, Buellesfeld L, Mueller R, John D, Yuecel S, et al. 'Device landing zone' calcification, assessed by MSCT, as a predictive factor for pacemaker implantation after TAVI. Catheter Cardiovasc Interv. 2010 Sep 1;76(3):431–9.

149. Greason KL, Williamson EE, Suri RM, Mathew V. High Agatston aortic valve calcium score predicts transcatheter paravalvular aortic regurgitation. J Thorac Cardiovasc Surg. 2014 Jun;147(6):1991.

150. Kong WKF, van Rosendael PJ, van der Kley F, de Weger A, Kamperidis V, Regeer MV, et al. Impact of Different Iterations of Devices and Degree of Aortic Valve Calcium on Paravalvular Regurgitation After Transcatheter Aortic Valve Implantation. Am J Cardiol. 2016 Aug 15;118(4):567–71.

151. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012 May 3;366(18):1686–95.

152. Van Belle E, Juthier F, Susen S, Vincentelli A, Iung B, Dallongeville J, et al. Postprocedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: analysis of predictors and impact on long-term mortality: insights from the FRANCE2 Registry. Circulation. 2014 Apr 1;129(13):1415–27.

153. Mirna M, Wernly B, Eder S, Lichtenauer M, Prinz E, Wintersteller W, et al. Transcatheter aortic valve implantation without prior balloon valvuloplasty is associated with less pronounced markers of myocardial injury. J Cardiovasc Surg (Torino). 2018 Oct 5;

154. Seiffert M, Fujita B, Avanesov M, Lunau C, Schön G, Conradi L, et al. Device landing zone calcification and its impact on residual regurgitation after transcatheter aortic valve implantation with different devices. Eur Heart J Cardiovasc Imaging. 2016 May;17(5):576–84.

155. Leber AW, Kasel M, Ischinger T, Ebersberger UH, Antoni D, Schmidt M, et al. Aortic valve calcium score as a predictor for outcome after TAVI using the CoreValve revalving system. Int J Cardiol. 2013 Jul 1;166(3):652–7.

Résumé

La prise en charge du rétrécissement aortique a connu une véritable révolution avec l'avènement du remplacement valvulaire aortique percutané (TAVI). Cette technique, s'adressant initialement à des patients à haut risque chirurgical, a été étendue à des patients à moindre risque du fait de l'amélioration des résultats et s'est accompagnée, au fil des années, d'une simplification de la procédure. Cependant, la sélection rigoureuse des patients en amont de la procédure reste la clé du succès de cette technique. Les facteurs cliniques et échographiques sont insuffisants pour permettre une évaluation précise du profil de risque. Certains biomarqueurs et les calcifications de la valve aortique, permettraient d'améliorer la stratification du risque. **L'objectif de ce travail** était d'évaluer la valeur pronostique de la troponine et du score calcique valvulaire dans le TAVI à l'ère de l'évolution des pratiques

Le premier chapitre de cette thèse a permis de confirmer la valeur pronostique de la troponine en pré et post-procédure TAVI et celle du score calcique avec les valves de la précédente génération. Le deuxième chapitre de ce travail a permis de mettre en évidence l'impact de la prédilatation sur l'élévation de troponine post-procédure avec un rôle pronostique potentiel.

Abstract: Biological and morphological prognostic markers in the era of TAVI simplification

Management of aortic stenosis was revolutionized by the advent of transcatheter aortic valve replacement (TAVI). This technique, initially targeting patients at high surgical risk, was extended to lower risk patients regarding to improved outcomes and was accompanied, over the years, by a simplification at each step of the procedure. However, the careful selection of patients upstream of the procedure remains the key to success. Clinical and echographic factors are not sufficient to allow an accurate assessment of their risk profile. Thus, biomarkers and aortic valve calcifications evaluation may improve risk profile stratification. **The objective of this thesis** was to evaluate the prognostic value of troponin and aortic valve calcium score in patients undergoing TAVI in the era of TAVI simplification

The first chapter of this thesis confirmed the prognostic value of pre- and post-procedure troponin (myocardial injury) in patients undergoing TAVI and of calcium score with previous generation prosthesis.

The second chapter highlighted the impact of predilatation on this post-procedure troponin elevation with a potential prognostic impact.