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Complications ischémiques et hémorragiques des procédures de réparation valvulaire aortique percutanée

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Nicolas Debry MD*, Eric Van Belle MD-PhD*, Flavien Vincent MD, Emmanuel Robin MD, Charlotte Cordonnier MD-PhD, Antoine Rauch MD-PhD, Grégory Kuchcinski MD, Fanny Lassalle, François Pontana MD-PhD, Cédric Delhaye MD, Guillaume Schurtz MD, Emmanuelle JeanPierre PharmD, Basile Verdier MD, Francis Juthier MD, Xavier Neiger MD, Natacha Rousse MD, Caterina, Casari PhD, Hugues Spillemaeker MD, Sina Porouchani MD, Thibault Pamart MD, Tom Denimal MD, Marjorie Richardson MD, Martin Bretzner MD, Jean Dallongeville MD-PhD, Julien Labreuche BST, Mikael Mazighi, MD, Annabelle Dupont-Prado PharmD-PhD, Peter J. Lenting PhD, Sophie Susen MD-PhD.

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Liste des abréviations

AIT : Accident ischémique transitoire

AOMI : Artériopathie oblitérante des membres inférieurs

AVC : Accident Vasculaire Cérébral

BAV : Valvuloplastie aortique au ballon (balloon aortic valvuloplasty)

CC : Choc cardiogénique

CEC : Chirurgie extra-cardiaque

ESC : Société européenne de cardiologie (European Society of Cardiology)

FEVG : Fraction d'éjection du ventricule gauche

ICS : Infarctus cérébral silencieux

IRM : Imagerie par résonnance magnétique

MACE : Evènements cardiovasculaires majeurs (major cardiovascular events)

MCB : Microbleeds cérébral

MMSE : Mini Mental State Examination

NYHA : New York Heart Association

STS : Society of Thoracic Surgeons score

RA: Rétrécissement aortique

TAVI : Remplacement valvulaire aortique percutané

TAx : Transaxillaire

TC : Transcarotide

TF : Transfémoral

VARC-2 : Valve Academic Research Consortium-2

VG : Ventricule gauche

vWF : facteur von Willebrand

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Introduction générale

A. Rétrécissement aortique

Le rétrécissement aortique (RA) est la valvulopathie la plus fréquente dans les pays développés (1). Il est le plus souvent dégénératif, lié à un remaniement fibro-calcaire de la valve aortique, dans un processus similaire à celui de l'athérosclérose, avec lequel il présente de nombreux facteurs de risque communs (2) (3), cette cause représente plus de 80% des rétrécissements aortiques. Les autres étiologies fréquentes sont rhumatismales et congénitales avec la bicuspidie aortique (4).

La prévalence augmente avec le vieillissement de la population, et va devenir un enjeu de santé publique dans les prochaines années (5). Le RA touche actuellement 2,8 % des patients âgés de 60 à 74 ans et 13,1 % des patients de 75 ans et plus, ce qui correspond à environ 16,1 millions de personnes dans les pays développés (5).

Dans le rétrécissement aortique, au cours du temps, les calcifications valvulaires se majorent progressivement, entraînant une augmentation de l'obstruction à l'ouverture de la valve aortique et donc une élévation des gradients transvalvulaires et une diminution de la surface valvulaire, aboutissant à une sténose aortique serrée. Au stade de rétrécissement aortique serré, il existe une phase asymptomatique suivie d'une phase symptomatique, avec des symptômes apparaissant initialement à l'effort, puis secondairement au repos : dyspnée, douleurs thoraciques et syncopes (6). Si il n'est pas traité, le RA serrée est associé à un taux de mortalité allant jusqu'à 50 %, dans les 3 à 5 ans après l'apparition des symptômes (5) (7).

Le diagnostic de rétrécissement aortique serré est échographique, défini par un gradient moyen transvalvulaire aortique supérieur ou égal à 40 mmHg et une élévation de la vélocité maximale du flux aortique supérieure ou égale à 4 m/s en l'absence d'hyperdébit, avec une surface valvulaire aortique inférieure ou égale à 1 cm^2 ou 0.6 cm^2/m^2. Le rétrécissement aortique peut également être serré malgré l'absence d'élévation au-dessus des seuils du gradient moyen et de la vélocité maximale du flux aortique si le volume d'éjection systolique est bas, situation justifiant d'autres examens complémentaires, l'échographie-dobutamine faible dose et le score calcique valvulaire aortique, définissant le rétrécissement aortique serré bas-débit bas-gradient (8) (9) (10).

Aucune thérapie médicamenteuse n'a prouvé son efficacité pour ralentir la progression ou améliorer le pronostic du rétrécissement aortique ; le seul traitement est le remplacement valvulaire aortique, qu'il soit percutané ou chirurgical (11).

Le traitement curatif était historiquement chirurgical, nécessitant une sternotomie, la mise en place d'une circulation extracorporelle, le clampage puis l'ouverture de l'aorte ascendante, la résection de la valve aortique calcifiée et la mise en place de la prothèse valvulaire, puis la fermeture et le déclampage de l'aorte, l'ablation de la circulation extracorporelle et la fermeture du sternum et des tissus musculo-cutanés. Cette technique est désormais réservée à des patients à faible ou moyen risque chirurgical, sans contre-indication à la chirurgie et principalement âgés de moins de 75 ans (12).

Le traitement percutané par cathétérisme du RA serré a connu d'immense progrès depuis 20 ans et repose sur la valvuloplastie aortique au ballonet et sur le remplacement aortique percutané transcathéter (TAVI) (13).

B. Traitement percutané du rétrécissement aortique serré

B.1. Valvuloplastie aortique au ballonnet (BAV)

La valvuloplastie aortique par ballonnet (BAV) existe depuis plus de 30 ans (14). Après l'enthousiasme initial qui a été tempéré par la suite par l'apparition de resténose valvulaire aortique précoce, ce traitement est réservé aux patients dans des situations cliniques complexes souvent d'urgence.

Les recommandations européennes actuelles stipulent que la BAV a une indication de classe IIb (niveau de preuve classe C) pour les patients (i) avec instabilité hémodynamique comme traitement de transition à un traitement définitif par chirurgie ou TAVI (9) ; (ii) comme traitement pour les patients nécessitant une chirurgie non cardiaque urgente et (iii) comme test thérapeutique chez les patients fragiles avec des comorbidités importantes.
Les recommandations américaines donnent également la même indication et le même niveau de preuve pour le BAV en tant que transition vers la chirurgie ou TAVI chez les patients symptomatiques, mais ne considèrent pas que la BAV joue un rôle chez les patients qui nécessitent une chirurgie non cardiaque urgente.

Déroulement de la procédure de BAV

L'imagerie pré-procédurale par échocardiographie ou scanner cardiaque et aortique est importante pour évaluer la taille de l'anneau aortique et sélectionner la taille de ballon la plus appropriée. L'évaluation échocardiographique permet d'écarter une fuite aortique sévère qui est une contre-indication au BAV et conduit généralement à des choix de ballons de BAV plus petits puisque c'est le diamètre antéropostérieure qui est mesuré.

La procédure est principalement effectuée via la voie artérielle fémorale, avec des gaines vasculaires allant jusqu'à 12 F de diamètre, selon le choix de ballon, mais des gaines de 8-9 F sont appropriées pour la plupart des procédures. Pour assurer l'accès artériel la ponction échoguidée doit être utilisée pour trouver un site de ponction sain non calcifié dans l'artère fémorale commune, loin de la bifurcation fémorale et avant que l'artère ne plonge dans le petit bassin. Une pré-fermeture vasculaire est souvent recommandée, par exemple en utilisant le ProGlide ou le ProStar système (Abbott, États-Unis). Les procédures sont réalisées sous anesthésie locale, avec sédation.

Historiquement, l'accès veineux fémoral était également requis pour la mise en place d'une sonde de stimulation temporaire dans le ventricule droit pour permettre une stimulation rapide pendant l'inflation du ballon. Plus récemment, il a été démontré que la stimulation VG pouvait être obtenue en utilisant le guide rigide ventriculaire gauche 0,035(15).
Une fois l'accès artériel obtenu, une sonde pigtail est avancée jusqu'à la racine aortique sous fluoroscopie et une aortographie peut être réalisée pour permettre la visualisation de l'anneau aortique. La valve est franchie à l'aide d'une sonde coronaire diagnostic, généralement une AL-1 (Amplatz gauche 1) ou une JR4 (Judkins droite 4), sur un guide droit 0,035. Un gradient transvalvulaire peut être mesuré à partir de la sonde pigtail et du port latéral du désilet fémoral ou mieux via une 2e pigtail aortique à partir d'un 2e abord. Après échange avec un guide VG rigide, une brève stimulation VG rapide à 180bpm peut être initiée, et vise à abaisser la pression artérielle systolique à ≤60 mmHg au cours de l'inflation du ballon de valvuloplastie aortique pour stabiliser l'aorte ascendante. Le ballon est gonflé grâce à un inflateur qui peut générer jusqu'à 6 bars. L'inflation du ballon peut être répété deux à trois fois pour obtenir un effet maximal (16). Le gradient de pression transvalvulaire doit être contrôlé après la valvuloplastie aortique. L'objectif hémodynamique est de réduire le gradient pic à pic ou le gradient moyen transvalvulaire de ≥ 50 %.

Résultats hémodynamiques

Les premières données des BAV provenaient de deux grands registres, le Registre NHLBI (17) et Registre Mansfield (18) rapportant les résultats de 674 et 492 patients

respectivement. Les deux ont signalé une augmentation de la surface valvulaire (de 0,5 à 0,8 cm^2) et une réduction du gradient pic à pic de 60 à 30 mmHg. Le registre Mansfield a également étudié les variables qui pouvaient améliorer les résultats hémodynamiques et a constaté que la durée d'inflation du ballon était le seul facteur. Depuis l'introduction du TAVI, les études les plus récentes chez 423 patients du Royaume-Uni (19) et 811 patients d'un un registre paneuropéen (20) rapportent des résultats hémodynamiques très similaires aux résultats des registres de lère pré-TAVI. Malgré les améliorations technologiques depuis plus de 20 ans, cela ne s'est pas traduit par des améliorations hémodynamiques significatives.

Résultats cliniques et mortalité de la BAV

Le registre NHLBI rapporté une mortalité intra hospitalière de 3 %, et une mortalité à 30 jours de 14 % et de 36% à 1 an (17). *Khawaja et al* ont signalé un taux de mortalité hospitalier de 2,5 % (19) similaire à celui dans une étude de 472 patients menée par *Ben-Dor et al* en 2013 (21). Des taux de mortalité intrahospitalier plus élevés ont été également rapporté, , par exemple *Alkhouli et al* ont étudié rétrospectivement plus de 3000 procédures aux USA de 2004 à 2013 et retrouvé des taux de mortalité hospitalier de 8,5% (22). La mortalité procédurale était de 1,4%, notamment en cas de choc cardiogénique, ou si la BAV était réalisée dans des centres ne réalisant que 1 à 2 procédures par an.
Les résultats à plus long terme (après 1 an) sont très limités. Les premiers grands registres ont signalé une mortalité à 1 an de 36 % (NHLBI et Mansfield) malgré un nombre significatif de ces patients traités par chirurgie. Les données plus récentes n'ont pas montré d'améliorations de ces résultats à plus long terme. Parmi les 415 patients consécutifs reportés par *Saia et al* une mortalité à 1 an de 33% (et 57,4 % à 2 ans) était annoncée (23). Le pronostic était encore plus sombre pour les patients bénéficiant d'une BAV en indication palliative (44% de mortalité à 1 an) et meilleure pour les patients en « bridge » vers une procédure TAVI (13 % de mortalité à 1 an). Dans l'essai PARTNER initial comparant le TAVI au traitement médical (comprenant la BAV), l'analyse de la mortalité à 5 ans chez les patients subissant une BAV était de 94 % par rapport au 72 % dans le bras TAVI (24) (25). Dans le suivi à plus court terme de PARTNER, la BAV en association avec un traitement médical comparé au traitement médical seul confère une amélioration de la survie à 30 jours (12).

Resténose et procédures répétées

Les résultats bénéfiques de la BAV sont généralement de courte durée (26). La plupart des valves se resténosent entre 3 mois et 1 an, nécessitant de nouvelles procédures de BAV ou

bien un traitement curatif. Les procédures itératives de BAV sont sûres et peuvent potentiellement prolonger l'espérance de vie (27) mais un traitement définitif doit être privilégié.

Complications ischémiques et hémorragiques

Les premières études ont rapporté des taux élevés de complications allant jusqu'à 25 % (17), dont une grande partie est due à des complications d'accès vasculaires (1-20%). Les autres complications signalées à des taux variables dans la littérature comprennent les infarctus périprocéduraux (0,2-4,4%), l'apparition ou l'aggravation d'une fuite aortique (0,5-2,3%) tamponnade (1,7%) par perforation ventriculaire, accident vasculaire cérébral (AVC) (3,2%), et des troubles de la conduction avec la nécessité d'implanter un stimulateur cardiaque (0,2-0,3%). Des données plus contemporaines montrent une tendance à l'amélioration des taux de complications. Les taux des complications vasculaires en particulier ont diminué avec l'expérience des opérateurs aux procédures TAVI avec la planification des procédures sur scanner, le préclosing, la ponction échoguidée, des désilets de plus petites tailles, et une meilleure gestion de l'hémostase. Parmi les 811 patients rapportés en 2015 par *Moretti et al* 25 (20), les complications vasculaires majeures survenaient chez moins de 6 % des patients selon les définitions VARC (28). Dans une étude avec plus de 5000 patients *Alkhouli et al* a rapporté un taux d'AVC et AIT de 2,2 % (22), et *Singh et al* signale aussi en 2015 un taux d'AVC de 3% (29).

B.2. Remplacement valvulaire aortique percutané (TAVI)

Le remplacement valvulaire aortique percutané transcathéter (TAVI) est apparu depuis 2002 comme un traitement alternatif à la chirurgie (30). Les essais cliniques randomisés du TAVI en comparaison avec la chirurgie ont d'abord été réalisé chez les patients chirurgicaux à haut risque ou contre indiqué à la chirurgie il y a plus de dix ans (12), puis chez ceux à risque intermédiaire il y a quelques années (31) et enfin chez les patients à bas risque en 2019 (32). Tous ces essais ont montré que le TAVI était soit non inférieur voire même supérieur à la chirurgie en termes de mortalité et sur les autres critères cardiovasculaires. Une première méta-analyse en 2016 regroupant des patients à risque élevé et intermédiaire a confirmé ces résultats et a rapporté une diminution significative de 13 % du risque relatif de mortalité toutes causes à 2 ans en faveur du TAVI (33). Une mise à jour récente de cette méta-analyse qui incluait les nouveaux essais portant sur les patients à faible risque chirurgical a confirmé

le bénéfice majeur du TAVI (34).

Déroulement de la procédure de TAVI

La procédure de TAVI est réalisée le plus souvent sous anesthésie locale ; elle nécessite plusieurs abords. La voie principale permettant l'introduction et la montée de la valve jusqu'en position aortique, est artérielle, le plus souvent fémorale, voie offrant le moins de complication (35) et plus rarement sous-clavière, ou carotidienne. La voie dite secondaire, artérielle radiale le plus souvent, permet de réaliser une angiographie sus-sigmoïdienne pour repérer le plan de l'anneau aortique au moment du largage de la valve, puis rechercher une fuite résiduelle post-implantation; elle sert aussi au monitoring hémodynamique perprocédural. Une voie veineuse fémorale est parfois utilisée pour mettre en place une sonde d'entrainement électrosystolique dans le ventricule droit, qui pallie au risque de bloc atrio-ventriculaire per-procédure, et permet une stimulation ventriculaire rapide pour stabiliser les mouvements cardiaques au moment du largage de la prothèse.

Les prothèses utilisées sont biologiques, et sont de deux types : les prothèses expansibles au ballon correspondent aux valves Edwards SAPIEN, ayant progressivement évolué vers le modèle utilisé actuellement, la valve SAPIEN 3. Leur diamètre est de 23 à 29 mm. Les prothèses auto-expansibles sont principalement représentées par les Medtronic Corevalve, correspondant aux modèles Evolut R et Evolut PRO (présence d'une jupe), de diamètre 23 à 34 mm. On peut également citer dans cette classe les valves Acurate Neo (Boston Scientific), et Portico Tavi (Abbot Vascular).

Actuellement, les recommandations ESC datant de 2017 proposent de réaliser le TAVI chez les patients contre-indiqués à la chirurgie (recommandation de classe 1, niveau de preuve de grade B) et chez les patients à moyen ou haut risque (STS-score ou Euroscore II ≥ 4% ou Logistic Euroscore I ≥ 10%), ou ayant des facteurs de risque non pris en compte dans les scores comme la fragilité, les séquelles de radiothérapie thoracique ou l'aorte porcelaine (recommandation de classe 1, niveau de preuve de grade B) (9).

Voie d'abord

Tous les patients candidats au TAVI doivent bénéficier d'un scanner injecté de l'aorte et des artères périphériques incluant les vaisseaux fémoraux, et les axes artériels supra-aortiques (36).

L'accès transfémoral (TF) est favorisé par les recommandations internationales en raison de sa supériorité par rapport à l'approche transthoracique, elle est utilisée dans plus de

90% des procédures (37) (38). Il y a eu beaucoup de progrès en ce qui concerne la simplification de la TAVI transfémorale ces dernières années. Cela comprend une évolution vers une sédation consciente plutôt qu'une anesthésie générale, un accès fémoral percutané plutôt qu'une incision chirurgicale, une stimulation temporaire à grâce au guide rigide ventriculaire gauche au lieu d'une sonde d'entrainement électrosystolique, des dispositifs de fermeture vasculaire dédiés, fonctionnant sans écho-guidage transœsophagien et des plans de soins post-opératoires conçus pour favoriser la marche et la sortie précoces (39) (40) (41).

Cette approche TAVI moderne et « minimaliste » est devenue la norme de soins pour les cas simples de TAVI. Cependant, en raison d'une maladie athéroscléreuse sévère, de tortuosité, de calcification ou d'angulation sévère, l'accès transfémoral peut ne pas être réalisable dans environ 10 à 15 % des cas (42). Un diamètre luminal > 5,5mm est en effet généralement requis. De même, une intervention chirurgicale ou un stenting antérieur de l'aorte, des artères iliaques ou fémorales peuvent représenter une contre-indication relative. Dans de tels cas, initialement les voies transapicales ou transaortiques étaient préférées mais sont maintenant délaissées pour des voies moins invasives extrathoraciques.

Le TAVI transaxillaire a été initialement réalisé par incision chirurgicale. Cependant, le TAVI transaxillaire entièrement percutanée est de plus en plus réalisé. Une étude portant sur 100 patients consécutifs dans deux centres a démontré un taux de réussite du dispositif de 95 % avec 0 % de complications majeures et 11 % mineures au site d'accès (43). Les taux de mortalité étaient de 6 % à 30 jours et de 14,8 % à 1 an. De plus petites séries publiées ont démontré des résultats similaires (44) (45).

Mylotte et al a décrit une grande série de TAVI transcarotide, avec 96 patients opérés dans trois centres TAVI à haut volume en France pendant 4 ans (2009-2013) (46). Les patients inclus dans ce registre avaient un petit calibre, fortement calcifié, tortueux ou sténosé. anatomie ilio-fémorale ou pathologie aortique descendante importante. Cette série utilisait principalement la CoreValve (92,7%). Une tamponnade s'est produite dans 4 % des cas et il n'y a eu aucune conversion en remplacement chirurgical de la valve aortique. Aucune hémorragie majeure ou complication vasculaire liée au site d'accès n'est survenue. La mortalité à 30 jours était de 6,3 % (n=6), dont la moitié étaient des décès liés à la procédure (n=3). Il n'y a eu aucun accident vasculaire cérébral à l'hôpital mais il y a eu trois accidents ischémiques transitoires (3,1 %). Dans cette étude, la scanner pré TAVI a été utilisée pour déterminer les dimensions des artères carotides, sous-clavières et vertébrales avec un diamètre luminal minimal d'au moins 7 mm. La réalisation d'une IRM cérébrale du polygone de Willis avant la procédure est essentielle pour déterminer si un flux sanguin cérébral collatéral

adéquat est présent. L'artère carotide commune gauche est généralement préférée car elle offre un alignement coaxial supérieur.

Résultats hémodynamiques

Plusieurs études ont démontré que les valves expansibles au ballon avaient moins de fuite périprothétiques postopératoires mais un profil hémodynamiques moins optimal avec des gradients transvalvulaires plus élevés et une surface fonctionnelle plus basse que les valves auto-expansibles (47). Ceci est expliqué par la position supra-annulaire et la plus faible force radiale de la valve auto-expansible.

Résultats cliniques et mortalité du TAVI

L'étude PARTNER 3 était une étude multicentrique ayant randomisé 1000 patients avec un score de risque STS moyen de 1.9% entre TAVI avec des valves expansibles au ballon SAPIEN 3 et la chirurgie conventionnelle ; elle a montré la supériorité du TAVI sur la chirurgie avec respectivement 8.5% et 15.1% de survenue du critère composite de décès, AVC et réhospitalisation à 1 an (HR 0.54 ; 95% CI 0.37 à 0.79, p = 0.001) (32). À 30 jours, le TAVI a entraîné un taux d'AVC inférieur à celui de la chirurgie (0,6 % contre 2,4 % ;RR: 0,25 ; IC à 95 % : 0,07 à 0,88 ; P = 0,02) et des taux plus faibles de décès ou d'AVC que la chirurgie (1,0 % contre 3,3 % ; rapport de risque : 0,30 ; IC à 95 % : 0,11 à 0,83 ; P = 0,01).

L'étude EVOLUT LOW RISK était une étude multicentrique de non-infériorité ayant randomisé 1468 patients ayant un score de risque STS moyen de 1.9% entre TAVI avec des valves auto-expansibles de Medtronic et chirurgie conventionnelle ; elle a montré la non-infériorité du TAVI sur la chirurgie conventionnelle avec respectivement 5.3% et 6.7% de survenue d'un critère composite de mortalité et AVC invalidant à 2 ans (probabilité de non infériorité > 0.999) (48). L'incidence des décès toutes causes à 30 jours était de 0,5 % dans le groupe TAVI et de 1,3 % dans le groupe chirurgie.

Complications ischémiques et hémorragiques

Les complications rares sont représentées par la tamponnade et l'infarctus.
La tamponnade survient dans 0,2 à 4,3 % des cas, avec une probabilité plus élevée avec les techniques transvasculaires qu'avec l'accès transapical (49). Il existe trois situations physiopathologiques majeures pouvant conduire à cette complication grave : une rupture de la racine annulaire ou aortique pendant la valvuloplastie par ballonnet ou lors de l'implantation; une perforation du ventricule droit causée par la sonde de stimulation temporaire ; et enfin la

perforation du VG par le guide extra-rigide VG.
L'occlusion d'un ostium coronaire pendant l'implantation de la valve met en jeu le pronostic vital, et se produisant dans 0,2 à 0,4 % des cas (50). L'occlusion est souvent causée par l'obstruction des ostia par les feuillets natifs calcifiés qui sont déplacés par l'impaction de la bioprothèse. Il peut être lié au design de la valve, car il semble se produire avec une probabilité plus élevée chez les patients traités avec les prothèses expansible au ballon Edwards Sapien qu'avec la prothèse autoexpansible Medtronic Evolut. Il existe plusieurs facteurs anatomiques qui prédisposent également à cette complication : hauteur basse des ostia coronaires (<10 mm), le valve in valve, le sexe féminin et des sinus de valsalva étroits.

Les complications ischémiques et hémorragiques plus fréquentes sont représentées par les complications vasculaires et cérébrales.

Concernant les complications vasculaires du site de ponction, l'expérience des opérateurs et la réduction progressive des profils des cathéters de délivrance ont rendu le TAVI tranfémoral plus sûr, mais les taux de saignements mettant en jeu le pronostic vital et les saignements majeurs sont estimés à 4,6 % (IC à 95 %, 3,6 % à 5,6 %) et 12,1 % (95 % IC, 3,4 % à 20,8 %) (51). La ponction échoguidée réduit efficacement les complications vasculaires et les saignements du point de ponction (52). La voie d'accès influence également le taux de complications vasculaires (53) avec des taux de complications vasculaires de 11% et d'hémorragie grave de 4,5% avec la voie carotidienne.

Les complications cérébrales sont représentées par les accidents vasculaires cérébraux (AVC), les infarctus cérébraux silencieux (ICS), les microsaignements cérébraux silencieux (MCB). Selon le VARC-2, les accidents vasculaires cérébraux (AVC) sont définis par la survenue d'un déficit neurologique focal (hémiplégie, trouble de la conscience, aphasie …) durant plus de 24h, ou moins de 24h mais avec une imagerie cérébrale prouvant une nouvelle hémorragie ou un nouvel infarctus, ou aboutissant au décès du patient (28). (54). L'accident ischémique transitoire (AIT) est défini par un déficit neurologique de moins de 24h, avec une imagerie ne retrouvant pas de lésion. L'AVC est donc de nature ischémique ou hémorragique. On différencie les AVC invalidants ou non invalidants selon l'échelle modifiée de Rankin évaluée à 90 jours.

En IRM, l'AVC ischémique apparaît en hypersignal en séquence de diffusion dès les premières heures, et en hypersignal T2 FLAIR après 6 heures ; l'AVC hémorragique

apparaîtra en hypersignal T2* (55). L'incidence est estimée à 2.3% pour les AVC, et 0.4% pour les AIT à 30 jours après le TAVI, dans le registre américain des TAVI, portant sur plus de 100 000 patients entre 2011 et 2017 (56). Une méta-analyse de *Eggebrecht et al*., portant sur plus de 10 000 TAVI réalisés entre 2004 et 2011 retrouvait une incidence d'AVC/AIT de 3.3% à 30 jours (57). Dans les études PARTNER, portant sur les résultats des valves expansibles au ballon SAPIEN en comparaison au traitement standard ou à la chirurgie, l'incidence des AVC a tendance à décroitre avec la diminution du risque opératoire et les années : elle est de 6,7% chez les patients non opérables (2010), 5,5% chez des patients à haut risque (2011), 5.5% chez des patients à risque intermédiaire (2016), 0,6% chez des patients à bas risque (2019) (12) (58) (31) (32). Dans la période post-opératoire, ils surviennent principalement dans les premiers jours : la moitié le premier jour, les deux tiers dans les trois jours après l'intervention (56).

Les AVC en post-TAVI sont responsables d'une surmortalité à 30 jours, 3,5 à 6 fois plus importante à 30 jours (56) (57). Leur survenue est favorisée par le choix d'un accès non transfémoral (35) (53), ainsi que par la post-dilatation au ballon de la bioprothèse, l'embolisation de la valve, la survenue d'un premier épisode de FA post-TAVI (59) (60). Cette complication semble être liée à l'embolisation au cours de la procédure de matériel, principalement représenté par des calcifications, du tissu issu de la valve aortique native et de la paroi aortique, retrouvée dans les dispositifs de neuroprotection (61), un mécanisme embolique lié à la FA est également possible (59) (60). A plus long terme, des thromboses infracliniques de valve sont associées à un sur-risque d'AVC et d'AIT (62).

La voie d'abord transcarotidienne est associée avec un taux d'AVC/AIT à 30 jours de 5,7 %, (53).

Les infarctus cérébraux silencieux (ICS)

Il n'existe pas de définition consensuelle des infarctus cérébraux silencieux (ICS) ; ils correspondent à des lésions ischémiques cérébrales, mises en évidence en imagerie ou en anatomopathologie, sans traduction clinique (63). La plupart des auteurs les considèrent à partir d'un diamètre minimal de 3 mm, certains considèrent également un diamètre maximal, le plus souvent fixé à 15 mm ; ces lésions sont caractérisées par un hyposignal T1 et un hypersignal T2 (64).

Ces lésions sont fréquentes : la prévalence de ces lésions recherchées en IRM est estimée entre 8 et 28% dans la population générale, 17 à 60% chez les patients coronariens

(65), 32% chez les patient aux antécédents de FA (66), 57% chez les patients aux antécédents d'AVC (67).

Plusieurs études ont observé la survenue d'infarctus cérébraux silencieux après le TAVI ; l'incidence est estimée de 64 et 90% après l'intervention. Leur survenue est corrélée avec l'âge, la dyslipidémie, la durée de la procédure, la réalisation d'une post-dilatation, la présence et la sévérité d'une athéromatose aortique (68) (69)(70). La présence d'infarctus cérébraux est liée à la survenue de démence (HR 2.26; 95%, CI : 1.09 to 4.70) et d'un déclin cognitif plus marqué qu'en l'absence de ces lésions (71). Une étude récente de *De Carlo et al.* confirme cette tendance dans le contexte post-TAVI, en retrouvant une diminution du MMSE plus marquée durant l'hospitalisation et à 3 mois de l'intervention chez les patients ayant présenté des infarctus cérébraux silencieux (72). Cependant, d'autres études observant la trajectoire cognitive des patients ayant présenté des ICS en post-TAVI n'ont pas retrouvé de différence avec les patients indemnes de lésions cérébrales après l'intervention (68)(73). Il n'a pas été retrouvé de différence en terme de qualité de vie liée à ces lésions (70).

Ces lésions sont également décrites, mais sont significativement moins fréquentes après remplacement valvulaire aortique par chirurgie conventionnelle, où l'incidence y est estimée entre 43 et 48% (70) (74).

Enfin, il est à noter que l'absence de définition uniformisée des infarctus cérébraux silencieux limite l'interprétation des données des différentes études (64).

Dispositifs de protection cérébrale

L'utilisation systématique de dispositifs de protection cérébrale pour la prévention des accidents vasculaires cérébraux dans le TAVI est controversée. Leur utilité potentielle a été mise en évidence dans l'essai SENTINEL, où des débris emboliques ont été capturés chez 99% des patients (75). Ces débris correspondent non seulement à du thrombus et du calcium, mais également à des corps étrangers (35 % des patients) dont du plastique, de la paroi artérielle, de tissu valvulaire et du myocarde (76). Cette étude n'a montré aucune réduction cliniquement significative des accidents vasculaires cérébraux; cependant, il y avait une réduction de 42 % du volume des lésion sur l'IRM de diffusion dans le groupe avec dispositif par rapport à celui du groupe non protégé (75).

Les microbleeds (MCB)

Les microsaignements cérébraux silencieux (MCB) sont des collections de sang focales intraparenchymateuses, au niveau des espaces sous-arachnoïdiens ou des ventricules,

sans origine traumatique et sans traduction clinique, mis en évidence en imagerie ou en anatomopathologie (63). En IRM, elles ont un aspect d'hyposignal en séquence T2*, de diamètre maximal à 10 mm (77). L'apparition de ces lésions fait partie du vieillissement normal (78) ; liée à l'âge, l'hypertension artérielle, la présence de lacunes et les anomalies de substance blanche. Une étude réalisée sur 280 patients de 60 ans en moyenne sans maladie neurologique retrouvait 6% de patients porteurs de microsaignements (79). Les études portant sur les conséquences cognitives des microsaignements cérébraux suggèrent des conséquences cognitives avec diminution du MMSE et augmentation du risque de démence (80). Les microsaignements cérébraux sont également associés à la survenue d'AVC ischémiques et hémorragiques, et de récidive d'AVC chez les patients ayant déjà présenté un AVC ischémique (81).

La présence de microbleeds est également rapportée dans des situations cliniques de décompensations aigue de valvulopathies (82) (83) et lors de l'utilisation de dispositifs d'assistances circulatoires (84) ou cardiaques (85). Leur relation avec la procédure de réparation aortique percutanée n'est pas encore décrite.

Objectifs

L'étude des complications ischémiques et hémorragiques de la mise en place de dispositifs médicaux dans le cadre de pathologie cardiovasculaire tel que le rétrécissement aortique, ou l'assistance cardiaque/circulatoire est une thématique de l'équipe 2 INSERM U1011 depuis plus de 20 ans (86). Les travaux cliniques précédents de l'équipe 2 INSERM U1011 ont notamment permis d'étudier les modifications chroniques et aigues de l'hémostase (dont le facteur willebrand) qui surviennent lors d'une assistance circulatoire (87), ou d'un rétrécissement aortique (88) et de sa correction lors du remplacement percutané - TAVI (89), l'intérêt de la ponction échoguidée en cas d'abord fémoral pour le TAVI (52) ; et nous avions également étudié les complications de la voie transcarotide TAVI (53).

L'objectif de ce travail de thèse est de poursuivre l'étude des complications cliniques ischémiques et hémorragiques et principalement vasculaires et cérébrales lors des procédures de réparation valvulaire aortique percutanée. En effet, malgré les nets progrès que nous avons décrits plus haut, des questions subsistent essentiellement aux deux extrémités du spectre des patients atteints de RA serré symptomatique:

-Pour les situations cliniques d'urgence tels que le choc cardiogénique ou la nécessité d'une chirurgie extracardiaque urgente, où le TAVI et la chirurgie cardiaque peuvent être contre-indiqués ou difficile à réaliser, la place de la valvuloplastie aortique ou du traitement médical est encore mal définie.

-Pour les patients à haut risque opératoire qui présentent souvent une artériopathie oblitérante des membres inférieurs avec une contre indication à la voie transfémorale, la voie d'abord alternative optimale n'est pas connue.

-Pour les patients avec un risque opératoire plus faible, qui sont souvent aussi plus jeunes, la présence potentielle de complications hémorragiques cérébrales après TAVI, leur facteur de risque et leur impact n'ont jamais été exploré.

<u>Réparation valvulaire aortique percutanée et situations cliniques d'urgence</u>

Le TAVI n'est pas encore validé dans certaines situations urgentes où la présence d'un rétrécissement aortique serré nécessite une approche particulière. La sténose valvulaire aortique décompensée est une affection caractérisée par une mortalité élevée si elle est traitée médicalement et un risque significativement accru de mortalité et de morbidité périopératoires en cas de remplacement chirurgical de la valve aortique (4). La stratégie de traitement

optimale des patients sévèrement décompensés présentant une sténose aortique est ainsi inconnue. Avec l'augmentation de l'espérance de vie, l'incidence des rétrécissements aortiques calcifiés dégénératifs augmente et de nombreux patients nécessitent une chirurgie non-cardiaque. En outre, la disponibilité généralisée de l'échocardiographie a conduit à une reconnaissance accrue des patients asymptomatiques avec RA.

Dans la première partie de ce travail de thèse nous avons développé un registre des valvuloplasties aortique au ballon effectuées au CHRU de Lille à l'ère du TAVI (de 2011 à 2019) dans les situations cliniques urgentes où le TAVI n'a pas encore d'indication formelle dans la prise en charge du rétrécissement aortique, et où la valvuloplastie aortique garde une place avec le traitement médical (collection des données et rédaction par le Dr Debry). Il s'agit du choc cardiogénique et la nécessité de chirurgie extracardiaque urgente :
Ce sont deux situations où la place de la valvuloplastie est encore définie par des bas grades de recommandations des sociétés savantes européennes (ESC) ou américaines (AHA/ACC). Nous souhaitions étudier la place de la valvuloplastie aortique au ballon et ses complications ischémiques et hémorragiques dans ces deux situations cliniques (objectif numéro 1).

Réparation valvulaire aortique percutanée et voies d'abord alternatives à la voie fémorale

L'accès transfémoral pour le TAVI est préférable aux autres d'accès, car il est associé à un avantage en termes de mortalité et de morbidité, à des séjours hospitaliers plus courts et à une récupération plus rapide, cependant certains patients présentent des contre-indications à cet abord. Dans la deuxième partie de ce travail nous avons utilisé une cohorte de patients traités par TAVI réalisés dans 4 centres français à haut volume avec des accès alternatifs à la voie fémorale, que nous avions précédemment exploré dans un précédent papier (53). Nous avons souhaité comparer cette fois-ci les deux voies alternatives les plus courantes (transaxillaire et transcarotide) en cas de contre-indication à la voie fémorale sur les évènements ischémiques et hémorragiques (objectif numéro 2) (collection des données et rédaction par le Dr Debry).

Réparation valvulaire aortique percutanée et lésions cérébrales hémorragiques

Enfin, dans la troisième et dernière partie de ce travail nous avons réalisé une étude ancillaire à partir de l'essai clinique PHRC Méthystroke dont le Dr Debry est le rédacteur et

coordonateur (NCT02972008; PHRCI Nord Ouest n° API15-24) permettant d'évaluer l'incidence, la relation avec les perturbations de l'hémostase, et l'impact des lésions cérébrales hémorragiques au cours de la procédure TAVI. L'équipe INSERM U1011 a une expertise importante sur l'étude des perturbations des acteurs de l'hémostase, notamment le facteur willebrand, et les pathologies cardiaques. Le facteur Willebrand (vWF) est une protéine multimérique qui a une sensibilité unique aux forces de cisaillement et aux variations hémodynamiques du flux sanguin comme celles rencontrées lors d'utilisation de dispositifs cardiovasculaires tels qu'un remplacement valvulaire aortique transcathéter (TAVI) ou une assistance circulatoire mécanique à flux continu (90). En réponse à une augmentation des forces de cisaillement, le vWF passe d'une conformation globulaire circulante à une conformation dépliée et devient ainsi sensible à la protéolyse de l'ADAMTS13 et perd ses capacités hémostatiques (91) engendrant des complications hémorragiques.

Nous souhaitions évaluer l'incidence, les facteurs de risque et l'impact clinique des lésions cérébrales hémorragiques dans cette cohorte de patients atteints de RA serrés avec un vWF acquis (objectif numéro 3).

CHAPITRE 1: Situations cliniques d'urgence et traitement percutané du rétrecissement aortique (RA)

A) Urgent balloon aortic valvuloplasty in patients with cardiogenic shock related to severe aortic stenosis: time matters.

Debry N, Kone P, Vincent F, Lemesle G, Delhaye C, Schurtz G, Spillemaeker H, Porouchani S, Coisne A, Auffray JL, Sudre A, Lamblin N, Bonello L, Van Belle E.

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Nous avons établi un registre rétrospectif à l'ère du TAVI (recueil des données, réalisation des procédures, et rédaction du manuscrit) des patients avec RA sévères traités par valvuloplastie aortique (BAV) au CHRU de Lille entre 2011 et 2019. Entre 2011 et 2016, 44 patients ont bénéficié de ce traitement dans le cadre d'un choc cardiogénique en rapport avec une sténose aortique serrée.

Ces patients ont un mauvais pronostic avec une morbidité et une mortalité élevées (50-75%), et un risque opératoire élevé pour le remplacement chirurgical de la valve aortique (SAVR) (jusqu'à ≈25% de mortalité opératoire).

Récemment, il y a eu un regain d'intérêt pour le BAV car, comme indiqué dans les recommandations de l'ESC pour la prise en charge des valvulopathies cardiaques, « le BAV peut être considéré comme un pont vers la chirurgie ou le TAVI chez les patients hémodynamiquement instables qui sont à haut risque pour la chirurgie ».

Cependant, seules quelques études monocentriques incluant de petites cohortes de patients atteints de choc cardiogénique (n=7 à 23 patients) ont été menées, la plupart avant l'ère TAVI. Plus récemment, une étude multicentrique a étudié le rôle du BAV dans les situations d'urgence mais n'a pas clarifié le rôle du BAV chez les patients présentant un choc cardiogénique.

Le but de la présente étude était d'évaluer les résultats périopératoires et à un an de la BAV en tant que traitement de sauvetage chez les patients atteints de choc cardiogénique lié à un RA sévère.

Urgent balloon aortic valvuloplasty in patients with cardiogenic shock related to severe aortic stenosis: time matters.

Abstract

Aims: The aim of the study was to assess the outcomes of balloon aortic valvuloplasty (BAV) as a rescue therapy in patients with cardiogenic shock (CS) related to severe aortic stenosis (AS).

Methods and results: Forty-four consecutive patients, n=31 with hypotensive CS (HCS) and n=13 with non-hypotensive CS (NHCS) due to acutely decompensated severe AS, from two centres were treated with urgent BAV. The composite primary endpoint was mortality or recurrent CS at one-year follow-up. These patients (77.3±8.1 years old; 75% male) had a mean EuroSCORE II of 41.6±13.7%. One-month mortality was 47%. Twelve patients (27%) had either a staged TAVR (n=10) or surgical aortic valve replacement (SAVR) (n=2) with a median delay of 79 days after BAV: n=6 (19%) in the HCS subgroup and n=6 (46%) in the NHCS population (p=0.06). At one year, the rate of composite all-cause death or recurrent CS was 75% and significantly higher in the HCS subgroup (83% vs. 53%; p=0.03). Overall one-year mortality was 70% (n=31) with a trend for a better prognosis in NHCS patients (54% vs. 77%; p=0.09). Univariate predictive factors of the primary endpoint included preoperative dose of dobutamine >5 microg/kg/min (100% vs. 57%; p=0.001) and delayed BAV >48 hrs (90% vs. 59%; p=0.01).

Conclusions: Despite the initial success of urgent BAV, morbidity and mortality of CS related to severe AS remain high and directly related to the time of the valvuloplasty. Performing BAV before or within 48 hours of starting inotropic agents appears to be key to survival.

Abbreviations

AS: aortic stenosis

AVR: aortic valve replacement

BAV: balloon aortic valvuloplasty

BMI: body mass index

CS: cardiogenic shock

GFR: glomerular filtration rate
HCS: hypotensive cardiogenic shock
LVEF: left ventricular ejection fraction
NHCS: non-hypotensive cardiogenic shock
PASP: pulmonary arterial systolic pressure
SAVR: surgical aortic valve replacement
TAPSE: tricuspid annular plane systolic excursion
TAVR: transcatheter aortic valve replacement
TTE: transthoracic echocardiography
VARC-2: Valve Academic Research Consortium-2

Introduction

Management of patients with cardiogenic shock (CS) related to severe aortic stenosis (AS) is a challenging topic (1). These patients have a poor prognosis with high morbidity and mortality (50-75%) (2,3) and a high operative risk for surgical aortic valve replacement (SAVR) (up to ≈25% operative mortality) (4). Percutaneous balloon aortic valvuloplasty (BAV) is a therapeutic option described by Cribier et al in 1986(5), particularly for the treatment of patients with CS related to severe AS (6). After initial enthusiasm in the 1990s, the use of BAV decreased dramatically, because of the early high restenosis rate (70%), and it was reserved for palliative indications (7).

For a decade, transcatheter aortic valve replacement (TAVR) has been an alternative to medical treatment for those who are contraindicated to surgery (8,9). Recently, there has been renewed interest in BAV (10,11) because, as stated in the ESC guidelines for the management of valvular heart disease, "BAV may be considered as bridge to surgery or TAVR in haemodynamically unstable patients who are at high risk for surgery" (12).

However, only a few single-centre studies including small cohorts of patients with CS (n=7 to 23 patients) have been conducted (10,11,13-16), most of them before the TAVR era (13,14). More recently, a multicentre study investigated the role of BAV in emergency conditions but did not clarify the role of BAV in patients with cardiogenic shock (17).

The purpose of the present study was to assess the periprocedural and one-year outcomes of BAV as a rescue therapy in contemporary patients with CS due to severe AS.

Methods

PATIENT SELECTION

Between 2011 and 2016, we identified consecutive patients suffering from CS related to severe AS referred to the intensive care units of two French university centres (APHM Marseille and CHRU Lille). Each case was discussed by the institutional multidisciplinary Heart Team, which included on-call interventional cardiologists and surgeons, and on-site intensive care physicians and anaesthetists. The Heart Team agreed that a BAV should be performed as life-sustaining rescue therapy for every patient, as emergency aortic valve surgery was excluded.

In those patients, cardiogenic shock was defined as the combination of 1) a low cardiac index less than 2.2 L/min/m2 (transthoracic echocardiography [TTE] evaluation) together with clinical signs of pulmonary congestion resistant to a high dose of intravenous loop diuretic treatment, and 2) peripheral hypoperfusion identified by the combination of several parameters including altered mental status, cold/clammy skin and extremities, oliguria with urine output of less than 30 ml/hr, or serum lactate level higher than 2.0 mmol/L.

As proposed by *Menon et al* from the SHOCK trial registry (18), two "subsets" of patients with CS were defined, non-hypotensive CS (NHCS) and hypotensive CS (HCS), as they are continuous pathophysiological conditions.

(i) Non-hypotensive or normotensive-hypoperfused CS is defined as above by the combination of low cardiac output/peripheral hypoperfusion together with a "normal" systolic blood pressure >90 mmHg without vasopressor circulatory support.

(ii) "Classic" CS or hypotensive CS (HCS), as in the IABP-SHOCK II trial (19), is defined as above by the combination of low cardiac output/peripheral hypoperfusion together with a low systolic blood pressure of less than 90 mmHg for more than thirty minutes or infusion of inotrope drugs needed to maintain a systolic pressure above 90 mmHg.

All patients had severe AS (indexed aortic valve area [AVA] <0.6 cm^2/m^2).

Patients with CS related to other causes such as ST-segment elevation myocardial infarction (STEMI), tamponade, stress cardiomyopathy, pulmonary embolism, myocarditis, severe aortic regurgitation, severe mitral regurgitation/stenosis, or patients with concomitant sepsis or severe bleeding were excluded. No right cardiac catheterisation or PiCCO® (Maquet, Orleans, France) was performed, but an electrocardiogram, echocardiography, biological assessments and angiocoronarography were performed before the procedure to confirm the diagnosis.

PREPROCEDURAL SCREENING

Patients received standard care therapy as previously described (20). Invasive blood pressures were monitored with arterial and venous catheters. Patients with hypotensive CS were all catecholamine (dobutamine and/or norepinephrine)-dependent at baseline.

Severe AS was assessed according to the guidelines of the European Society of Cardiology (12).

BAV PROCEDURES

A coronarography angiogram was systematically performed before the BAV in order to exclude patients with significant left main or proximal left anterior disease.

BAV was performed using rapid pacing as previously described (6) under local anaesthesia, through the transfemoral access. The procedure was considered successful when at least a 50% reduction of the aortic gradient was obtained without a moderate to severe aortic regurgitation (6). This was assessed by TTE after the procedure.

CLINICAL ENDPOINTS

The primary endpoint was a composite of mortality or recurrent CS related to AS at one-year follow-up, and secondary endpoints included one-year mortality and predictive factors of the primary endpoint and one-year mortality. Other analyses included one-month mortality and post-procedural outcomes, and were described according to the Valve Academic Research Consortium-2 (VARC-2) criteria (21).

STATISTICAL ANALYSIS

Results for continuous variables were expressed as means with standard deviations when data were symmetrically distributed or otherwise as medians with ranges. The normality of distribution was assessed using the Shapiro-Wilk test and normality diagrams. Results for categorical variables were expressed as frequencies and percentages. Comparative analyses were obtained using the chi-square test for categorical data; when not applicable because of the sample size, Fisher's exact test was used. For numerical variables, we used the ANOVA test or Kruskal-Wallis test if normality of distribution was not present. Survival was graphically depicted using Kaplan-Meier curves and between-group differences were compared using the log-rank test. P-values <0.05 were considered statistically significant. Statistical analysis was performed using commercial software (SPSS version 18.0; SPSS Inc., IL, USA). A multivariate analysis was not possible because of the low number of patients.

Results

BASELINE PATIENT CHARACTERISTICS

We identified 44 patients (around 15% of total BAV procedures in the two institutions) with either HCS (n=31, 84% male, mean age 77.3±8.6 years) or NHCS (n=13, 53% male, mean age 77.3±7.3 years), with a global mean EuroSCORE II of 41.6±13.7%. Baseline characteristics and comorbidities are presented in **Table 1.** Other indications for BAV in our two institutions (n=250) were (i) to assess the clinical response of a reduction in aortic gradient in borderline patients prior to consideration of definitive TAVR intervention (60%), (ii) as a bridge to TAVR because of a long waiting list (40%). Details about haemodynamic evaluation and peripheral injury can be found in the **Supplementary Appendix** and **Table 2.**

Table 1. Baseline patient characteristics.

Baseline characteristics	All N=44	HCS n=31	NHCS n=13	*p*-value
Clinical data				
Age (years), mean±SD	77.3±8.1	77.3±8.6	77.3±7.3	1.0
Male gender, n (%)	33 (75%)	26 (84%)	7 (54%)	0.04*
BMI (kg/m²), mean±SD	26.9±5.6	27.1±5.9	26.6±5.1	0.78
Chronic renal failure GFR <60 mL/min, n (%)	23 (52%)	17 (55%)	6 (46%)	0.60
Dialysis, n (%)	2 (4%)	2 (6%)	0 (0%)	0.35
Prior MI, n (%)	14 (31%)	12 (38%)	2 (15%)	0.11
Prior CVA/TIA, n (%)	6 (13%)	5 (16%)	1 (8%)	0.46
COPD, n (%)	9 (20%)	5 (16%)	4 (31%)	0.27
Atrial fibrillation, n (%)	24 (54%)	16 (52%)	8 (62%)	0.55
Diabetes, n (%)	14 (31%)	10 (32%)	4 (31%)	0.92
PVD, n (%)	11 (25%)	9 (29%)	2 (15%)	0.34
Previous cardiac surgery, n (%)	3 (6%)	2 (6%)	1 (8%)	0.88
Previous CABG, n (%)	2 (4%)	1 (3%)	1 (8%)	0.52
Liver disease - cirrhosis, n (%)	3 (6%)	3 (10%)	0 (0%)	0.24
EuroSCORE II, mean±SD	41.6±13.7	45.8±13.5	31.7±8.3	0.001*
STS score, mean±SD	23.4±11.6	25.9±11.9	18.1±9.3	0.05*
Preoperative TTE				
LVEF (%), mean±SD	30±14	29±13	34±19	0.30
LV volume (ml), mean±SD	156.7±40.0	166.5±32.3	138.2±47.9	0.04*
Mean Ao gradient (mmHg), mean±SD	39.0±14.2	38.6±15.0	40.3±12.7	0.73
AVA (cm²), mean±SD	0.61±0.17	0.65±0.15	0.54±0.18	0.06
Grade I-II AR, n (%)	19 (43%)	11 (35%)	8 (62%)	0.11
Grade I-II MR, n (%)	22 (50%)	14 (45%)	8 (62%)	0.32
PASP (mmHg), mean±SD	54.1±11.5	54.6±12.9	53.3±8.3	0.78
RV TAPSE (mm), mean±SD	14.5±3.9	14.2±3.6	15.4±4.6	0.43
RV Sdti (cm/s), mean±SD	8.7±3.2	8.6±2.9	9.1±4.2	0.71
Bicuspid aortic valve, n (%)	8 (18%)	6 (19%)	2 (15%)	0.75

*p-value <0.05. Ao: aortic; AR: aortic regurgitation; AVA: aortic valve area; BMI: body mass index; CABG: coronary artery bypass graft; CVA/TIA: cerebrovascular accident/transient ischaemic attack; COPD: chronic obstructive pulmonary disease; HCS: hypotensive cardiogenic shock; LV: left ventricular; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MR: mitral regurgitation; NHCS: non-hypotensive cardiogenic shock; PASP: pulmonary artery systolic pressure; PVD: peripheral vascular disease; RV: right ventricle; STS score: Society of Thoracic Surgeons score; TAPSE: tricuspid annular plane systolic excursion; TTE: transthoracic echocardiography

Table 2. Baseline haemodynamic and biological evaluations.

	All N=44	HCS n=31	NHCS n=13	*p*-value
Clinical parameters				
Heart rate/min, mean±SD	94.9±7.6	92.8±15.6	99.5±21.5	0.30
Mechanical ventilation, n (%)	6 (13%)	5 (16%)	1 (8%)	0.46
Cardiac index (TTE)				
Pre-BAV cardiac index (l/min/m²), mean±SD	1.60±0.78	1.38±0.74	1.90±0.54	0.01*
Preoperative medication and score				
Dobutamine dose (microg/kg/min), mean±SD	5.8±5.4	8.2±4.9	0.0±0.0	0.001*
Norepinephrine dose (mg/hr), mean±SD	1.0±2.3	1.5±2.7	0.0±0.0	0.05*
Loop diuretic dose (mg/24 hrs), mean±SD	1,405±302	1,430±265	1,354±376.3	0.48
VIS score, mean±SD	25.6±44.6	36.3±49.5	0.0±0.0	0.01*
SOFA score, mean±SD	6.0±2.9	6.9±1.8	4.0±1.2	0.001*
Preoperative biological data				
Creatinine (mg/l), mean±SD	19.1±9.1	19.4±8.8	18.7±10.3	0.83
Troponin T Hs (ng/l), mean±SD	343.4±567.8	392.1±629.5	136.1±133.7	0.24
NTproBNP, mean±SD	18,151±21,008	18,375±23,652	17,444±10,185	0.93
Lactate (mg/l), mean±SD	269.9±157.8	281.3±160.5	150.5±41.7	0.27
Factor V (%), mean±SD	54.4±32.5	52.1±32.6	64.3±35.6	0.47
PT (%), mean+/SD	63.3±20.0	60.3±20.6	71.6±16.8	0.12
Haemoglobin (g/dl), mean±SD	10.9±1.8	10.9±1.9	11.1±1.6	0.81
CRP (mg/l), mean±SD	57.6±55.2	56.6±64.2	41.6±50.2	0.24

*p-value <0.05. BAV: balloon aortic valvuloplasty; CRP: C-reactive protein; Hb: haemoglobin; HCS: hypotensive cardiogenic shock; NHCS: non-hypotensive cardiogenic shock; PT: prothrombin time; SOFA score: sequential organ failure assessment score; TTE: transthoracic echocardiography; VIS score: vasoactive-inotropic score

PROCEDURAL DATA

In the NHCS group, BAV was performed as soon as the diagnosis of non-hypotensive CS was established, 1.2±0.5 days after admission to the intensive care unit and before starting inotropes. In the HCS group, BAV was performed 4.1±2.9 days after admission to the intensive care unit and 3.2±3.8 days after the introduction of catecholamines. No patient received mechanical circulatory support.

Thirty-nine (88%) procedures were considered successful with a significant reduction of the aortic gradient. The immediate haemodynamic changes produced by BAV are shown in **Supplementary Table 1.** Postoperative TTE evaluation showed a significant overall decreased mean transaortic gradient (from 39.9±14.2 mmHg to 25.3±11.2 mmHg; p=0.01) and increased AVA (from 0.61±0.17 cm2 to 0.82±0.20 cm2; p=0.01).

OUTCOMES

i) In-hospital (Supplementary Table 2) and one-month outcomes (Supplementary Table 3)

Three patients (13%) died during the procedure (n=2 [6%] in the HCS subgroup and n=1 [7%] in the NHCS subgroup) due to a tamponade (n=1), severe aortic regurgitation (n=1), or haemodynamic collapse (n=1). Four patients (13%) with an efficient procedure were successfully weaned from inotropic support within the first 72 hours after the procedure in the hypotensive CS group. The total hospital mortality rate was 45% (n=20), n=16 in the HCS subgroup and n=4 in the NHCS subgroup (p=0.20). Twelve patients (27%) were discharged home before two weeks after BAV, n=4 (13%) in the HCS subgroup and n=8 (62%) in the NHCS subgroup (p=0.001). There were no major vascular complications or life-threatening bleedings, but n=3 (7%) major bleeding and n=2 (4%) minor bleeding. No patients were on dialysis at the time of BAV. Five patients (11%) required haemodialysis after the procedure **(Supplementary Table 2)**. Intra-hospital mortality was significantly lower in patients with a successful procedure (n=13 [33%] vs. n=4 [80%]; p=0.04). Similarly, surviving patients had a lower post-procedural transaortic maximal velocity (2.9±0.9 m/s vs. 3.5±0.5 m/s; p=0.05) and a lower post-procedural transaortic mean gradient (22.5±9.7 vs. 30.5±12.6 mmHg; p=0.03). A vasoactive-inotropic (VIS) score ≥10 (n=13 [76%] vs. n=8 [29%]; p=0.002) or a sequential organ failure assessment (SOFA) score ≥7 (n=15 [93%] vs. n=6 [21%]; p<0.001) was highly predictive of one-month mortality after BAV.

The mortality rate at one month reached 47% (n=21). Causes of death before and after one month are presented in **Supplementary Table 4.**

During the follow-up, n=12 (27%) patients had either a staged TAVR (n=10) or SAVR (n=2) with a median delay of 79±49 days after BAV, n=6 (19%) in the HCS group and n=6 (46%) in the NHCS group (p=0.06). Among the 12 patients who finally underwent TAVR or SAVR, n=4 (33%) were dead at one year. Follow-up after BAV for the entire cohort (n=44) is shown in **Figure 1.**

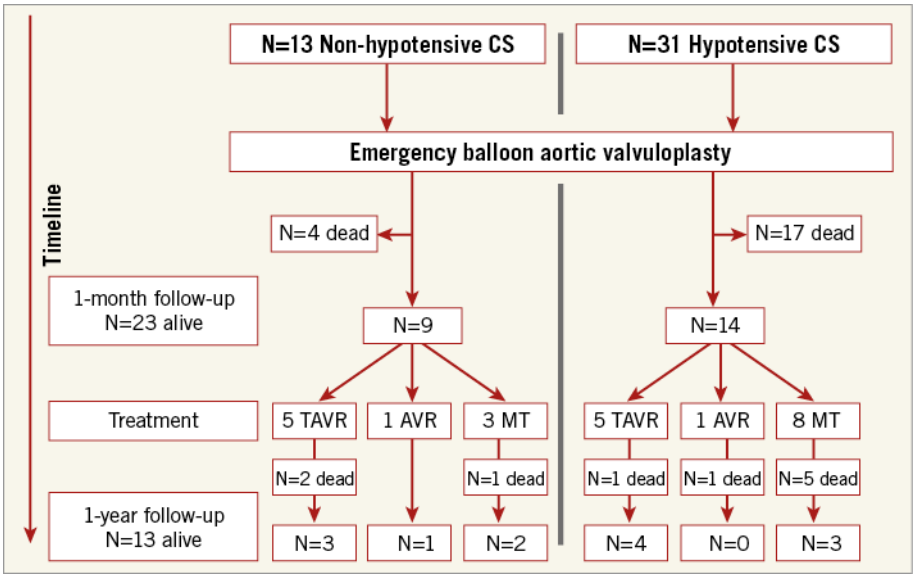

Figure 1. Follow-up after percutaneous balloon aortic valvuloplasty (BAV). AVR: aortic valve replacement; MT: medical treatment; TAVR: transcatheter aortic valve replacement

ii) One-year outcomes (Supplementary Table 3)

At one year, the rate of composite all-cause death or recurrent CS was 75% (n=33) and was significantly higher in the HCS subgroup (n=26 [83%] vs. n=7 [53%]; p=0.03). The mortality rate at one-year follow-up was 70% (n=31) in the overall cohort with a trend for better prognosis in the NHCS subgroup (mortality in HCS n=24 [77%] and in NHCS n=7 [53%]; p=0.11). One-year cumulative survival also showed a trend for better prognosis for the NHCS population with a log-rank p=0.09 **(Figure 2)**.

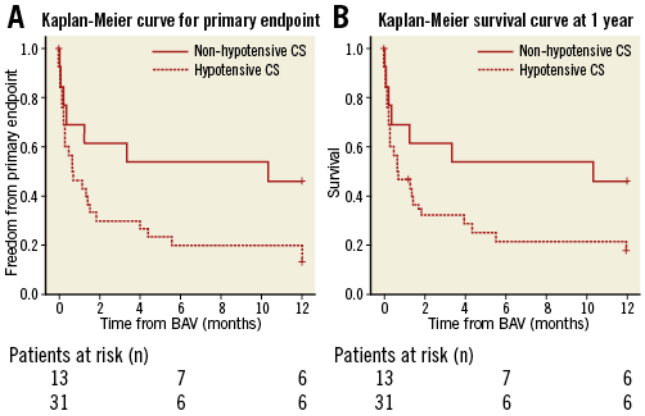

Figure 2. NHCS and HCS survival. A) Kaplan-Meier curve for the primary endpoint of patients undergoing BAV for hypotensive CS (HCS) and non-hypotensive CS (NHCS) due to severe aortic stenosis (log-rank p=0.05). B) Kaplan-Meier survival curve of patients undergoing BAV for hypotensive CS (HCS) and non-hypotensive CS (NHCS) due to severe aortic stenosis (log-rank p=0.09).

PREDICTIVE FACTORS OF THE PRIMARY ENDPOINT AND ONE-YEAR MORTALITY

In the global cohort, univariate predictive factors of the primary endpoint included a preoperative dose of dobutamine >5 microg/kg/min (100% vs. 57%; p=0.001) and delayed BAV >48 hrs (90% vs. 59%; p=0.01). Likewise, the predictive factors for one-year mortality were a preoperative dose of dobutamine >5 microg/kg/min (94% vs. 53%; p=0.02) and delayed BAV >48 hrs (86% vs. 54%; p=0.02). The prognosis of the three populations – NHCS, HCS with BAV ≤48 hrs and HCS with BAV >48 hrs– differed significantly at one-year follow-up regarding the primary endpoint (log-rank p=0.01) and survival (log-rank p=0.04) **(Figure 3)**.

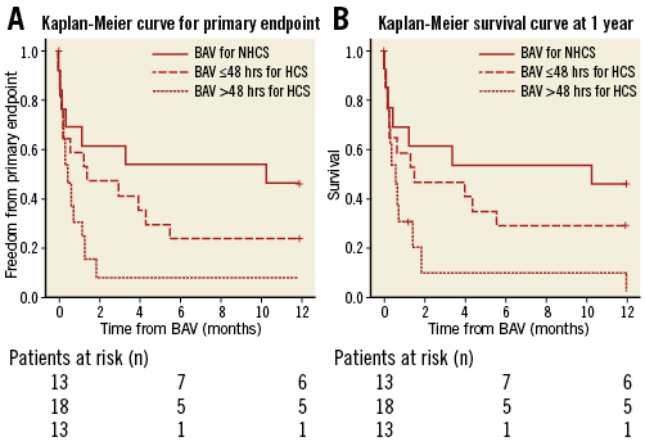

Figure 3. Timing of BAV. A) Kaplan-Meier curve for the primary endpoint of patients with BAV for NHCS, BAV ≤48 hrs for HCS, or BAV >48 hrs for HCS (log-rank p=0.01). B) Kaplan-Meier survival curve at one year for patients with BAV for NHCS, BAV ≤48 hrs for HCS, or BAV >48 hrs for HCS (log-rank p=0.04).

Discussion

The present study, including 44 patients and conducted in two centres, is one of the largest published cohorts of patients undergoing BAV for cardiogenic shock related to a severe AS **(Table 3)**. It discloses four key findings: (1) mortality at one year in contemporary patients remains high (70%), (2) mortality is directly related to the duration of shock before performing BAV, (3) more specifically, initiation of inotropic agents appears to be a critical time point, with a short time window (<48 hrs) after which conducting BAV becomes associated with a dire outcome, (4) the most favourable situation to perform BAV appears to be before the introduction of catecholamines, as it allows bringing 50% of patients to staged

TAVR or AVR.

MORTALITY HAS NOT IMPROVED OVER THE YEARS

We have not seen any improvement regarding early mortality since 1994 **(Table 3)**. In the modern era of TAVR, we confirm that BAV for CS remains associated with a dramatically poor prognosis, with only 27% of patients able to be treated by either TAVR or SAVR within the year, and 70% mortality at one year.

Table 3. Summary of BAV and CS studies.

	Study design	N	Age (years)	Mean aortic gradient (mmHg)	LVEF (%)	Catecholamine dose known?	One-month mortality	Ref.
Moreno et al 1994	Single centre	21	74±3	49±4	29±3	No	43%	13
Buchwald et al 2001	Single centre	14	74±11	?	?	No	71%	14
Hamid et al 2010	Single centre	7	77±12	?	28±10	No	?	10
Saia et al 2013	Single centre	23	77±10	?	?	?	56%	15
Theiss et al 2014	Single centre	18	78±1	?	32±3	No	27%	16
Olasinska et al 2016	Single centre	7	72±11	?	?	No	?	11
Debry et al 2018	Two centres	44	77±8	39±14	30±14	Yes	47%	–

For the first time, we report that NHCS patients have a lower risk of death or recurrent CS at one year than the HCS subgroup (p=0.03) and that there is a trend towards lower mortality in that population at one month (p=0.14) and at one year (p=0.09). BAV may be useful for NHCS patients since it allows performing staged SAVR or TAVR in half of the cases.
Old studies included smaller cohorts of patients and details about haemodynamic monitoring were scarce. In particular, biological data regarding renal or hepatic failure and catecholamine doses at the time of valvuloplasty are lacking (13,14). Even a recent study does not give much information about medical shock management and outcomes after BAV (16). Trials exploring the outcomes of emergency TAVR for cardiogenic shock related to AS seem to have the same weakness (22,23). Nevertheless, we report a one-month mortality rate of 47%, consistent with previous studies with in-hospital or one-month mortality varying from 43% (13) to 71% (14).

KEY ROLE OF THE TIME OF BAV RELATIVE TO INOTROPE SUPPORT

Our results illustrate the difficulty of improving the outcomes of patients in CS related to a severe AS. Duration of shock symptoms before causal treatment (to relieve valve obstruction), if attempted, seems to determine outcome. We show that the time of introduction of inotropic agents is crucial, since patients without amines (NHCS) have a better prognosis at

one year. The valvuloplasty should be addressed as soon as signs of impaired end-organ perfusion appear, instead of starting inotropic agents.
When catecholamines have been initiated, a delay in performing BAV can be deadly. Performing an early BAV, during the first 48 hours, before for example increasing dobutamine dose beyond 5 microg/kg/min to maintain a systolic pressure above 90 mmHg, could be the answer to rapid deterioration of haemodynamic status. A delayed BAV after 48 hours may be useless, as hepatic and renal failure worsens. In a much smaller series (n=14), Buchwald et al also suggested a beneficial effect of an early BAV within the first 48 hours of shock diagnosis (14).

IS IT TIME FOR 24 HRS A DAY "URGENT TAVR"?

Because one-year mortality remains high in AS patients with CS treated with BAV (47% in the present study), we can legitimately ask about the potential of emergency TAVR in the management of these patients. However, a retrospective study of patients (n=27) with AS and CS treated by emergency TAVR reported a 30-day and one-year mortality rate of 33% and 41%, respectively (22). Another recent multicentre study investigating emergent TAVI and BAV (n=118) also showed high immediate procedural and 30-day mortality (33%), with more stroke and vascular complications for the TAVI group as compared to the BAV group (17). Altogether, this may suggest that emergent TAVR is not the ultimate option in AS patients with cardiogenic shock. Still, our data may suggest that to organise centres to perform emergent BAV in these patients would save lives.

Limitations

This was not a randomised trial and the low number of patients with cardiogenic shock prohibited multivariate analysis of factors impacting on 30-day survival. However, the selection of patients was very stringent and included an extensive screening (ECG, biology, echography and coronarography) allowing the exclusion of CS with uncertain aetiology or non-related to pure aortic stenosis. We believe that this very well characterised population may help to define predictive factors of mortality in this very difficult situation and thus help to define "when" and "for which patients" this procedure may be more beneficial. These data must be confirmed in large prospective multicentric cohorts.

Conclusions

Despite the initial success of urgent BAV, morbidity and mortality of CS related to severe AS remains dramatically high and is directly related to the duration of shock. Performing BAV before starting inotropic agents or within 48 hours of their initiation appears to be key to survival. With the improvement of the outcomes of TAVR, there is a need for a randomised trial comparing urgent BAV followed by staged TAVR and emergency TAVR for these unstable patients.

Impact on daily practice

Despite the initial success of urgent BAV, morbidity and mortality of CS related to severe AS remains dramatically high and is directly related to the duration of shock. Performing BAV before starting inotropic agents or within 48 hours of their initiation appears to be key to survival.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Supplementary data

Results

Severe aortic stenosis

All patients had a severe AS (**Table 1**), with a mean aortic gradient of 39.0 +/- 14.2 mmHg (HCS= 38.6 +/- 15.0 mmHg; NHCS= 40.3 +/- 12.7 mmHg; p=0.72), and a mean aortic valve area of 0.61 +/- 0.17cm^2 (HCS= 0.65 +/- 0.15 cm^2; NHCS= 0.54 +/- 0.18 cm^2; p=0.06). Mean LVEF was 30 +/- 14% (HCS= 29 +/- 13%; NHCS= 34 +/- 19%; p=0.30).

Hemodynamic evaluation

Mean Cardiac Index evaluated by TTE was very low (1.60 +/- 0.78 L/min/m^2). In the HCS subgroup, high dose of catecholamines were used at the time of BAV: mean dobutamine dose of 8.2 +/- 4.9 micrograms/kg/min (p=0.001), and mean norepinephrine dose of 1.5 +/- 2.7 mg/h (p=0.05).

Impaired end-organ perfusion was observed at the time of the procedure for all patients with (i) severe renal failure (mean creatinine = 19.1 +/- 9.1 mg/l), (ii) hepatic injury (mean Prothrombin Time = 63.3 +/- 20.0 % and mean factor V = 54.4 +/- 32.5%), (iii) cardiac injury (mean troponin T Hs = 343.4 +/- 567 ng/l) and (iv) anaerobic metabolism (lactate = 269 +/- 157 mg/l) (**Table 2**).

Supplementary Table 1: BAV Procedural data

Procedural data	All n=44	HCS n=31	NHCS n=13	P value
Delay between catecholamines introduction and BAV mean +/- SD	2.3 +/- 3.4	3.2 +/- 3.8	0.0 +/- 0.0	**0.002***
Procedural success, n (%)	39 (88%)	27 (87%)	12 (92%)	0.62
Balloon diameter (mm), mean +/- SD	22.4 +/-1.7	22.4 +/-1.6	22.5 +/- 2.1	0.86
BAV sheath size (French), mean +/- SD	11.6 +/- 0.9	11.7 +/- 0.7	11.3 +/- 1.3	0.15
Number of inflations, mean +/- SD	1.7 +/- 0.6	1.6 +/- 0.6	1.9 +/- 0.7	0.28
Local anesthesia, n (%)	38 (83%)	26 (83%)	12 (92%)	0.46
Pre-Closure device n (%)	24 (54%)	16 (51%)	8 (61%)	0.54
Manual Compression n (%)	20 (45%)	15 (49)	5 (39)	0.54
Proc fluotime (sec), mean +/- SD	602 +/- 284	637 +/- 279	534 +/- 299	0.33
TTE Mean Ao gradient (mmHg) before BAV, mean +/- SD	39.0 +/- 14.2	38.6 +/- 15.0	40.3 +/- 12.7	0.73
TTE Mean Ao gradient (mmHg) after BAV, mean +/- SD	23.3 +/- 11.2	22.5 +/- 10.7	25.4 +/- 12.5	0.46
TTE Grade III-IV AR, n (%)	1 (2%)	1 (2%)	0 (0%)	0.51

Ao=aortic; BAV= balloon aortic valvuloplasty; Fluotime= time of fluoroscopy; HCS= hypotensive cardiogenic shock; NHCS= non-hypotensive cardiogenic shock; Proc Procedural; TTE transthoracic echocardiography

Procedural success: when at least 50% reduction of the aortic gradient was obtained without a moderate to severe aortic regurgitation, which was assessed by TTE after the procedure

* P values < 0.05

Supplementary Table 2: In-hospital outcomes according to VARC-2 criteria and postoperative data

Outcomes	All n=44	HCS n=31	NHCS n=13	P value
Clinical data	-	-	-	-
In-hospital mortality, n (%)	20 (45%)	16 (52%)	4 (31%)	0.20
Procedural mortality, n (%)	3 (6%)	2 (6%)	1 (8%)	0.88
Major Vascular complication, n (%)	0 (0%)	0 (0%)	0 (0%)	1.0
Blood transfusion unit, mean +/-SD	0.9 +/- 1.6	1.3 +/- 1.9	0.3 +/- 1.2	0.13
Stroke, n (%)	1 (2%)	1 (3%)	0 (0%)	0.51
TIA, n (%)	0 (0%)	0 (0%)	0 (0%)	1.0
Pace maker implantation, n (%)	0 (0%)	0 (0%)	0 (0%)	1.0
Acute kidney injury 3, n (%)	9 (20%)	7 (23%)	2 (15%)	0.57
Need of hemodialysis, n (%)	5 (11%)	4 (13%)	1 (8%)	0.62
Cardiac tamponade, n (%)	1 (2%)	0 (0%)	1 (8%)	0.12
Stay ICU (days), mean +/-SD	9.9 +/- 8.9	11.5 +/- 9.1	6.1 +/- 7.6	0.08
Stay duration (days), mean +/-SD	18.2 +/- 11.9	18.3 +/- 12.4	18.1 +/- 10.9	0.96
Discharge home after ICU, n (%)	12 (27%)	4 (13%)	8 (62%)	**0.01***
Postoperative TTE	-	-	-	-
LVEF (%), mean +/- SD	31.8 +/- 16.3	29.5 +/- 11.5	36.8 +/- 23.3	0.21
Mean Ao gradient (mmHg), mean +/- SD	23.3 +/- 11.2	22.5 +/- 10.7	25.4 +/- 12.5	0.46
AVA (cm^2), mean +/- SD	0.82 +/- 0.20	0.79 +/- 0.15	0.86 +/- 0.27	0.47
Grade III-IV AR, n (%)	1 (2%)	1 (2%)	0 (0%)	0.51
RV TAPSE (mm), mean +/- SD	15.2 +/- 3.3	15.3 +/- 3.8	15.2 +/- 2.7	0.93
RV Sdti (cm/s), mean +/-SD	9 +/- 2	9 +/- 2	9 +/- 1	1.00
PASP (mmHg), mean +/-SD	45.4 +/- 16.7	46.8 +/- 13.7	43.8 +/- 20.9	0.71
Postoperative Biological data	-	-	-	-
Lactate max (mg/l), mean +/- SD	255.3 +/- 169.5	273.2 +/- 175.1	136.7 +/- 12.9	0.20
Troponin T Hs max (ng/l), mean +/-SD	834.8 +/- 1285.2	905.4 +/-1367.7	552.6 +/- 948.9	0.59
Creatinine max (mg/l), mean +/-SD	25.2 +/- 12.3	26.7 +/- 12.4	21.3 +/- 12.0	0.24
Hemoglobin nadir (g/dl), mean +/-SD	9.8 +/- 1.8	9.7 +/- 1.9	10.0 +/- 2.0	0.77

AR= aortic regurgitation; AVA= aortic valve area; HCS= hypotensive cardiogenic shock; ICU= intensive care unit; LVEF= left ventricular ejection fraction; Max maximum; NHCS= non-hypotensive cardiogenic shock PASP= pulmonary artery systolic pressure; NHCS= non-hypotensive CS; RV right ventricle; TAPSE= tricuspid annular plane systolic excursion; TIA= transient ischemic attack; TTE= transthoracic echocardiography. * P values < 0.05

Supplementary Table 3 One-month and One-year outcomes

Follow-up after BAV	All n=44	HCS n=31	NHCS n=13	P value
1-month outcomes	-	-	-	-
1-month mortality, n (%)	21 (47%)	17 (55%)	4 (31%)	0.14
1-month Stroke/TIA, n (%)	1 (2%)	1 (3.2%)	0 (0%)	0.52
1-month Recurrent Heart Failure, n (%)	5 (11%)	5 (16%)	0 (0%)	0.12
1-month NYHA IV, n (%)	2 (4%)	2 (6%)	0 (0%)	0.32
Staged procedures during FU	-	-	-	-
TAVR, n (%)	10 (22%)	5 (16%)	5 (38%)	**0.01***
SAVR, n (%)	2 (4%)	1 (3%)	1 (8%)	0.52
1-year outcomes	-	-	-	-
1-year mortality, n (%)	31 (70%)	24 (77%)	7 (53%)	0.11
1-year mortality or recurrent CS, n (%)	33 (75%)	26 (83%)	7 (53%)	**0.03***

CS= cardiogenic shock; FU= follow-up; HCS= hypotensive cardiogenic shock; NHCS= non-hypotensive cardiogenic shock; TAVR= transcatheter aortic valve replacement; SAVR= surgical aortic valve replacement, TIA= transient ischemic attack. * P values < 0.05

Supplementary Table 4: Causes of death before and after 1-month follow-up

Causes of death after BAV	Before 1-month FU n=21 deaths	After 1-month FU n=10 deaths
Refractory cardiogenic shock n (%)	8 (38%)	2 (20%)
Hemorrhagic shock n (%)	2 (9%)	0 (0%)
Septic shock n (%)	1 (5%)	0 (0%)
Recurrent Heart failure n (%)	0 (0%)	2 (20%)
Myocardial infarction n (%)	1 (5%)	1 (10%)
Acute kidney injury n (%)	2 (9%)	0 (0%)
Pneumonia n (%)	3 (15%)	2 (20%)
Tamponade n (%)	1 (5%)	0 (0%)
Cancer n (%)	0 (0%)	2 (20%)
Severe aortic regurgitation n (%)	1 (5%)	0 (0%)
Unknown n (%)	2 (9%)	1 (10%)

FU follow-up

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B) **Balloon Aortic Valvuloplasty for Severe Aortic Stenosis Before Urgent Noncardiac Surgery.**

Debry N, Altes A, Vincent F, Delhaye C, Schurtz G, Nedjari F, Legros G, Porouchani S, Coisne A, Richardson M, Cosenza A, Verdier B, Denimal T, Pamart T, Spillemaeker H, Sylla H, Sudre A, Janah D, Aouate D, Marsou W, Appert L, Lemesle G, Labreuche J, Marechaux S, Van Belle E.

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Nous avons poursuivi le registre rétrospectif de valvuloplastie aortique (BAV) au CHRU de Lille jusqu'en 2019, et analysé l'intérêt de la BAV chez les patients (n=93) qui devaient bénéficier d'une chirurgie extracardiaque urgente. Nous avons comparé ce groupe de patient à un groupe de patients avec RA serré (n=40) suivi dans un autre centre qui privilégie un traitement médical non invasif avant une intervention urgente extra cardiaque.

Pour le sous-groupe spécifique de patients avec RA sévère nécessitant une chirurgie urgente non élective, les données cliniques sont rares. Le risque d'effectuer une intervention semi-urgente (< 7 jours) ou d'urgence (< 48 heures) n'est pas bien connu car ces conditions chirurgicales à haut risque sont généralement sous-représentées (environ 10 %) dans les études. En outre, l'utilité du BAV préopératoire dans ce contexte particulier est inconnue : aucune étude randomisée comparant les résultats des patients avec RA sévère subissant une chirurgie urgente sous une approche conservatrice ou invasive n'a été menée à ce jour et le bénéfice net de la BAV en tant que préparation à ces interventions est incertaine en raison du taux élevé de complications potentielles de BAV dans ces conditions. Ceci explique pourquoi la pratique clinique est très variable avec certains centres utilisant une stratégie invasive-valvuloplastie aortique percutanée par ballonnet chez tous les patients alors que d'autres n'en font jamais (stratégie conservatrice).

Dans la présente étude, nous avons entrepris de réévaluer à l'époque actuelle les résultats des patients avec RA sévère nécessitant une chirurgie extracardiaque urgente non élective et le bénéfice potentiel d'une stratégie invasive (BAV) par rapport à une stratégie conservatrice médicale.

Balloon Aortic Valvuloplasty for Severe Aortic Stenosis Before Urgent Noncardiac Surgery.

Abstract

Aims: We evaluated the clinical benefit of an invasive strategy (IS) with preoperative balloon aortic valvuloplasty (BAV) in patients with severe aortic stenosis (SAS) requiring urgent noncardiac surgery (NCS).

Methods and Results: From 2011 to 2019, a registry included n=40 with SAS without preoperative BAV (conservative strategy-CS) and n=93 patients with SAS treated with preoperative BAV (IS) before urgent NCS. All analyses were adjusted for confounding using inverse probability of treatment weighting (IPTW) (10 clinical and anatomical variables). The primary outcome was the MACE at 1-month follow-up after NCS including mortality, heart-failure, and other cardiovascular outcomes. In patients managed conservatively, occurrence of MACE was 20.0%(n=8) and death was 10.0%(n=4) at 1 month. In patients undergoing BAV, occurrence of MACE was 20.4%(n=19) and death was 5.4%(n=5) at 1-month. Among patients undergoing conservative management, all events were observed after NCS while in patients undergoing BAV, 12.9%(n=12) had postBAV complications including 3 deaths(before NCS) and 2 deaths after NCS. In IPTW-propensity analyses, the incidence of the primary outcome (20.4% vs. 20.0%;OR=0.93;95%CI:0.38-2.29) and 3-months survival (89.2% vs. 90.0%;IPTW-adjustedHR=0.90;95%CI:0.31-2.60) were similar in both groups.

Conclusions: Patients with SAS managed conservatively before urgent NCS are at high risk of events. A systematic invasive strategy using BAV does not provide a significant improvement in clinical outcome.

Classifications: balloon aortic valvuloplasty, aortic stenosis, noncardiac surgery

Condensed Abstract

From 2011 to 2019, a prospective registry included n=93 patients with SAS treated with preoperative BAV (invasive strategy,IS), and n=40 with SAS without preoperative BAV (conservative strategy,CS) before urgent noncardiac surgery(NCS). Patients treated with the invasive strategy were compared to those treated with conservative strategy using IPTW propensity score (10 clinical and anatomical variables). In CS patients, occurrence of MACE was 20.0%(n=8) and death 10.0%(n=4) at 1-month after NCS. In IS patients, occurrence of MACE was 20.4%(n=19) and death 5.4%(n=5) at 1-month. In IPTW-propensity analyses, the incidence of the primary outcome (20.4% vs. 20.0%;OR=0.93;95%CI:0.38-2.29) and 3-months survival (89.2% vs. 90.0%;IPTW-adjusted HR=0.90;95%CI:0.31-2.60) were similar in both groups.

Abbreviations:

Acute kidney injury:AKI
Aortic regurgitation:AR
Balloon aortic valvuloplasty:BAV
Chronic obstructive pulmonary disease:COPD
Coronary artery bypass surgery:CABG
Conservative strategy:CS
Invasive strategy:IS
Left ventricular ejection fraction:LVEF
Major advert cardiac event:MACE
Noncardiac surgery:NCS
Severe Aortic stenosis:SAS
Society of thoracic surgeons score:STS score
Transcatheter aortic valve implantation:TAVI
Transient ischemic attack:TIA
Transthoracic echocardiography:TTE

Introduction

Management of severe aortic stenosis (SAS) patients undergoing noncardiac surgery (NCS) is a challenging and relatively frequent topic (1), with no clear evidence-based strategy.

Performing elective NCS in patients with SAS has been associated with a relatively high rate of MACE (18.8%) and mortality (5.9%) at 1-month (2). In that context an invasive strategy based on balloon aortic valvuloplasty (BAV) before NCS has been proposed as an option to reduce this risk (3,4). The 2017 ESC and 2014 ESC/AHA/ACC recommendations, which are largely based on small and observational studies that are now more than three decades old (5-7) , suggest to differ the NCS whenever it is possible, while BAV can be proposed with a low level of evidence class IIbC (7).

For the specific subgroup of SAS patients requiring urgent non-elective NCS, clinical data are even more scarce (8,9). The risk of performing urgent (< 7days) or emergency (<48hr) NCS is not well known as these high-risk surgical conditions are usually under-represented (around 10%) in studies investigating the risk of NCS in SAS patients (2,10). Besides, the utility of preoperative BAV in this particular setting is unknown. No randomized study comparing the outcomes of SAS patients undergoing urgent NCS under conservative or invasive approach has been conducted to date and the net benefit of BAV as a preparation for urgent NCS is uncertain because of the potential high complication rate of BAV in these conditions (11,12). This explains why the practice is very wide with some centers using an invasive strategy-percutaneous balloon aortic valvuloplasty (BAV) in all SAS patients before urgent NCS while others in none (conservative strategy).

In the current study we set forth to re-evaluate in the contemporary era the outcomes of SAS patients requiring urgent non-elective NCS and the potential benefit of an invasive strategy (preoperative BAV for urgent NCS) vs. conservative strategy. This was conducted by comparing the outcomes of SAS patients undergoing BAV prior urgent NCS to the outcomes of SAS undergoing urgent NCS without prior BAV and used as a control group.

Methods.

Patient selection

In this retrospective study, we involved two centers with different strategy regarding the management of SAS patients before urgent noncardiac surgery from 2011-2019.

(i) One center with a default *invasive strategy* using routine BAV before NCS,

(ii) One center with a default *conservative strategy* without BAV by before NCS.

Severe aortic stenosis was considered to be present at the time of surgery if documented within 12 months before surgery. Severe aortic stenosis was defined using current echocardiographic (TTE) criteria (aortic valve area ≤1 cm^2, peak systolic flow velocity ≥4 m/s, mean gradient ≥40 mmHg) in conjunction with typical 2D echocardiographic appearance of severe AS (13). Patients undergoing aortic valve replacement before non-cardiac surgery were excluded. Patients with high gradients or velocities attributable to increased cardiac output (anaemia, septic shock, etc.), as well as those with concomitant diseases that may have influenced Doppler indexes of SAS (hypertrophic obstructive cardiomyopathy, sub- or supravalvular aortic stenosis, coarctation of the aorta, or complex congenital heart diseases) were excluded.

Baseline demographic data, type of surgical intervention, comorbidities, symptoms potentially associated with SAS (dyspnoea), and echocardiographic data just before surgery were extracted from the electronic medical record.

Regarding BAV procedure, the size of the balloon was chosen according to the annulus measurement according to the TTE before BAV. NuMed Nucleus® and ZMed Braun® balloons were used for transfemoral BAV, and VACS II Osypka® balloons for transradial BAV. Valvuloplasty was considered successful if significant reduction (≥50%) of the mean transaortic gradient assessed by hemodynamic measures was obtained.

This study was approved by the institutional ethics committee.

Echocardiography

All echocardiograms were performed as clinically indicated, and in accordance with current European and American Society of Echocardiography recommendations (13). In

patients with multiple echocardiograms, the study closest to the time of surgery was selected. Aortic valve parameters (valve area and valve area index, peak aortic velocity and mean aortic valve gradient), as well as left ventricular size, ejection fraction, and estimated pulmonary artery systolic pressure (based on tricuspid regurgitant velocity) were extracted from the echocardiographic database.

Non-elective non-cardiac surgery (NCS)

Surgical interventions were classified according to current ESC/ACC/AHA guidelines into low, intermediate, and high risk (5). Patients undergoing low (transurethral resection of the prostate, superficial, eye, breast surgery…; reported cardiac risk <1%), intermediate (intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopaedic surgery, prostate surgery; reported cardiac risk 1–5%) and high-risk procedures (aortic and other major vascular surgery, peripheral vascular surgery; reported risk >5%) (5) under general or locoregional anaesthesia were included. Semi-urgent NCS included patients who were operated within 2 to 7 days and emergency NCS those who were operated within 48hr. Ambulatory, ophthalmological and percutaneous interventions were excluded.

Clinical endpoints

We compared the outcomes after NCS of invasive vs. conservative strategy of management of SAS patients. The primary endpoint (MACE) was a composite endpoint of 1-month mortality, heart failure, myocardial infarction, stroke/transient ischemic attack, new atrial fibrillation, acute kidney injury (rise of >2 fold of baseline creatinine and/or <0.5ml/kg/hr urine output), and life-threatening bleeding (hypovolemic shock or severe hypotension requiring vasopressors or surgery, or packed red blood cells (RBCs) transfusion ≥4 units) after NCS. The secondary outcome included predictive factors of 1-month MACE. Other analyses included 3-months survival after NCS. All medical files were carefully reviewed and in case of doubts clinical events were adjudicated by a medical committee of two physicians.

Statistical Analysis

Quantitative variables are expressed as means (standard deviation) in the case of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and the Shapiro-Wilk test. Patients were divided in two groups according to the strategy used. Baseline characteristics were described according to the two study groups and the magnitude

of the between-group differences in pre-specified confounders was assessed by calculating the absolute standardized difference; an absolute standardized difference >10% was interpreted as a meaningful difference (14). Between-group comparisons in surgical procedure characteristics, and association of potential predictors of primary clinical endpoint (1-month MACE) were done using Chi-square test or Fisher's exact in case of expected cell frequencies <5. Comparison in outcomes between the two study groups was done using logistic regression model for MACE, linear regression model for length of hospital stay (after log-transformation values to satisfy the residual normality) and Cox's proportional hazard model for 3-month all-cause mortality; effect sizes and their 95% confidence intervals were derived from regression models using patients treated with conservative strategy (without preoperative BAV) as control group. In order to take into account the pre-specified confounders, comparisons in outcomes were further done by using pre- inverse probability of treatment weighting (IPTW) propensity score method (using stabilized inverse propensity score as weighty in regression models). The propensity score was estimated using a multivariable logistic regression model, with study groups as the dependent variable and a pre-specified confounders as covariates (**Table 1**) (15). Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analyzed by J.L. using the SAS software version 9.4. (SAS Institute, Cary, NC).

Results

Study Population

(i) SAS patients undergoing conservative strategy before NCS

As presented in **Figure 1**, from 2011 to 2019, we identified 40 patients with SAS (Aortic valve area=0.77 ± 0.22cm^2) undergoing NCS without BAV prior before NCS.

(ii) SAS patients undergoing invasive strategy (BAV) procedure before NCS

We also identified 93 patients with severe aortic stenosis (Aortic valve area=0.72 ± 0.15cm^2) treated with preoperative BAV before NCS (**Figure 1**). BAV was performed 4 (2-11) days before noncardiac surgery.

Baseline Characteristics

Baseline characteristics and comorbidities of the different groups are presented in **Table 1** (main pre-specified confounders for IPTW score) and in **Table 2**.

When comparing TTE characteristics in both groups at baseline (**Table 1),** there was no significant difference in mean aortic gradient (45.0mm±13.6mmHg vs. 42.3±8.1mmHg; P=0.24) or maximal velocity (4.2±0.6m/s vs. 4.1±0.4m/s; P=0.45), and aortic valve area (0.72±0.15cm^2 vs. 0.77±0.22cm^2; P=0.16).

After IPTW using propensity score, the between-group differences in main confounders (**Table 1**) were reduced as shown in **supplemental Figure 1**.

BAV procedure and outcomes in the invasive strategy group before urgent NCS

Mean Balloon size was 21.6±1.7mm and mean number of inflations was 1.6±0.6. N=5 (5.3%) were performed through the radial artery. Complications (n=12, 12.9%) of BAV included: 2 (2.1%) perprocedural death due to cardiac arrest after crossing the valve for BAV, 1 (1.0%) death following a major stroke, 3 (3.2%) patients requiring a permanent pace-maker implantation after the procedure, 4 (4.3%) patients had a clinical hematoma at the femoral puncture site without need of transfusion, 1 (1.0%) patient presented a transient (<24h) hemiplegia after the BAV, and 1 (1.0%) patient had a homolateral acute limb ischemia requiring an urgent reperfusion. BAV was successful in most severe AS cases (70% had a significant reduction (≥50%) of the mean transaortic gradient assessed by hemodynamic measures) with a significant reduction of the transaortic gradient: 45.0±13.6mmHg vs. 32.4±11.4; P<0.001, the aortic maximal velocity: 4.2±0.6m/s vs. 3.6±0.6 P<0.001, and the

AVA: 0.72±0.15 cm^2 vs. 0.91±0.2 P<0.001 evaluated by transthoracic echocardiography. Finally 90 patients who had a preoperative BAV were undergoing NCS.

Non-elective Noncardiac surgery

Period of NCS (before or after 2015), timing of surgery (emergency or semi-urgent) and type of anaesthesia (general or not) were well balanced in the two groups (**Table 2)**. Details about noncardiac surgery procedures are depicted in **Table 3**.

Outcomes after non-elective noncardiac surgery (NCS)

(i) Primary endpoint

The rate of MACE at 1-month was 20.4% in the invasive strategy group and 20.0% in the conservative strategy group, unadjusted analysis OR=1.03; 95%CI:0.40-2.59 and IPTW-adjusted analysis OR=0.93; 95%CI:0.38-2.29. Details in individual events included in MACE are available in **Table 4**. Reasons for death in the CS group were limb ischemia (n=1) and multiple organ failure (n=1) after vascular surgery, cardiac arrest (asystole) after hip repair, and critical sepsis (n=1) after abdominal surgery. Other causes of death in the IS group after NCS included n=1 mitral endocarditis after acute gonarthritis, and n=1 digestive cancer.

(iii) Predictive factors of 1-month MACE

In the global SAS cohort, univariate predictive factors of primary endpoint included higher ASA score≥3 (28.3% vs. 4.7% ; P=0.001) and preoperative pulmonary hypertension>35mmHg (33.0% vs. 14.7% ; P=0.007).

In the invasive strategy group, univariate predictive factors of primary endpoint included ilio-femoral artery disease (38% vs. 15%; P=0.02), higher ASA score ≥3 (29.1% vs. 3.6%; P=0.003) and preoperative pulmonary hypertension>35mmHg (37.2% vs. 11.8% P=0.003).

(iii) Other outcomes

Among one-month events, heart failure, life-threatening bleeding, stroke/TIA and acute kidney injury occurred at the same rate in the two groups (**Table 4**). Regarding length of hospital stay for NCS, invasive strategy was associated with a non-significant shorter duration (median 6 days; IQR 4 to 9) than conservative strategy (median 8 days; IQR 4 to 16, **Table 4**). In the overall cohort 34 (25.5%) patients had a TAVI procedure after NCS (invasive strategy 31.2% vs. conservative strategy SAS 12.5%) with a median delay of 103 days (52;200). No patient had surgical aortic valve replacement.

As shown in the **Figure 2,** there was no difference in 3-months survival between CS and IS with an IPTW-adjusted HR of 0.90 (95%CI:0.31-2.60).

There was no difference regarding 1-month MACE (26.1% vs. 23.4%; P=0.82) or 1-month mortality (15.2% vs. 8.9%; P=0.39) between conservative and invasive strategies before emergency NCS (<48hr).

There was also no difference regarding 1-month MACE (33.9% vs. 40.0%; P=0.82) or 1-month mortality (33.5% vs. 20.8%; P=0.61) between conservative and invasive strategies before high-risk NCS.

Discussion

The best preoperative management of SAS patients before urgent NCS is unknown. This study is the first (i) to provide the largest set of SAS patients undergoing urgent NCS, and to include a large proportion (>60%) of emergent (<48h) NCS, and (ii) to compare conservative and invasive strategy before urgent NCS using IPTW analysis. Overall it reflects the real life of managing old patients with SAS who suffer, for example, from hip fracture which requires emergency surgery to preserve their autonomy (8).

The main findings from this IPTW analysis are: (i) Patients with SAS managed conservatively before NCS are at high risk of events: high 1-month MACE (20.0%) and 1-month mortality (10.0%), (ii) Performing BAV in such population is not "benign" and is associated with 3.2% mortality and 9.6% non-fatal complications at 7 days, (iii) While "immediate" one-month mortality after NCS might be lower in "survivors" of the invasive strategy, overall one month MACE and 3-months survival are similar in SAS patients treated with or without BAV, (iv) ASA score≥3 or preoperative pulmonary hypertension>35mmHg seems to impact prognosis after NCS.

Some studies have previously described the outcomes of AS patients vs. non-AS patients undergoing NCS (**Table 5**). Patients with AS undergoing non-cardiac surgery have not been shown to be at increased risk of mortality, but have significantly higher rates of adverse cardiovascular events compared to patients without AS (16), especially those with symptomatic SAS have more MACE (acute myocardial infarction, acute heart failure, arrhythmia) than asymptomatic SAS (36% vs. 16% respectively) and higher mortality rates than moderate AS (16% vs. 4%) (17).

We report higher 1-month mortality (10.0%) and MACE (20.0%) rates with conservative strategy after urgent NCS, than *Tashiro et al*. from the Mayo Clinic, but the latter explored only asymptomatic patients with AS after scheduled NCS (1-month mortality 3.3% and MACE 12%) (2).

No randomized study comparing the outcomes of SAS patients undergoing urgent NCS under conservative or invasive approach has been conducted to date. Invasive strategy reduced "immediate" 1-month mortality rate after NCS (3.2% vs. 10.0%;P=0.04) but not if we take into account the mortality induced by the BAV itself (5.4% and 10.0%; P=0.33).

Partly because of the insufficient "hemodynamic result" and the complications linked to the invasive strategy, both attitudes have similar one-month MACE after NCS. While we confirm that routine invasive strategy using for SAS patients isn't recommended, it may be beneficial for some selected patients.

Asymptomatic SAS patients, or patients requiring low-intermediate risk NCS could be managed conservatively (10). As the *Tashiro* study reminds us, urgent and scheduled NCS have not the same morbidity as emergency NCS alone is also a strong predictor of 30-day mortality (2). Published reports indicates that on the basis of TTE adverse events during NCS occurred primarily in AS patients with an AVA ≤0.7 cm^2 and a mean gradient ≥50 mm Hg (9). In our study, because of a small cohort and the presence of severe AS in both groups, we were not able to identify anatomical aortic criteria that should encourage us to perform BAV before NCS. However preoperative pulmonary hypertension>35mmHg and ASA score ≥3 are associated with higher short-terms MACE and mortality rates. Invasive strategy in patients with these criteria could be discussed to improve prognosis after NCS.

The first way to decrease morbi-mortality after NCS may be to reduce the morbidity related to the BAV procedure. Using smaller unilateral (18) or bilateral sheath slender (19) transradial access for BAV is safe and feasible. BAV with low-profile compliant balloons (20), without pace maker back-up (21), or with pacing on the left ventricular guidewire (22) has also recently been described.

The second way may be to improve the hemodynamic result of the procedure. In our study, 30% of the patients did not experienced a significant improvement of the hemodynamic parameters following BAV. In addition, in the remaining 70% with an improvement, the mean residual gradient was 30.0+/-0.4mmHg. The only way to achieve a clear hemodynamic improvement, and possibly a decrease in morbi-mortality after NCS, might be to perform direct TAVI to some very selected patients. The improvement of SAS with TAVI is obvious compared to BAV in terms of hemodynamic, symptoms, recurrence and mortality. But in this particular preoperative situation, TAVI can be difficult to perform because it requires a dedicated technical platform with on-site multislice CT-scan and available cathlab. It requires at least a 14F vascular access, larger than for a transradial BAV (9F), and may be associated with more complications. In our study, only 25% of the global SAS cohort had a TAVI procedure within 3 months after NCS highlighting that this population has fewer symptoms, a combination of frailty and multiple comorbidities including cancer, disabilities, which in the

end may postpone or even cancel the TAVI procedure. However, other studies reported that cancer patients with severe AS who underwent AVR had an improved survival, regardless of cancer status (23). Finally direct TAVI can be at specific risk in case of bacteriemia for example before urgent digestive surgery, or septic orthopaedic surgery with a high risk of endocarditis. On the other hand, when compared to aortic surgery, TAVI under local anesthesia is less invasive and may avoid the possibility of cancer dissemination due to extracorporeal circulation for patients with malignancy.

Finally we insist on the crucial importance of the pluridisciplinary discussion among the Heart-Team for each patient before NCS. Large-scale prospective cohort studies are needed to clarify the above interrogations and delineate the role of TAVI in this population.

Large-scale prospective cohort studies are needed to delineate the role of minimally-invasive BAV procedure or "direct" TAVI in selected high-risk patients.

Limitations

Limitations to this study are inherent to the non-randomized design. The present findings are derived from observational analyses, which are subject to well-known limitations. The main is the potential for confounding by measured or unmeasured variables, which cannot be ruled out, even after IPTW adjustment. In particular, we could not exclude a residual bias related to age or NCS risk since both remained not *completely* balanced in IPTW-adjusted analysis, *as well as to other patient's characteristics not included in propensity score calculation*. No formal sample size calculation was done and we therefore caution that we could not excluded a lack of adequate statistical power to detect the between-group differences. In a posteriori power calculation, our study sample size (93 patients with invasive strategy and 40 patients with conservative strategy) allows, with 80% power, to detect with type-1 error of 5%, an odd ratio of MACE at 1-month of 3.2 (or 0.19 for protective effect) for patients with invasive strategy versus conservative strategy. These calculations were done by considering the observed rate of MACE at 1-month in conservative group (20%) a 80% power and two-sided type-1 error of 5%.

Conclusions

Patients with SAS managed conservatively before urgent NCS are at high risk of events. A systematic invasive strategy using BAV does not provide a significant improvement in clinical outcome.

Impact on daily practice

The presence of SAS in patients requiring urgent non-elective NCS (including 62% emergency surgery performed <48hr) is at high risk of mortality and clinical events. Our study suggests that the performance of BAV before NCS does not provide enough safety and hemodynamic benefit to be performed in a systematic fashion. The indication of BAV needs to be discussed on an individual basis. Large-scale prospective cohort studies are needed to delineate the role of minimally-invasive BAV procedure or "direct" TAVI in selected high-risk patients before NCS.

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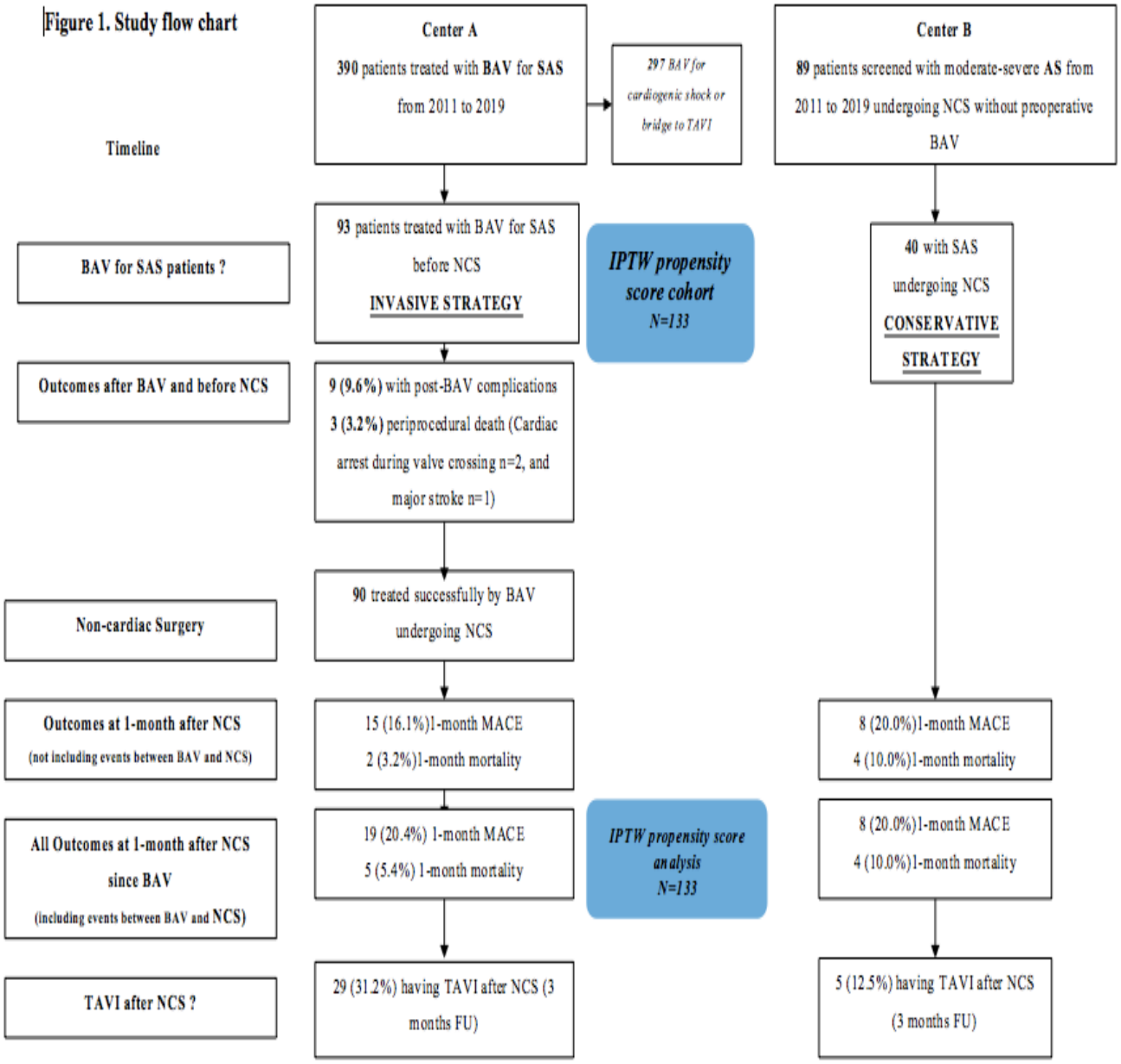
Figures legends

Figure 1. Study flow chart
Figure 2. 3-months survival after NCS in patients with invasive (BAV) or conservative (without BAV) strategy
Central Illustration: Figure 1



Abbreviations: SAS= severe aortic stenosis; BAV=Balloon aortic valvuloplasty; FU=follow-up; NCS=noncardiac surgery; SAS=severe aortic stenosis, TTE=transthoracic echocardiography

Figure 2

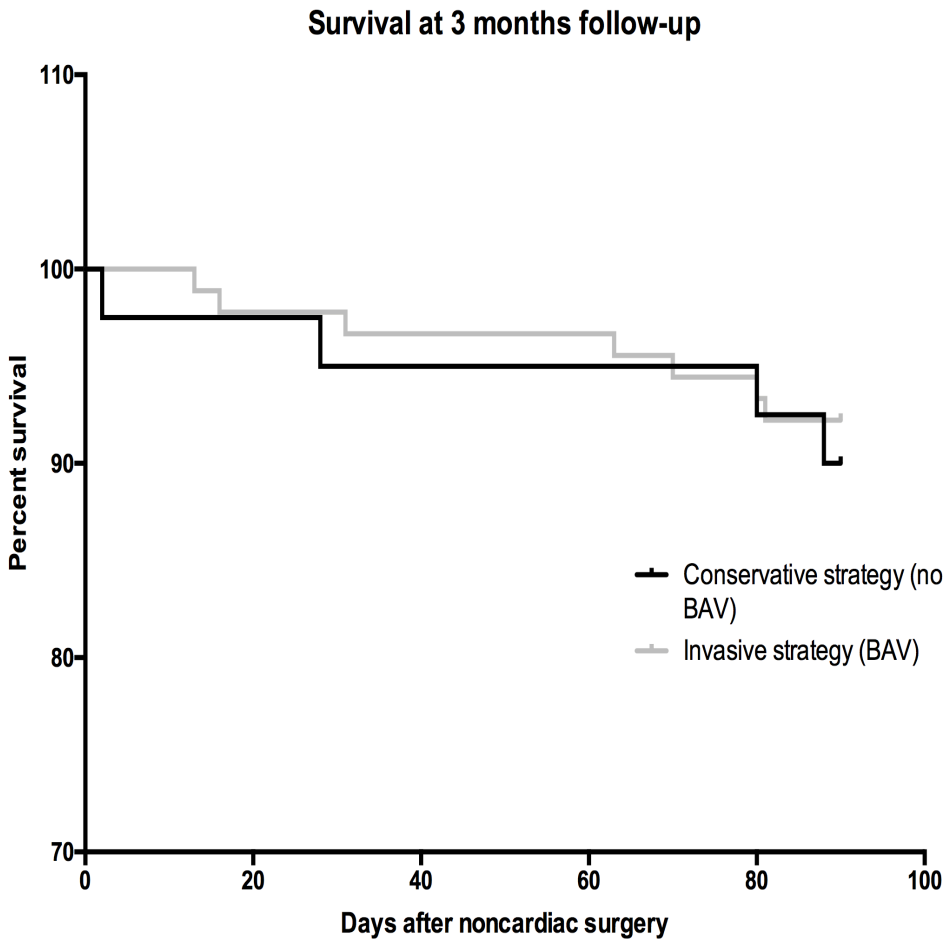

Survival at 3 months follow-up
110
100
90
80
70
Percent survival
0
20
40
60
80
100
Days after noncardiac surgery
Conservative strategy (no BAV)
Invasive strategy (BAV)

Table 1. Main Baseline Characteristics(pre-specified confounders) in aortic stenosis patients before urgent NCS

Characteristics	*Severe AS (n=133)*		
	Invasive strategy (n=93)	**Conservative strategy (n=40)**	**ASD, %**
Patient's characteristics			
Age (years)	79.9 ± 9.5	83.0 ± 8.0	35.4
Male gender	38 (40.9)	19 (47.5)	13.4
Surgery Period > 2015	45 (48.4)	19 (47.5)	1.8
ASA score			
-2	31 (33.3)	13 (32.5)	5.0
-3	37 (39.8)	15 (37.5)	
-4	25 (26.9)	12 (30.0)	
STS score (nov. 2018 %)	3.0 ± 1.3	3.2 ± 1.4	10.9
TTE characteristics[1]			
LVE fraction (%)	56.6 ± 12.2	59.2 ± 9.3	23.7
AVA (cm2)	0.72 ± 0.15	0.77 ± 0.22	24.8
Mean Transaortic gradient (mmHg)	45.0 ± 13.6	42.3 ± 8.1	24.1
Aortic Maximal Velocity (m/s)	4.2 ± 0.6	4.1 ± 0.4	15.6
Surgery characteristics			
Noncardiac surgery risk[2]			
-Low	21 (22.6)	9 (22.5)	29.1
-Intermediate	57 (61.3)	28 (70.0)	
-High	15 (16.1)	3 (7.5)	

Values expressed as numbers (%) unless otherwise indicated. These variables were used for the IPTW score.

[1] evaluated by TTE before BAV and before noncardiac surgery. [2] according to ESC 2014 and 2017 recommendations

Abbreviations: ASA=American society of anesthesiologists score; ASD=absolute standardized difference; AVA=aortic valve area (cm^2); BAV=balloon aortic valvuloplasty; LVE=left ventricular ejection; SAS=severe aortic stenosis; TTE=transthoracic echocardiogram.

Table 2. Baseline Characteristics (considered as non- specified confounders) in aortic stenosis patients

	Invasive strategy (n=93)	Conservative strategy (n=40)
Patient's characteristics	-	-
Hypertension	72(77)	30(75)
Diabetes mellitus	27(29)	12(30)
Obese (BMI>30)	13(14)	5(12)
Ilio-femoral artery disease	21(23)	15(37)
Coronary disease	33(35)	12(30)
Previous CABG	2(2)	2(0.5)
Active cancer	33(35)	3(7)
Renal dysfunction, n (%)	24(26)	10(25)
COPD	13(14)	6(15)
Atrial fibrillation	29(31)	12(32)
Prior Stroke/TIA	11(12)	9(22)
Preoperative pacemaker	8(9)	4(1)
Dyspnea III-IV before NCS	72(77)	12(30)
Medication at the time of surgery	-	-
Anticoagulant	24(25)	10(25)
Antiplatelet	60(64)	34(85)
Statins	56(60)	27(67)
CEI/ARAII	45(48)	19(47)
B-blockers	25(27)	10(25)
Other TTE characteristics before surgery	-	-
LVE fraction (%)	57.5+/-12.1[1]	59.2 ± 9.3
AVA (cm^2)	0.91+/-0.21[1]	0.77 ± 0.22
Mean Transaortic gradient (mmHg)	32.4+/-11.4[1]	42.3 ± 8.1
Aortic Maximal Velocity (m/s)	3.6+/-0.6[1]	4.1 ± 0.4
Bicuspid aortic valve	7(7)	4(10)
Left ventricle volume (mL), mean±SD	100.6 ± 28.4[1]	105.4 ± 30.2
Mitral regurgitation	31(33)[1]	14(35)
Left atrium volume (mL), mean±SD	45.7 ± 17.9[1]	44.8 ± 19.3
Sdti (cm/s), mean±SD	10.8 ± 2.1[1]	11.1 ± 3.0
Systolic PAP (mmHg), mean±SD	35.5 ± 11.1[1]	33.5 ± 10.7
Surgery characteristics	-	-
Timing of surgery	-	-
-Emergency(<48hr)	61(65)	22(55)
-Semi-urgent(2-7days)	32(35)	18(45)
General anesthesia	84(90)	33(83)

Values expressed as numbers (%) unless otherwise indicated. Renal dysfunction defined as GFR ≤60ml/min/m^2.

[1] evaluated by TTE after BAV and before noncardiac surgery.

Abbreviations: ARAII=angiotensin II receptor antagonist; ASA=American society of anesthesiologists score; AVA=aortic valve area; CABG= coronary artery bypass graft; BAV=balloon aortic valvuloplasty; CEI=converting enzyme inhibitors; COPD= chronic obstructive pulmonary disease; IQR=interquartile range; LVE= left ventricular ejection; PAP=pulmonary artery pressure; SAS=severe aortic stenosis; SD=standard deviation; Sdti= tricuspid lateral *annular* systolic velocity; TIA=transient Ischemic Attack; TTE= transthoracic echocardiogram

Table 3: Surgical procedures according to 2014 ESC recommendations

	Severe AS (n=133)		P value
	Invasive strategy (n=93)	**Conservative strategy (n=40)**	
High-risk surgery	*15(16.1)*	*3(7.5)*	*0.18*
Aortic and major vascular surgery	5(5.3)	2(5.0)	0.93
Pneumonectomy	2(2.1)	0(0.0)	0.35
Major digestive surgery[1]	8(8.6)	1(2.5)	0.20
Intermediate-risk surgery	*57(61.3)*	*28(70.0)*	*0.34*
Major orthopaedic surgery	21(22.5)	9(22.5)	0.99
Major urological/renal surgery	6(6.4)	2(5.0)	0.75
Major neurological surgery	4(4.3)	1(2.5)	0.62
Major gynecologic surgery	3(3.2)	1(2.5)	0.82
Minor vascular surgery [2]	5(5.3)	7(17.5)	0.03
Intraperitoneal surgery [3]	18(19.3)	8(20.0)	0.93
Low-risk surgery	*21(22.6)*	*9(22.5)*	*0.99*
Superficial surgery	2(2.1)	2(5.0)	0.38
Minor orthopaedic surgery	14(15.0)	6(15.0)	0.99
Minor gynecologic surgery	3(3.2)	1(2.5)	0.82
Minor urological surgery	2(2.1)	0(0.0)	0.35

[1] duodena-pancreatic, liver, bile-duct, perforated bowel surgery or esophagectomy; [2] carotid symptomatic, endovascular aneurysm, peripheral arterial surgery; [3] splenectomy, hiatal hernia repair, cholecystectomy

Table 4. One-month outcomes after urgent NCS in patients with SAS after IPTW Propensity-Score

			Unadjusted analysis		IPTW-adjusted analysis	
	Severe AS (n=133)					
Outcomes	**Invasive strategy (n=93)**	**Conservative strategy (n=40)**	**Effect size (95%CI)**	**P**	**Effect size (95%CI)**	**P**
Composite cardiovascular outcome (MACE)	19 (20.4)*#	8 (20.0)	1.03 (0.40 to 2.59)[1]	0.96	0.93 (0.38 to 2.29)[1]	0.88
Heart Failure	*8 (8.6)*	*4 (10.0)*				
Myocardial infarction	*1 (1.1)*	*1 (2.5)*				
New atrial fibrillation	*7 (7.5)*	*2 (5.0)*				
Life-Threatening bleeding	*3 (3.2)*	*0 (0.0)*				
Stroke/TIA	*1 (1.1)#*	*0 (0.0)*				
Acute kidney injury	*5 (5.4)*	*5 (12.5)*				
Mortality	*5 (5.4)**	*4 (10.0)*				
Length of hospital stay, days, median (IQR)	6 (4 to 9)	8 (4 to 16)	-0.20 (-0.53 to 012)	0.22	-0.29 (-0.62 to 0.04)	0.082

The propensity score was estimated using a multivariable logistic regression model, with study groups as the dependent variable and a pre-specified confounders as covariates (age, sex, surgery period, ASA score, STS score, LVEF, AVA, mean transaortic gradient, maximal velocity, NCS risk).

[1] odds ratio calculated using unweighted (unadjusted analysis) and weighted (IPTW-adjusted analysis) logistic regression models using conservative strategy group as reference.

[2] mean difference (95%CI) calculated on log-transformed values among patients discharged alive (n=129) by using unweighted (unadjusted analysis) and weighted (IPTW-adjusted analysis) linear regression models

*including 3 deaths after BAV before NCS; #including 1 TIA after BAV before NCS

Abbreviations: AR=aortic regurgitation ; BAV=balloon aortic valvuloplasty ; CI=confidence interval ; MACE=major advert cardiovascular event; NCS=noncardiac surgery, SAS=severe aortic stenosis; TIA=transient ischemic attack.

Table 5. Summary of studies with AS patients and noncardiac surgery

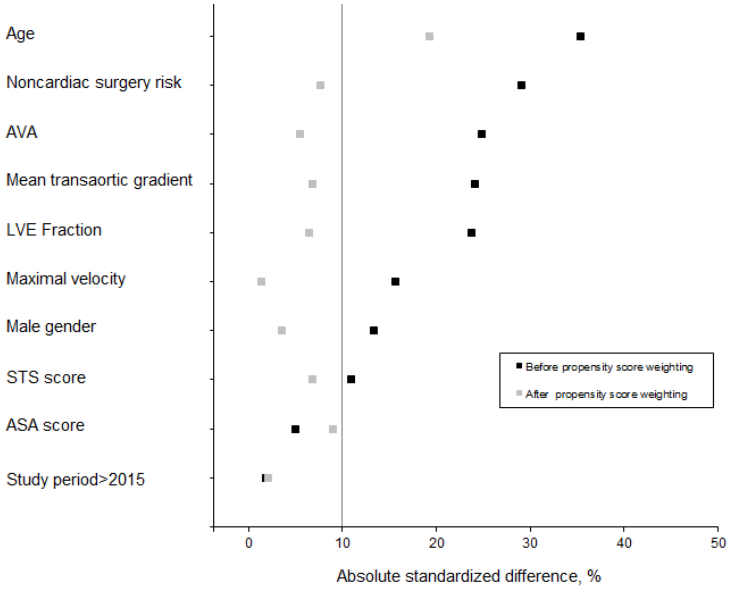
Study	N	Urgent non elective NCS(n,%)	Preop BAV(n)	Type of NCS	NCS requiring General anesthesia (%)	NCS within 7 days	ASA score	Risk score of NCS[1]	Comparative group	Ref.
Hayes et al. Mayo Clin Proc(1989)	15	9(60%)	15(100%)	Miscellaneous	60%	80%	NA	NA	No comparison	4
Leibowitz et al. Gerontology(2009)	32	32(100%)	0(0%)	Hip fracture	30%	100%	NA	NA	Matched control comparison without AS	9
Calleja et al. AJC(2010)	30	3(10%)	0(0%)	Miscellaneous	73%	NA	NA	Intermediate -low	Matched control comparison without AS	10
Tashiro et al. EHJ(2014)	256	24(10%)	0(0%)	Miscellaneous	NA	NA	NA	High-intermediate	Matched control comparison without AS	2
Keswani et al. Injury(2016)	65	65(100%)	0(0%)	Hip fracture	60%	100%	ASA3,4 100%	NA	Matched control comparison without AS	8
MacIntyre et al. Anaesth Intensive Care(2018)	147	30%	0(0%)	Miscellaneous	NA	NA	ASA 4=18-37%	High: 4-15%	Comparison moderate vs. severe AS (no propensity)	17
Debry et al. (2020)	133	133(100%)	93(70%)	Miscellaneous	90%	100%	ASA 4=15-24%	High:10-15%	IPTW comparison between invasive(BAV) and conservative strategy	-

Abbreviations: AS=aortic stenosis, BAV=balloon aortic valvuloplasty, GA=general anesthesia, NCS=noncardiac surgery, TC=transcarotid, TAx=transaxillary, Tao=transaortic, TF=transfemoral, Tap=transapical, NA not available

[1] according to ESC 2014 recommendations

Supplementary data

Supplemental Figure 1. Absolute Standardized differences between invasive or conservative strategies before and after IPTW Propensity Score



Abbreviations: ASA= american society of anesthesiologists; AVA=aortic valve area; BAV=balloon aortic valvuloplasty; LVEF= left ventricular fraction; STS= society of thoracic surgeons;

CHAPITRE 2: TAVI et voies d'abord alternatives à la voie fémorale

Transaxillary compared with transcarotid access for TAVR: a propensity-matched comparison from a French multicentre registry

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Après avoir étudié la réparation aortique percutanée dans des situations où la correction définitive du RA n'est pas toujours possible, nous nous sommes focalisés sur les patients traités par TAVI via des voies non fémorales. En effet, notre équipe avait déjà étudié la voie transcarotidienne pour les patients avec RA sévère à haut risque lié à une artériopathie contre-indiquant la voie transfémorale pour le TAVI. Nous avons établi un registre des voies alternatives les plus couramment utilisées (transcarotidienne et transaxillaire) réalisé dans 4 centres français à haut volume entre 2010 et 2018 afin de comparer via un propensity matching ces 2 voies alternatives.

L'accès optimal pour les patients subissant une TAVI qui ne sont pas candidats à une approche transfémorale (TF) n'a pas été clairement élucidé. L'utilisation de la technique transapicale et transaortique a été délaissée au profit d'autres voies. Des alternatives extra-thoraciques possibles pour les patients ne se prêtant pas à un TAVI transfémorale comprennent les voies transcarotidienne (TC) et transaxillaire/sous-clavière (TAx).

Des études récentes avec l'accès TAx rapportent des résultats similaires à la voie fémorale, y compris des taux d'hémorragie menaçant le pronostic vital (12 %), des taux de mortalité à 30 jours (6 %). La voie TAx a également une mortalité à 30 jours plus faible, des durées de séjour à l'hôpital plus courtes que les voies transthoraciques, y compris l'accès transapical et transaortique. Cependant, certains auteurs suggèrent que la voie TAx peut avoir un taux d'AVC plus élevé et plus de complications vasculaires que l'accès TF. Nous avons précédemment étudié la sécurité et la faisabilité du TAVI transcarotidien à l'aide de prothèse auto-extensible et par ballonnet, gérée sous anesthésie générale ou stratégie mini-invasive avec des résultats cliniques favorables. Le but de cette étude était de comprendre quelle approche devrait être l'alternative préférée en comparant leurs résultats à l'aide d'une comparaison par propensity matching dans un registre multicentrique français.

Transaxillary compared with transcarotid access for TAVR: a propensity-matched comparison from a French multicenter registry

Abstract

Aims:

No randomized study comparing the outcomes of transcarotid (TC) and transaxillary (TAx) TAVR has been conducted to date.

Methods and Results

From 2010 to 2018, a French multicenter prospective registry included 502 patients with n=374 undergoing TC-TAVR and n=128 TAx-TAVR for symptomatic aortic stenosis. Patients treated through TAx access were matched 1:2 to patients treated through TC route by using propensity score (20 clinical, anatomical and procedural variables) and by date of the procedure. The first outcome was the mortality at 1-month follow-up. The second outcome was 1-month stroke/transient ischemic attack (TIA).

In matched-propensity analyses, the incidence of the primary outcome was similar in TAx and TC group (TAx 5.5% vs. TC 4.5%; OR=1.23; 95%CI:0.40-3.70). The secondary outcome was similar in TAx (3.2%) and TC (6.8%; OR=0.52; 95%CI:0.14-1.84). Minor bleeding (2.7% vs. 9.3%; OR=0.26; 95%CI:0.07-0.92) and main access hematoma (3.6% vs. 10.3%; OR=0.034; 95% CI:0.09-0.92) were significantly more frequent with the TC access. One-month clinical efficacy and safety and 1-year mortality did not differed according to different routes.

Conclusions

One-month mortality, 1-month stroke/TIA and 1-year mortality are similar with TAx and TC TAVR. However TC-TAVR is accompanied by more minor bleeding and main access hematoma compared with the transaxillary route.

Classifications: TAVI, aortic stenosis, subclavian, subclavian, other

Condensed Abstract

From 2010 to 2018, a French multicenter prospective registry included 502 patients with n=374 undergoing TC-TAVR and n=128 TAx-TAVR for symptomatic aortic stenosis. Patients treated through TAX access were matched 1:2 to patients treated through TC route by using propensity score (20 clinical, anatomical and procedural variables) and by date of the procedure. In matched-propensity analyses, the incidence of the 1-month mortality was similar in TAx and TC groups (TAx 5.5% vs. TC 4.5%; OR=1.23; 95%CI:0.40 to 3.70; p=0.71). One-month stroke/TIA rate was similar in TAx (3.2%) and TC (6.8%; RR=0.52; 95% CI:0.14-1.84; p=0.31). Minor bleeding (2.7% vs. 9.3%; RR=0.26; 95% CI:0.07-0.92; p=0.035) and main access hematoma (3.6% vs. 10.3%; RR=0.034; 95% CI:0.09-0.92; p=0.034) were more frequent with the TC access.

Abbreviations:

Acute kidney injury:AKI
Aortic regurgitation:AR
Carotid artery:CA
Cerebral magnetic imaging:MRI
Chronic obstructive pulmonary disease:COPD
Coronary artery bypass surgery:CABG
General anesthesia:GA
Multi Slice Computed tomography:MSCT
Percutaneous coronary intervention:PCI
Surgical aortic valve replacement:SAVR
Transaxillary/subclavian:TAx
Transcarotid:TC
Transient ischemic attack:TIA
Transcatheter aortic valve replacement:TAVR
Transthoracic echocardiography:TTE
Valve academic research consortium-2:VARC-2

Introduction

The transfemoral(TF) access is the primary access route for the vast majority of patients undergoing Transcatheter aortic valve replacement (TAVR) thanks to the refinement of the procedure and material (1). In 2019, the penetrance of the transfemoral approach was as high as 85% in the United States (2) and France (3), and 99% in low-risk patients (4).

The optimal access for patients undergoing TAVR who are not candidates for a transfemoral approach has not been clearly elucidated (5,6). The use of transapical and transaortic technique has been surpassed by other routes (7). Possible extra-thoracic alternatives for the patients not amenable to transfemoral TAVR, have been developed recently, including the transcarotid(TC) and transaxillary/subclavian(TAx) routes.

Recent studies with TAx access report similar outcomes, including life-threatening bleeding rates (12%), 30-days mortality rates (6%) than TF procedures (8,9). TAx pathway has also lower 30-day mortality, shorter lengths-of-hospital stay than transthoracic routes including transapical and transaortic access (10-12). However, some authors suggest that TAx route may have a higher stroke rate (11,13) and more vascular complications (13) than the TF access. We previously investigated the safety, feasibility of transcarotid TAVR using self and balloon-expandable prosthesis, managed under general anesthesia or minimally-invasive strategy with favourable clinical outcomes (14-17). We currently use TC or TAx access as first-line alternative approach for TAVR whenever the transfemoral access is prohibited.

The purpose of this study was to understand which approach should be the preferred alternative by comparing their outcomes using a propensity-matched comparison in a French multicenter registry.

Methods

Patient selection

Between 2010 and 2018, consecutive patients undergoing transcarotid and transaxillary TAVR at four French institutions (Institut Coeur-Poumons, CHU Lille, Lille, France; Hôpital Marie Lannelongue, Le Plessis-Robinson, France; CHU Montpellier,

Montpellier, France, CH Lens, Lens, France) were included in a collaborative prospective registry. In all cases, the transfemoral approach was precluded by diseased descending aorta (aortic dissection, aortic aneurysm, porcelain aorta), or severe peripheral arterial disease (small caliber≤5.5mm, severely tortuous, heavily calcified, dissected, significant stenosis) or prior ilio-femoral intervention or surgery. Selection of alternative access was then individualized to each patient's anatomic features and comorbidities.

The yearly number and proportions of total TAVR cases that were not transfemoral, in the 4 participating centers (2010-2018) are depicted in **Figure 1**, and represents around 10% of total TAVR procedures in these institutions. The mean case volume per site per year was 4.0 for TAx and 11.6 for TC procedures.

Details about Pre-procedural screening and Procedural technique can be found in the Supplementary data

Clinical endpoints

The primary endpoint of interest was 1-month mortality (2,18) in TC and TAx TAVR. Secondary endpoints were: 1-month stroke/transient ischemic attack (TIA), 1-month clinical efficacy (all-cause mortality, disabling or non-disabling stroke, or hospitalizations for valve-related symptoms or worsening congestive heart failure (CHF)), 1-month early safety (all-cause mortality, stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury, coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure), and 1-year mortality. Further analyses included major outcomes including acute kidney injury (AKI), aortic regurgitation, bleeding or vascular access complications according to the Valve Academic Research Consortium-2 consensus definitions (18).

All medical files were carefully reviewed and in case of doubts clinical events were adjudicated by a medical committee of two physicians.

Statistical Analysis

Quantitative variables are expressed as means (standard deviation) in the case of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and the Shapiro-Wilk test. Patients were divided in two groups according to access site of TAVR

(transaxillary vs. transcarotid). Baseline characteristics were described according the two study groups and the magnitude of the between-group differences was assessed by calculating the absolute standardized difference; an absolute standardized difference >10% was interpreted as a meaningful difference.

Details about the propensity-matched comparison can be found in the supplementary data (19).

Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Population

Depiction of TC and TAx TAVR procedures is presented in **Figure 1 and 2**.

Baseline characteristics before matching and handling missing values are presented in **Supplemental Table 1**. Baseline characteristics according to access, before and after propensity score- matching and after handling missing values by multiple imputation are presented in **Table 1**. The distributions of propensity score according to access are reported in **Supplemental Figure 1** and absolute standardized differences between TAVR routes before and after Propensity Score Matching are reported in **Supplemental Figure 2**.

Before matching, most characteristics were already well balanced (absolute standardized difference ≤10%), except that patients treated with a TAx-TAVR had a higher prevalence of ilio-femoral severe disease, severe renal dysfunction, and COPD. TAx-TAVR procedures were more often performed after 2015, with a second-generation prosthesis (S3 and Evolut R), with more predilation and using the right access more frequently. These differences were controlled after propensity-score matching (**Table 1, Supplemental Figure 2**) where n=113 TAx-TAVR could be matched to n=201 TC-TAVR.

Impact of access site on the outcomes

(i) Mortality and composite outcomes

In the propensity-score matched cohort, there was no difference in 1-month mortality (TAx 5.5% vs. TC 4.5%; OR=1.23; 95%CI:0.40-3.70), 1-month early safety (TAx 88.6% vs. TC 85.8%; OR=1.38, 95%CI:0.64-2.94) or clinical efficacy (TAx 88.6% vs. TC 85.9%;

OR=1.22; 95%CI:0.57-2.58) between the two access sites (**Table 2**). There was also no difference in mortality at 1-year follow-up, with a matched HR of 0.83(95%CI:0.41-1.70).

(ii) Morbidity including vascular complications

Among procedural and in-hospital events, major vascular access complications, life-threatening and major bleeding occurred at the same rate in the two groups. Lower rates of minor bleeding (TAx 2.7% vs. TC 9.3%; OR=0.26; 95%CI:0.07-0.92) and main access hematoma (TAx 3.6% vs. TC 10.3%; OR=0.29; 95%CI:0.09-0.92; p=0.034) were also found in patients treated through the TAx-route, while difference in minor vascular access complications did not reach the significance level (TC 7.0% vs. TAX 2.7%; OR=0.31; 95%CI:0.08-1.15; p=0.078). There is no significant difference in postprocedural mean transprothetic maximal velocity between the two groups populations (mean difference between TAx vs. TC=0.10; 95%CI:-0.08-0.29).

(iii) Cerebrovascular events

Overall, they have 30 (6.0%) VARC2-defined 1-month cerebrovascular events: 16(3.2%) strokes (NIHSS score 1 n=1, 2 n=1, 3 n=3, 4 n=3, 5 n=3, 6 n=4, and 8 n=1) and 14(2.8%) TIAs, as assessed by clinical and neuroimaging criteria. Nine patients with stroke (56%) had no sequelae at hospital discharge. Cerebrovascular events happened shortly after the procedure: n=15 at day 0, n=5 at day 1, n=2 at day 2, n =3 at day 3, n=2 at day 5, n=2 at day 6, n=1 at day 11. The clinical deficits were localized as ipsilateral(n=8) or contralateral(n=12) to the vascular access site. Clinical features of the events included confusion(n=4), hemiparesis(n=4), hemiplegia(n=15) and aphasia(n=5), Claude-Bernard Horner signs(n=2); neuroimaging showed new ischemic lesions in the 16 stroke cases (multiple embolic lesions). One patient(0.8%) in the transaxillary group had a brachial plexus sideration. After propensity-matching, 1-month stroke/TIA rate did not differed between the two procedure both groups (TAx 3.2% vs. TC 6.8%; OR=0.52; 95%CI:0.14-1.84).

Discussion

Herein, we describe one of the largest series of patients undergoing transcarotid or transaxillary vascular access for TAVR. The main findings from this propensity-matched cohort are: (i) TC and TAx TAVR have similar 1-month mortality, 1-month stroke/TIA, and clinical safety and efficacy with balloon or self-expanding valves, (ii) Less minor bleeding and main access hematoma appear in the transaxillary access group.

Comparative data about these two most currently used alternative routes for TAVR are unavailable. Numerous articles have previously described these routes in comparison to transthoracic TAVR with favorable results (**Table 3**).

Non-femoral peripheral TAVR

A recent French registry in a non-femoral peripheral TAVR cohort found a similar stroke rate (3.35%), lower major vascular complications (0.68%) and higher major bleeding (8.56%) (20) than in our analyse. We also report similar device success (95.4%) and 1-month mortality (5.0%) rates as *Dahle et al.* (11). However this STS/ACC registry (11) using only balloon expandable valves report extremely low major vascular complications (1.1%) and life-threatening bleeding rates (0.1%). Evaluation of VARC-2 outcomes was not clinically adjudicated in these registries (11,16,20), and it cannot be excluded that some clinical events, in particular TIA, might have been partly underreported, since it is also significantly lower than reported in clinical trials (21). Indeed, we report similar rates of major vascular complications (9.0% vs. 11.9%) and less major and life-threatening bleeding (3.6% vs. 11.4%), than other previous TAx studies (9,13) with only self-expanding valves. Potential explanations for this detrimental result with non-femoral TAVR include a procedural learning curve. The transaxillary or transcarotid accesses may also be more delicate than the iliofemoral ones and prone to vessel dissection, stenosis or thrombosis, and is not accessible for effective manual compression.

Comparison of TAx and TC TAVR

In line with previous report (22), our study suggests that both approaches are equally safe without difference in early (30-day) and late (1-year) mortality and similar early stroke/TIA rates. In the case of transcarotid TAVR, even if it offers a more direct-straighter access, a less angular path to reach the aortic valve, with less vascular interaction, local

complications including local hematoma and minor bleeding, debris embolization, and the transient reduction in cerebral blood flow during the procedure may explain the non-significant increase of 1-month stroke/TIA rate (6.8% vs. 3.2%). The TIA/stroke rate with the TC route did not decrease significantly between the early period (2010-2015 and the use of first generation prosthesis) and after 2015 (7.0% vs. 5.4%, p=0.53). The rate of 30-day stroke/TIA that we report is in the upper margin of those previously reported by *Amer et al.*(22) (3%), and *Mylotte et al.*(15) had also a 3.2% rate of 30-day stroke/TIA. These above figures are also consistent with those of a previous report of ours in which a 5.7% rate of periprocedural cerebrovascular events and a 11.4% rate of global vascular access complications with TC TAVR were reported (14). Passive antegrade carotid perfusion using a temporary femoro-carotid shunt during TC-TAVR was used for the first TC-TAVR patients during the early days (2010) and is no more used.

The more direct access from the carotid artery allows more precise positioning of the prosthesis, especially for self-expanding valves, which could have resulted in a reduction in periprothetic regurgitation. This may not be the case because the angle of the delivery catheter from the carotid with respect to the plane of the ring is less favourable than for the left axillary artery which allows the delivery catheter to position itself on the lateral wall of the aorta and finally to cross the plane of the ring more perpendicularly than from the carotid (**Figure 3**).

We also prefer the left axillary/carotid artery over the right because it avoids injury or embolization to the innominate artery that supplies the right carotid and vertebral distribution. Also, isolated injury to the left axillary/carotid artery is easier to repair than innominate artery injury. While our rates of percutaneous TAx access is low, it remains unclear how surgical and percutaneous TAx approaches mays ultimately differs as centers gain more experience with each approach (23).

The observed incidence of combined vascular and bleeding complications in both groups underscores the need for a detailed multidisciplinary preprocedure assessment of vascular anatomy to determine the optimal alternative TAVR approach.

Limitations of the study:

Limitations to this study are inherent to the non-randomized design. The present findings are derived from observational analyses which are subject to well-known limitations.

The first is the potential for confounding by measured or unmeasured variables, which cannot be ruled out, even after propensity score matching or adjustment. A second limitation was the presence of missing data in some covariates, including in the propensity score calculation, as well as in outcomes. Although we used multiple imputations to handle missing data as appropriate, we could not exclude that missing data could introduce a bias in estimates.

Conclusion

TC and TAx TAVR have similar 1-month mortality, 1-month stroke/TIA and clinical safety and efficacy with balloon or self-expanding valves. Less minor bleeding and main access hematoma appear in the transaxillary access group. Randomized studies are required to ascertain whether transcarotid or transaxillary TAVR yields similar results.

Impact on daily practice

Early post-procedural complications following alternative peripheral accesses TAVR dropped significantly over the years with growing experience, and are similar through TAx or TC routes overall. However these data may suggest that less minor bleeding and main access hematoma appear in the transaxillary access group.

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Figure 1. Yearly number and proportion of total transcarotid (TC) or transaxillary/subclavian (TAx) TAVR procedures

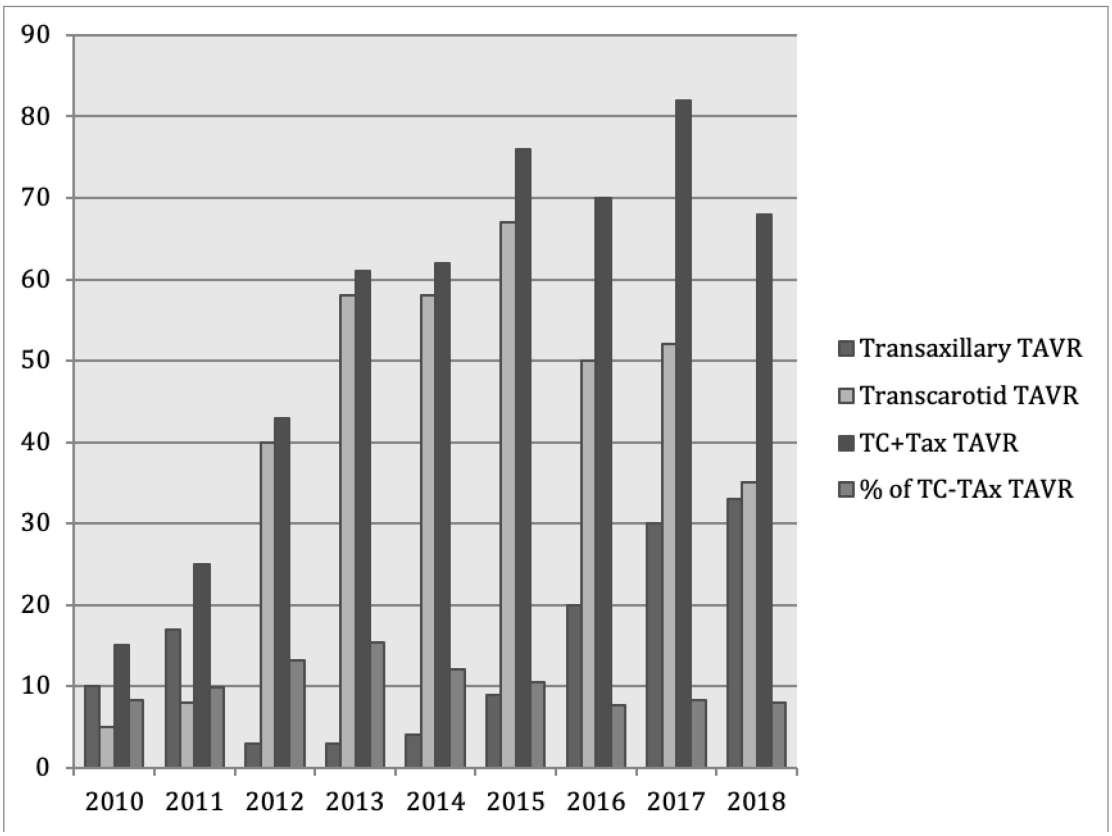


Figure 2. Study flow chart

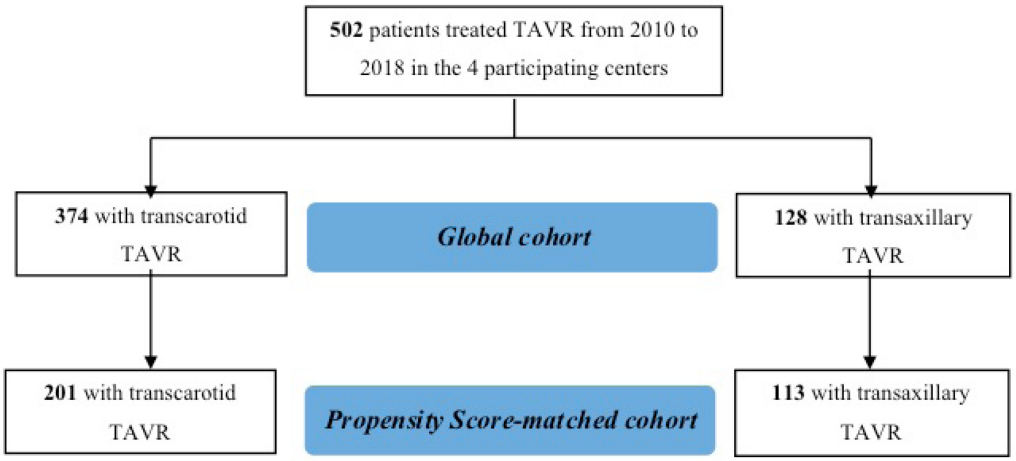
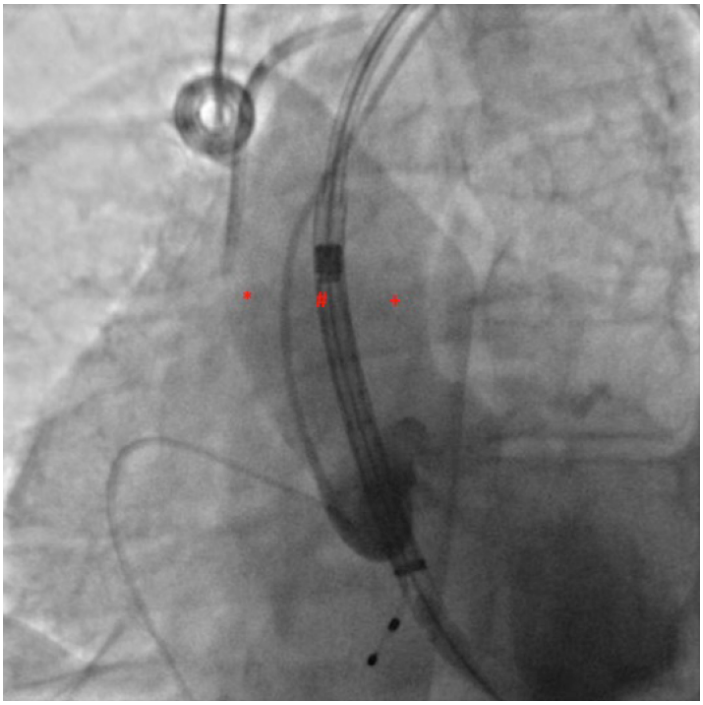


Figure 3. Optimising the delivery of self-expandable valves according to vascular access. When using the left axillary artery, as the delivery catheter positionate itself on the lateral wall of the aorta (*), it is better to open the prosthesis at 6mm under the annulus. When using, the carotid or the right axillary artery (+), delivery should start from 0mm. And when arriving at the center of the native valve (#), and therefore perpendicular to the annulus, delivery should start 3mm under the annulus.



TABLES

Table 1. Main Baseline Characteristics In patients with Trans-catheter aortic valve replacement (TAVR) According to Access Site Before and After Propensity Score-Matching

Characteristics	Before Matching			After Matching		
	Transcarotid TAVR (n=374)	Transaxillary TAVR (n=128)	ASD,%	Transcarotid TAVR (n=201)	Transaxillary TAVR (n=113)	ASD,%
Patient's characteristics						
Age, years median(IQR)	83(77-86)	82(79-86)	1.2[1]	83(77-87)	82(78-86)	2.2[1]
Male gender	223(59.6)	80(62.5)	5.9	126(62.7)	70(62.2)	1.2
Diabetes mellitus	122(32.6)	36(28.1)	9.8	63(31.4)	33(28.8)	5.6
Ilio-femoral artery disease	227(60.7)	88(68.8)	16.9	135(67.4)	77(68.4)	2.1
Previous PCI	233(62.3)	81(63.3)	2.0	119(59.2)	72(63.8)	9.4
Previous CABG	68(18.2)	27(21.1)	7.3	37(18.6)	21(18.6)	0.2
Previous AVR	27(7.2)	7(5.5)	7.2	12(6.2)	6(5.4)	3.4
Severe renal dysfunction	137(36.6)	64(50.0)	27.2	91(45.3)	50(44.1)	2.3
COPD	111(29.8)	50(39.1)	19.9	78(38.6)	43(37.8)	1.4
Prior Stroke/TIA	58(15.6)	14(10.9)	13.5	26(13.1)	12(10.8)	6.8
STS score (2018), %, median(IQR)	5.4(3.6-8.3)	5.8(3.9-8.6)	8.7[1]	5.5(3.5-8.1)	5.8(3.9-8.5)	8.6[1]
TTE characteristics						
LVE fraction, %, median(IQR)	55(45-60)	55(45-61)	0.1[1]	55(41-60)	55(45-61)	8.1[1]
Procedural characteristics						
Intervention after 2015	201(53.7)	91(71.1)	36.4	132(65.9)	77(67.9)	4.4
Right access	66(17.6)	30(23.4)	14.4	41(20.5)	24(21.3)	1.9
Predilation	135(36.1)	71(55.5)	39.6	104(51.6)	55(48.6)	6.0
Postdilation	54(14.4)	17(13.3)	2.8	25(12.4)	16(14.1)	5.2
Valve in valve	29(7.8)	6(4.7)	12.7	11(5.6)	6(5.4)	0.6
Local anesthesia	77(20.6)	6(4.7)	49.3	11(5.6)	6(5.4)	0.1
Bioprosthesis size						
23mm	43(11.5)	22(17.3)	24.6	29(14.2)	16(14.5)	10.7
26mm	132(35.3)	50(39.3)		77(38.3)	43(37.4)	
29mm	170(45.5)	49(38.0)		85(42.1)	47(41.8)	
31 or 34mm	29(7.8)	7(5.5)		10(5.4)	7(6.3)	
2nd generation devices	182(48.7)	91(71.1)	47.0	134(66.7)	77(67.9)	2.6

Values expressed as numbers (%) unless otherwise indicated. Values were calculated after handling missing data using multiple imputation procedure.

[1] estimated using the rank-transformed data. Severe renal dysfunction defined as GFR ≤30ml/min/m2.

2nd generation devices included SAPIEN S3 and EVOLUT R prosthesis.

Abbreviations: ASD=absolute standardized difference; AVR=aortic valve replacement; AR=aortic regurgitation; CABG=coronary artery bypass graft; COPD=chronic obstructive pulmonary disease; GFR=glomerular filtration rate; IQR=interquartile range; PCI=percutaneous coronary intervention; LVE=left ventricular ejection; TAVR=trans-catheter aortic valve replacement; TIA=transient Ischemic Attack; TTE=transthoracic echocardiogram.

Table 2. Procedural, Hospital, 1-month and 1-year outcomes in patients with Trans-catheter aortic valve replacement According to Access Site After Propensity-Score matching

Outcomes	Transcarotid TAVR(n=201)	Transaxillary TAVR(n=113)	Effect size(95%CI)	P
Procedural and in hospital outcomes				
Device success	192(95.4)	108(95.5)	0.95(0.28-3.16)[1]	0.93
Acute kidney injury 2-3	27(13.5)	25(22.5)	1.72(0.90-3.27)[1]	0.10
New pace maker implantation	38(19.0)	22(19.5)	0.99(0.53-1.81)[1]	0.97
LT or major bleeding	11(5.7)	4(3.6)	0.62(0.18-2.13)[1]	0.44
Minor bleeding	19(9.3)	3(2.7)	0.26(0.07-0.92)[1]	0.035
Major vascular access complications	17(8.5)	10(9.0)	1.20(0.48-2.96)[1]	0.70
Minor vascular access complications	14(7.0)	3(2.7)	0.31(0.08-1.15)[1]	0.078
Main access hematoma	21(10.3)	4(3.6)	0.29(0.09-0.92)[1]	0.034
Hospital stay, days median (IQR)	8(6-11)	9(6-13)	0.84(0.67-1.05)[2]	0.12
AR grade ≥ II,	19(9.3)	6(5.4)	0.54(0.20-1.45)[1]	0.22
Transprothetic maximal velocity, m/s, mean(SD)	2.1(0.8)	2.2(0.9)	0.10(-0.08-0.29)[3]	0.25
1-month and 1-year outcomes				
1-month mortality	9(4.5)	6(5.5)	1.23(0.40-3.70)[1]	0.71
1-month clinical efficacy	173(85.9)	100(88.6)	1.22(0.57 -2.58)[1]	0.61
1-month safety	172(85.8)	100(88.6)	1.38(0.64-2.94)[1]	0.40
1-month stroke/TIA	14(6.8)	4(3.2)	0.52(0.14-1.84)[1]	0.31
1-year all-cause Mortality, n(KM, %)	23(19.1)	16(16.1)	0.83(0.41-1.70)[4]	0.62

Values are number of events(%) unless otherwise as indicated. Number of events(%), mean(SD) and effect sizes were calculated after handling missing values for variables included in the propensity score and outcomes by multiple imputation(m=10).

[1]odds ratios calculated using a GEE model for binary data with a logit link function. [2]subhazard ratio calculated using a Fine and Gray regression model with alive discharge as outcome event and intrahospital mortality as competing event, with the robust sandwich variance estimate to account the matched sets. [3]mean between group difference calculated using Linear mixed model including matched sets as random effect. [4]hazard ratio calculated using a Cox's regression model with the robust sandwich variance estimate to account the matched sets.

Clinical efficacy defined as all-cause mortality, disabling or non-disabling stroke, or hospitalizations for valve-related symptoms or worsening congestive heart failure (CHF). Early safety defined as all-cause mortality, stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury, coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure.

Abbreviations: AR=aortic regurgitation; IQR=interquartile range; KM=kaplan Meier estimate; LT=life-threatening; SD=standard deviation; TAVR= trans-catheter aortic valve replacement; TIA=transient ischemic attack.

Table 3. Summary of recent studies with transcarotid and/or transaxillary TAVR

Study	Access	N. TAx or TC TAVR (And TC)	Prosthesis	Results for TAx or TC	Ref.
Overtchouk et al. JACCi(2019)	TC only	314(314)	Balloon expandable (Sapien 3)	Sapien 3 device is safe and effective	16
Watanabe et al. Circ J(2018)	TC vs. TF	83(83)	Balloon and self expandable	Feasibility and 30-day safety are similar	17
Chamandi et al. Circ Cardiovasc Interv(2018)	TC vs. Tap/TAo	101(101)	Balloon and self expandable	Less atrial fibrillation, major bleeding, acute kidney injury and shorter length of stay	7
Gleason et al. Ann Thorac Surg(2018)	TAx vs. TF	202(0)	Self expandable	Similar morbidity and mortality rates	9
Beve et al. Am J Cardiol(2019)	TAx+TC vs. Tao+Tap	87(14)	Balloon and self expandable	Shorter length of stay Comparable mortality and morbidity	12
Dahle et al. JACCi(2019)	TAx vs. Tap+Tao	1249(0)	Balloon expandable	Lower 30-day mortality, shorter length of stay, higher stroke rate	11
Amer et al. Ann Thorac Surg(2019)	TAx vs. TC	71(33)	Balloon and self expandable	Shorter scopy time with TC	22
Van der Wulp et al. Ann Thorac Surg(2019)	TAx only	362(0)	Self expandable	5% mortality at 1-month	24
Debry et al.(2019)	TAx vs. TC	502(374)	Balloon and self expandable	Similar 1-month mortality and 1-month stroke/TIA rate, more minor bleeding and vascular access complications with TC	-

Abbreviations: TC=transcarotid, TAx=transaxillary, Tao=transaortic, TF=transfemoral, Tap=transapical

Supplementary data

Pre-procedural screening

Suitable carotid and axillary artery anatomy and dimensions, and vertebral artery patency were carefully assessed with preoperative doppler ultrasound and multislice computed tomography (MSCT) as previously described (14,16). A common carotid or axillary artery minimal luminal diameter threshold of ≥ 6.0mm was considered appropriate for these vascular accesses.

Patients with significant (≥50%) common or internal carotid artery stenosis, plaque considered to be at high risk of embolization, were not considered for transcarotid TAVR. Prior ipsilateral carotid artery intervention, contralateral carotid artery occlusion, or stenosis / occlusion of the vertebral arteries were also considered to be contraindication to transcarotid TAVR.

Patients with steep subclavian to arch angulation (e.g., >80°), severe aortic root angulation or ipsilateral internal mammary artery used as a coronary bypass graft were a contraindication to transaxillary TAVR.

Procedural technique

The left common carotid or left axillary artery was preferentially selected as it afforded simpler cardiac catheterization with more favourable annular alignment, and operating room configuration. Selection of the bioprosthesis was determined following aortic root assessment using MSCT.

Standard transcarotid/transaxillary TAVR implantation technique was followed as previously described (9,10,14) with unfractionated intravenous heparin given to achieve an activated clotting time of ≥250 seconds. Surgical access for TAx was predominant as axillary percutaneous approach is relatively recent. All patients were receiving at least single-antiplatelet therapy at the time of TAVR. Procedures were performed under general or local anesthesia with invasive hemodynamic monitoring, according to operator preference. Doppler imaging of the carotid/axillary artery was systematically performed before discharge.

Statistical analysis

We compared the outcomes between the two study groups after taking to account the potential confounding factors by using propensity score matching method. The propensity score was estimated using a non-parsimonious multivariable logistic regression model, with study groups as the dependent variable and all of the characteristics listed in **Table 1** (considered as potential predictors as covariates). Patients treated by transaxillary TAVR were matched 1:2 to patients treated with transcarotid TAVR according to propensity score using the greedy nearest neighbor matching algorithm with a caliper width of 0.2 standard deviation of logit for propensity score. To evaluate bias reduction using the propensity score matching method, absolute standardized differences were calculated after propensity-score matching. Because of missing baseline and outcome data (range from 0 to 10.6%), we estimated the effect sizes in matched-propensity score cohort after handling missing covariate values by multiple imputations using a regression switching approach (chained equations with m=10 imputations). Imputation procedure was performed under the missing at random assumption using all baseline variables, study group and outcomes with a predictive mean matching method for continuous variables and logistic regression models (binary, ordinal or multinomial) for categorical variables. In each imputed dataset, we calculated the propensity score and assembled a matched cohort to provide adjusted effect sizes, which were later combined by using the Rubin's rules.

Between-group comparisons were done using a generalized estimating equations (GEE) model (binomial distribution, logit function) with a compound symmetry working correlation structure for binary outcomes, using Fine and Gray regression model for hospital duration (considering alive discharge as event of interest and by treating in hospital death as competing risk), a linear mixed model with the matched blocks as random effect for transprothetic maximal velocity, and by using Cox's regression model for 1-year all-cause mortality with robust sandwich variance estimator to account the matched design. Using patients treated with transcarotid TAVR as reference, we derived from these regression models, odds ratio (ORs) and hazard ratio (HRs) as treatment effect size measures, with their 95% confidence intervals (CIs). We assess the proportional hazard assumption for Fine and Gray, and Cox's models using Schoenfeld residuals plots.

Supplemental Table 1. Baseline Characteristics and Outcomes In patients with Trans-catheter aortic valve replacement (TAVR) According to Access Site Before Propensity Score-Matching and Before handling missing values by Multiple Imputations.

	Transcarotid TAVR, n=374	**Transaxillary TAVR**, n=128
Patient's characteristics	-	-
Age, years median (IQR)	83.0 (77.0 to 86.0)	82.0 (79.0 to 86.0)
Male gender	223/374 (59.6)	80/128 (62.5)
NYHA functional class III/IV	256/374 (68.4)	99/128 (77.4)
Diabetes mellitus	122/374 (32.7)	36/128 (28.1)
BMI, kg/m2, mean ± SD	25 (22 to 29)	26 (24 to 29)
Ilio-femoral artery disease	227/374 (60.7)	88/128 (68.8)
Coronary disease	88/374 (23.5)	47/128 (36.7)
Previous PCI	233/374 (62.3)	81/128 (63.3)
Previous CABG	68/374 (18.2)	27/128 (21.1)
Previous AVR	27/374 (7.2)	7/128 (5.5)
Severe renal dysfunction, n (%)	137/374 (36.6)	64/128 (50.0)
COPD	111/374 (29.7)	50/128 (39.1)
Atrial fibrillation	142/374 (38.0)	56/128 (43.8)
Prior Stroke/TIA	58/374 (15.5)	14/128 (10.9)
Preoperative pacemaker	54/374 (14.4)	8/128 (6.3)
STS score (2018), %, median (IQR)[1]	5.3 (3.5 to 8.4)	5.8 (3.9 to 8.6)
TTE characteristics		
Transprothetic maximal velocity, m/s, median (IQR)[2]	4.1 (4.0 to 4.7)	4.1 (3.9 to 4.6)
Aortic valve surface, cm2, median (IQR)[3]	0.7 (0.6 to 0.9)	0.7 (0.6 to 0.8)
AR grade ≥ II	36/373 (9.7)	8/71 (11.3)
LVE fraction, %, median (IQR)[4]	55 (45 to 60)	55 (45 to 61)
Procedural characteristics		
Period 2015-2018	201/374 (53.7)	91/128 (71.1)
Right access	66/374 (17.6)	30/128 (23.4)
Predilation	135/374 (36.1)	71/128 (55.5)
Postdilation	33/321 (10.3)	17/128 (13.3)
Valve in valve	29/374 (7.8)	6/128 (4.7)
Need of a second valve	7/374 (1.9)	2/128 (1.6)
Local anesthesia	77/374 (20.6)	6/128 (4.7)
Fluoroscopy time, sec, median (IQR)[5]	812 (627 to 1147)	1222 (848 to 1538)
Contrast injection, ml, median (IQR)	96 (70 to 133)	105 (78 to 145)
Heparin Dose, ui, median (IQR)[6]	5000 (3500 to 7000)	5000 (3750 to 7500)
Bioprosthesis characteristics		
Bioprosthesis size, mm		
23	43/374 (11.5)	22/127 (17.3)
26	132/374 (35.3)	50/127 (39.4)
29	170/374 (45.5)	48/127 (37.8)
31	29/374 (7.8)	6/127 (4.7)
34	0/374 (0.0)	1/127 (0.8)
Type of Bioprothesis		
Edwards Sapien XT	54/374 (14.4)	0/128 (0.0)
Corevalve	109/374 (29.1)	62/128 (48.4)
Sapien S3	137/374 (36.6)	37/128 (28.9)

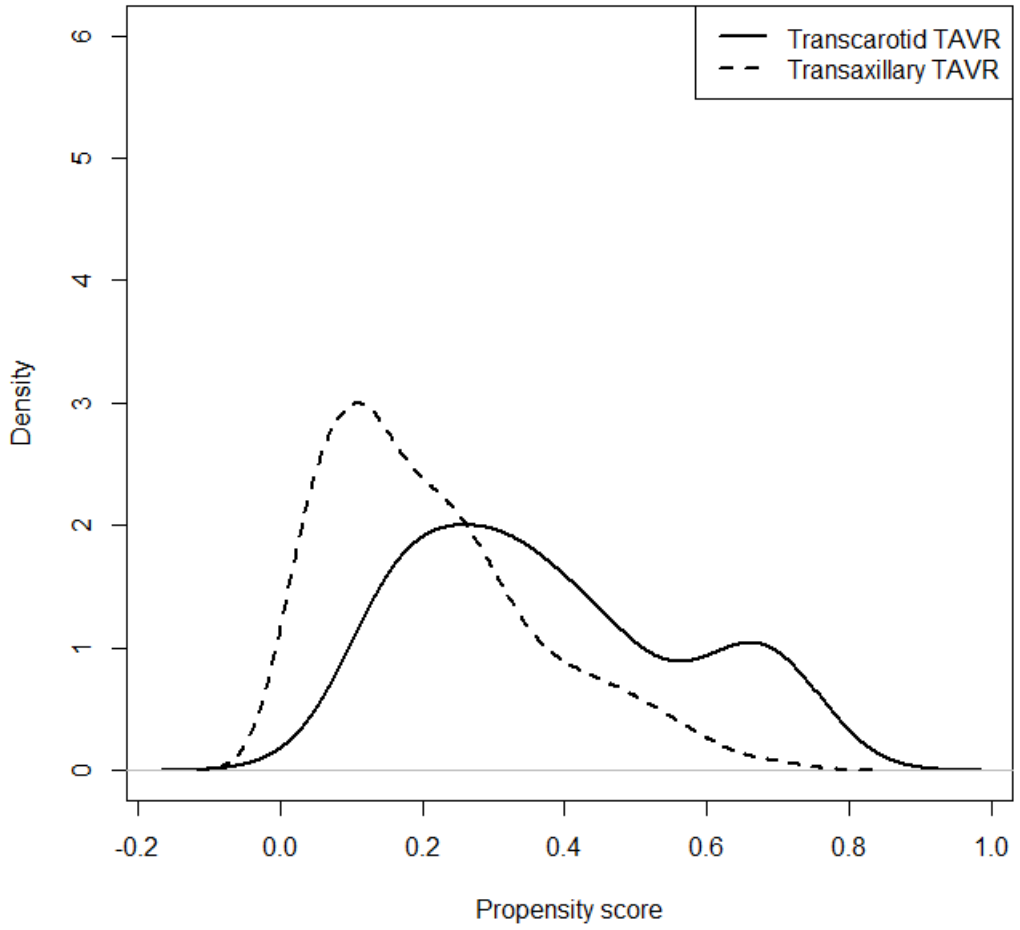
Evolut R/pro	72/374 (19.3)	28/128 (21.9)
Lotus	2/374 (0.5)	1/128 (0.8)
2nd generation devices	182/374 (48.7)	91/128 (71.1)
Outcomes		
Procedural and in hospital outcomes		
IH mortality	17/374 (4.5)	6/128 (4.7)
Device success	357/374 (95.5)	122/128 (95.3)
Acute kidney injury 2-3	45/374 (12.0)	26/128 (20.3)
New pace maker implantation	71/374 (19.0)	24/128 (18.8)
LT or major bleeding	17/374 (4.5)	4/128 (3.1)
Minor bleeding	31/374 (8.3)	4/128 (3.1)
Major vascular access complications	22/374 (5.9)	11/128 (8.6)
Minor vascular access complications	25/374 (6.7)	4/128 (3.1)
Main access hematoma	35/374 (9.4)	4/128 (3.1)
Hospital stay, days median (IQR)	7 (6 to 11)	9 (6 to 13)
TTE outcomes at hospital discharge		
AR grade ≥ II	29/356 (8.1)	7/128 (5.5)
Transprothetic maximal velocity, m/s, mean (SD)	2.0±0.5	2.2±0.7
1-month outcomes		
Clinical efficacy	325/374 (86.9)	113/128 (88.3)
Early safety	321/374 (85.8)	113/128 (88.3)
Stroke/TIA	24/374 (6.4)	6/128 (4.7)
All-cause mortality	18/374 (4.8)	7 (5.5)
1-year outcome		
All-cause Mortality	38/374 (10.2)	18/128 (14.1)

Values expressed as numbers (%) unless otherwise indicated. Clinical efficacy defined as all-cause mortality, disabling or non-disabling stroke, or hospitalizations for valve-related symptoms or worsening congestive heart failure (CHF). Early safety defined as all-cause mortality, stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury, coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure). Severe renal dysfunction defined as GFR ≤30ml/min/m^2.

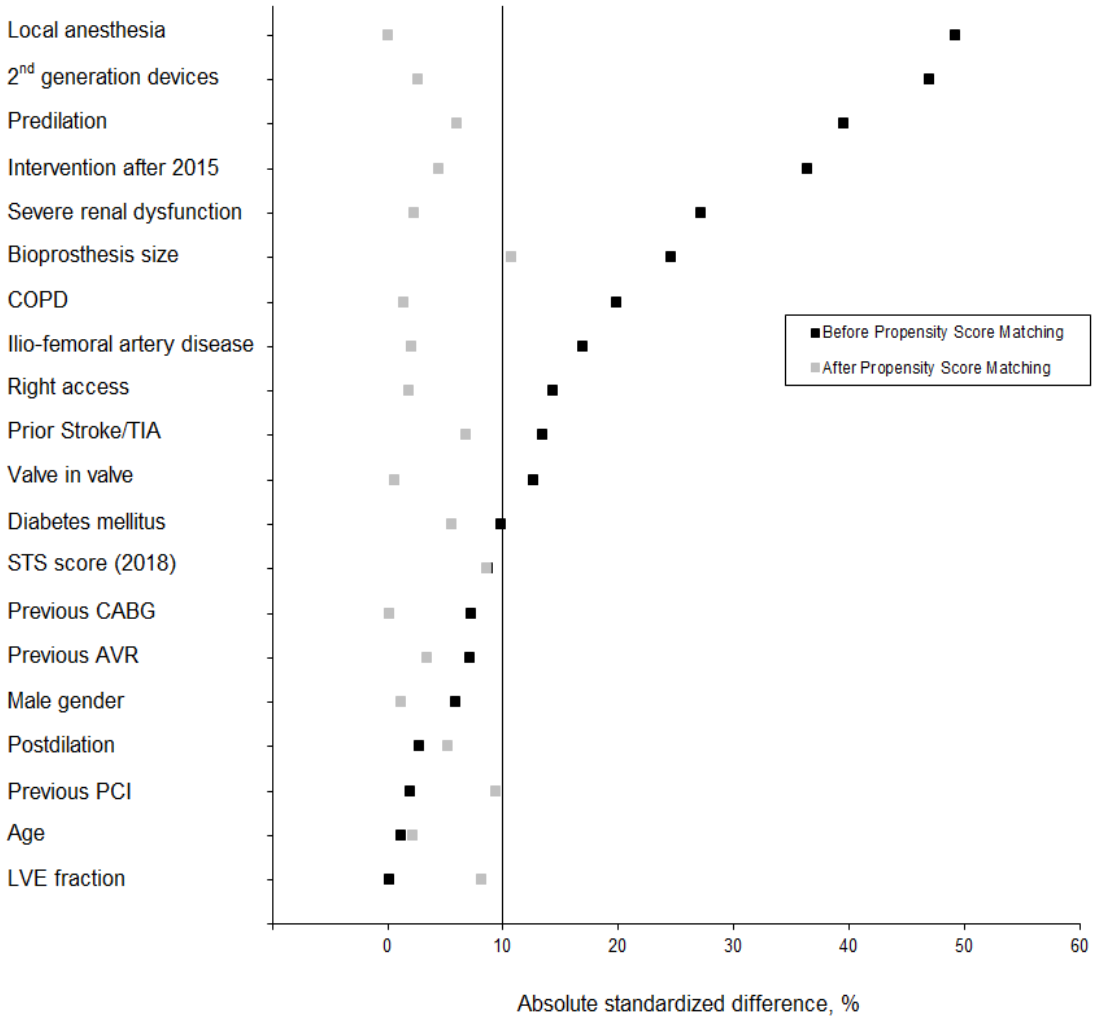
[1] 19 missing data (0 in Transaxillary TAVR); [2] 76 missing data (59 in Transaxillary TAVR); [3] 16 missing data (1 in Transaxillary TAVR); [4] 32 missing data (0 in Transaxillary TAVR); [5] 169 missing data (2 in Transaxillary TAVR; [6] 285 missing data (64 in Transaxillary TAVR).

Abbreviations: AVR= aortic valve replacement; AR= aortic regurgitation; CABG= coronary artery bypass graft; COPD= chronic obstructive pulmonary disease; IQR=interquartile range; PCI= percutaneous coronary intervention; LVE= left ventricular ejection; SD=standard deviation; TAVR= trans-catheter aortic valve replacement; TIA= transient Ischemic Attack; TTE= transthoracic echocardiogram

Supplemental Figure 1. Distribution of Propensity Score in Transcarotid TAVR and non- Transaxillary TAVR groups



Supplemental Figure 2. Absolute Standardized differences between Transcarotid TAVR and non-Transaxillary TAVR groups before and after Propensity Score Matching



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CHAPITRE 3: TAVI et lésions cérébrales hémorragiques

Cerebral microbleeds during TAVR : a prospective MRI cohort

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Après avoir étudiés les complications ischémiques et hémorragiques en situation cliniques urgentes et chez le patient polyvasculaire bénéficiant d'une réparation aortique percutanée, nous nous sommes intéressés au risque hémorragique cérébrale de la procédure TAVI à partir d'une étude ancillaire de l'essai Méthystroke réalisé au CHRU de Lille depuis 2017 (NCT02972008) qui comprend un examen neurologique et des IRM cérébrales réalisés avant et après l'intervention.

Les microbleeds (MCB) qui consistent en des extravasations de composants sanguins à travers des parois microvasculaires cérébrales fragiles, sont fréquentes chez les patients atteints de maladie des petites artères, et touche 10 à 25 % des sujets âgés de plus de 70 ans. Les CMB apparaissent progressivement au cours du temps (≤7,0%/an) et sont des facteurs de risque d'accidents vasculaires cérébraux ischémiques, de troubles cognitifs ou de démence, et d'hémorragie intracérébrale. Si certains facteurs de risque ont été identifiés, notamment le vieillissement, l'hypertension ou le diabète sucré, les mécanismes physiopathologiques conduisant à ces lésions hémorragiques restent inconnus. L'apparition aiguë de MCB a également été rapportée dans des conditions très particulières telles que les patients souffrant d'endocardite, subissant une chirurgie cardiaque ou bénéficiant d'appareils d'assistance circulatoire, qui ont tous en commun d'être des situations cardiovasculaires aiguës où la circulation sanguine est soumise à une contrainte de cisaillement élevée.

Le facteur von Willebrand (VWF) est une grande glycoprotéine multimérique impliquée dans l'hémostase, la structure vasculaire, l'inflammation et l'angiogenèse. Il est

important de noter que des modifications du flux sanguin et des conditions de cisaillement peuvent provoquer la dégradation protéolytique des plus gros multimères, qui sont les plus actifs dans hémostase. Par exemple, il est bien établi que les patients atteints d'une maladie valvulaire cardiaque sévère, en particulier les patients âgés atteints de rétrécissement aortique (RA), ont un défaut acquis du facteur de von-Willebrand (vWF) exposant à une augmentation risque d'hémorragie grave et en particulier gastro-intestinale. Ce trouble de l'hémostase est corrigé de manière aiguë par le remplacement valvulaire aortique par cathéter (TAVI) chez la plupart des patients, bien qu'il puisse persister chez ceux qui présentent une régurgitation périprothétique suite à un placement incorrect de la valve. Des études précliniques récentes ont en outre démontré que des modèles animaux (rats SHRSP) avec une pression artérielle différentielle élevée ont été associés à un risque plus élevé de MCB; et que la combinaison de l'inactivation du vWF et de la pression artérielle élevée déclenche une hémorragie cérébrale suggérant qu'un défaut du multimère vWF pourrait également favoriser l'apparition de micro-hémorragies cérébrales dans des conditions de pression pulsée élevée.

Sur la base de ces observations, nous avons conçu cette étude pour déterminer si les procédures TAVI, réalisées chez des patients atteints de RA et d'un défaut acquis-VWF, pourraient déclencher l'apparition de nouveaux microsaignements cérébraux. Dans le cadre de cette étude, nous avons également tenté d'évaluer si les paramètres liés au patient et/ou à la procédure, et les paramètres biologiques pouvaient influencer la survenue de micro-hémorragies cérébrales, et d'évaluer leur l'impact sur le l'évolution fonctionnelle neurologique.

Cerebral microbleeds during TAVR : a prospective MRI cohort

Abstract

Background - Cerebral microbleeds have been observed in healthy elderly patients undergoing systematic brain magnetic resonance imaging (MRI). The potential influence of acute triggers on the appearance of microbleeds remains unknown. We aimed to describe the incidence of new cerebral microbleeds during Trans Aortic Valve Replacement (TAVR) and to identify the clinical and procedural factors associated with this occurrence including haemostatic parameters and anticoagulation management.

Methods- A prospective cohort of patients with aortic stenosis referred for TAVR was included. A standardized neurological assessment, a brain magnetic resonance imaging (MRI) and an analysis of haemostatic parameters including von-Willebrand-Factor(VWF) were performed before and after TAVR. Numbers and location of microbleeds were rated by two independent neuroradiologists blinded to clinical data. Post-procedural outcomes including neurological functional outcome at 6-months was reported.

Results- Eighty-four patients (47% male, 80.9 ± 5.7 years old) were included. On pre-procedural MRI, 22 patients(26%, 95%CI=17-37%) had at least one microbleed. After TAVR, new microbleeds were observed in 19(23%, 95%CI=14-33%) patients. The occurrence of new microbleeds was independent of the presence of microbleeds at baseline and of diffusion-weighted imaging(DWI) hypersignals.

In univariate analysis, a previous history of bleeding (p=0.01), a higher total dose of heparin (p=0.02), a prolonged procedure (p=0.03), valve postdilation (p=0.03), absence of protamine reversion (p=0.04), higher final aPTT(p=0.05), lower final HMW-multimer-ratio(p=0.009) and a lower CT-CADP(p=0.02) were associated with the occurrence of new post-procedural microbleed(s).

In multivariable analysis, a prolonged procedure(RR=1.22[1.03-1.173] for every 5 min of fluoroscopy time, p=0.02) and post-procedural acquired-VWF-defect(RR=1.42[1.08-1.89] for every lower “0.1 unit” of HMW-multimer-ratio, p=0.004) were independently associated with the occurrence of new post-procedural microbleed(s). New cerebral microbleeds did not impact functional independence or quality of life at 6 months follow-up.

Conclusions- When undergoing TAVR, one patient out of 4 will develop new cerebral microbleeds. Procedural/antithrombotic management and persistence of acquired-VWF defect could play a major role in the occurrence of those new microbleeds.

Condensed Abstract

We aimed to define the occurrence of "acute" microbleeds during Trans Aortic Valve Replacement (TAVR) in a prospective cohort and the procedural factors associated with this occurrence.
Among the 84 patients (47% male, 80.9 ± 5.7 years old), on pre-procedural MRI, 22 patients (26%, 95%CI=17-37%) had at least one microbleeds. After TAVR, new microbleeds were observed in 19 (23%, 95%CI=14-33%) patients. The occurrence of new microbleeds was independent of the presence of microbleeds at baseline. A prolonged procedure(RR=1.22[1.03-1.173] for every 5 min of fluoroscopy time, p=0.02) and post-procedural acquired-VWF-defect (RR=1.42[1.08-1.89] for every lower "0.1 unit" of HMW-multimer-ratio, p=0.004) were the only factors associated with the occurrence of new microbleeds.

Key words
Microbleeds, Transcatheter aortic valve replacement, severe aortic stenosis, multimers, von Willebrand factor

Abbreviations list
AR: aortic regurgitation
AS: aortic stenosis
CE: cerebral emboli
CMB: cerebral microbleeds
FU: follow-up
HMW-multimers: high molecular weight multimers
MSCT: multi-slice CT
MRI: magnetic resonance imaging
PM: pacemaker
PVR: paravalvular regurgitation
TAVR: transcatheter aortic valve replacement
TEE: transesophageal echocardiography
TTE: transthoracic echocardiography
VWF: von Willebrand factor

Introduction

Cerebral microbleeds (CMB), which consist of extravasations of blood components through fragile cerebral microvascular walls[1,2], are common in patients with cerebral small-vessel disease, which frequently affects 10-25% of subjects >70 years old[3,4]. CMBs are considered to appear progressively over time(≤7.0%/yr)[4] and are risk factors of future ischemic strokes[5], cognitive impairment or dementia,[1] and of intracerebral hemorraghe especially in the setting of anti-thrombotic use[6]. While some risk factors have been identified, in particular aging, hypertension or diabetes mellitus[1,5,6], the underlying mechanisms leading to these haemorrhagic lesions remain elusive[8]. An acute appearance of CMBs has also been reported in very peculiar conditions such as patients suffering from endocarditis[9,10], undergoing cardiac surgery[11] or benefiting from circulatory assist devices[12,13], which have all in common to be acute cardiovascular situations where blood stream is subjected to a high shear stress.

Von Willebrand Factor(VWF) is a large multimeric glycoprotein involved in hemostasis[14], vascular structure[15], inflammation and angiogenesis[16]. Importantly, changes in blood flow and shear conditions may provoke the proteolytic degradation of the largest multimers, which are the most active in hemostasis[15]. For instance, it is well established that patients with a severe heart valve disease(HVD), in particular elderly patients with aortic stenosis(AS), have an acquired-von-Willebrand-Factor(VWF) defect exposing to an increased risk of mucosal and in particular gastro-intestinal bleeding[17]. This hemostasis disorder is corrected acutely by transcatheter aortic valve replacement(TAVR) in most patients, although it may persist in those with paravalvular regurgitation following incorrect placement of the valve[18,19,20]. Recent preclinical studies have further demonstrated that animals models(SHRSP rats) with high pulse pressure have been associated with higher risk of cerebral CMB; and that combination of inactivation of vWF and high pulse pressure trigger cerebral bleeding suggesting that a VWF-multimer defect could also favour the occurrence of cerebral microbleeds under conditions of high pulse pressure[21].

Based on these observations, we designed this study to investigate whether TAVR procedures, performed in patients with AS and acquired-VWF defect, could trigger the occurrence of new cerebral microbleeds. As part of this study, we further attempted to assess whether patient and/or procedural related parameters, including antithrombotic regimen, and biological parameters could influence the occurrence of cerebral microbleeds, and to evaluate the impact of those cerebral microbleeds on the neurological functional outcome.

Materials and Methods

Patient Selection

After approval by the local ethics committee, all patients with AS undergoing TAVI at our institution were included in an ancillary substudy of the prospective METHYSTROKE(NCT02972008) study in which pre and postprocedural cerebral MRI were planned. As part of the screening process, patients were verified to have no contraindication for pre-procedural MRI and to have a low probability of contra-indication of post-procedural MRI. In that regard, patients with previous implantation of a pace-maker(PM), signs of conduction abnormality at pre-procedural(RBBB) ECG or intended to undergo implantation a self-expandable valve were excluded. All patients gave informed written consent.
Participation included clinical data collection(including neurological examination), blood sampling(including VWF-related parameters analysis) during the procedure and follow-up. All patients who provided informed written consent were included in the METHYSTROKE study. The **Figure 1** describes the Standardized Timing(A) and flowchart(B) of Clinical and Imaging Evaluations of the study.

TAVR procedure

Patients underwent transfemoral TAVR with balloon-expandable Edwards Sapien valve because this device is known to require less pace maker implantation[22]. All patients received aspirin before the procedure, with ongoing aspirin therapy after the procedure. Clopidogrel was not administered unless the patient was already receiving long-term clopidogrel treatment. No clopidogrel loading was performed.

Standard TAVR implantation techniques with heparin(UFH) anticoagulation(50UI/kg) with optional additional heparin administration depending on procedure duration and/or activated clotting time(ACT) were followed as previously described[20,23]. Protamine(1mg for each 100 U heparin) was perfused at the end of the procedure at the discretion of the operator. Systolic blood pressure was maintained above 100mmHg throughout the procedure (except during rapid pacing).

Procedural outcomes

They were evaluated by two independent cardiologists according to the standardized VARC-2 [24] recommendations including device success, bleeding, acute kidney injury, access site complications, clinical transient ischemic attack(TIA)/stroke, death, new atrial

fibrillation(AF) episode and echocardiography valve assessment.

Per-procedural Von Willebrand Factor multimer and biology analysis

Two distinct assays have been performed to analyse the VWF multimer status: VWF multimer analysis via electrophoresis and via a functional whole blood assay(PFA-100®). Both assays were performed on samples taken before(pre-procedural) and 5 min after the end of the procedure(post-procedural), while the patient was still in the catheterization laboratory VWF multimeric analysis was performed as previously described[19,20,17]. The results are expressed as a ratio to normal pooled plasma(NP, standard human plasma *Siemens healthcare diagnostics, Marburg, Germany*). HMW-multimers defect is defined as a reduced ratio of HMW-multimers(>15-mer) present in plasma of patient. With this method, the HMW-multimer ratio is defined as the number of HMW-multimers in patient plasma sample divided by the number of HMW-multimers in normal pooled plasma. The HMW-multimers ratio of normal pooled plasma is 1(by definition) and a HMW-multimers defect is defined as a reduced HMW-multimers ratio(less than 1).

Platelet count($x10^9$/L) and activated partial throbomplastin time(aPTT, sec) were measured before the procedure, at the time of valve implantation and 5 min after the end of the procedure.

Closure time-ADP(CT-CADP) was assessed by the PFA-100®(*Siemens Healthcare Diagnostics, Marburg, Germany)* using ADP cartridges(CT-CADP, normal range=68-121sec) as previously described[19,20,17].

Pre and post-procedural cerebral MRI

MRI examination of the brain was performed on a 1.5T MRI(*Philips Ingenia, Philips Medical Systems, Best, the Netherlands*) the day before and repeated 3 days after the TAVR procedure. The imaging protocol included the following sequences to identify cerebral microbleeds and cerebral emboli: a transversal diffusion weighted imaging(DWI) sequence(repetition time, 4600ms; echo time, 100ms; slice thickness, 4mm; 2 diffusion gradient b-values, 0 and 1000 s/mm^2; field of view, 230mm; matrix 105×224; acquisition time, 55 s), a transversal T2*-weighted gradient-echo sequence(T2*-GRE) sequence(repetition time, 970 ms; echo time, 16ms; flip angle, 18°; slice thickness, 4mm; field of view, 230mm; matrix 205×432; acquisition time, 2min40 s), a transversal fluid-attenuated inversion recovery(FLAIR) sequence(repetition time, 11000ms; echo time, 125ms; inversion time, 2800ms; slice thickness, 4mm; field of view, 230mm; matrix 264×512

acquisition time; 3min50 s) and a transversal T1-weighted spin-echo sequence(repetition time, 6000ms; echo time, 10ms; slice thickness, 5mm; field of view, 230mm; matrix 205×432; acquisition time, 3min20s).

Cerebral microbleeds were defined as homogeneous, round foci, ≤10mm diameter, of low signal intensity on the T2*-GRE sequence. The number and distribution of cerebral-microbleeds were documented according to the Brain Observer MicroBleed Scale(BOMBS)[25]. Low-signal lesions on the T2*-GRE sequence within a lesion compatible with an infarct were considered as hemorrhagic transformations rather than microbleed and were excluded. Symmetrical foci of low signal intensity in the globus pallidus, were considered as calcifications and were also excluded. Flow void artifacts of the pial blood vessels were distinguished from microbleed by their morphology and correlation with T1 and FLAIR images[1,5](**Figure 2**).

Incident cerebral microbleed(s) were defined by the appearance of new microbleed(s) in a new location on the post-procedural MRI, in comparison to the pre-procedural MRI.

New cerebral emboli(CE) were defined by the appearance of hyperintense lesions on post-procedural DWI in comparison to pre-procedural DWI, which was not present on the preprocedural MRI.

All brain MRIs were rated by two independent neuroradiologists trained in the analysis of cerebral microbleeds, blinded to clinical data. Validated qualitative and quantitative methods were applied(*Syngo®.via Version VA30, Siemens Healthcare, Siemens AG, Germany*). In case of disagreement, the final evaluation was obtained by consensus.

Inter-observer kappa coefficients for the presence CMB and CE were 0.91 [95%CI:0.83-0.98] and 0.92 [95%CI:0.86-0.98], which corresponds to very good agreement.

Neurological functional examination

The neurological trajectory covering neurological function/dysfunction, cognition, ability/disability and quality of life was evaluated using a multimodal and repeated testing approach in line with the recent Neurologic Academic Research Consortium recommendations for neurological assessment for TAVR trial[26,27](**Figure 1**).

The neurological and cognitive status was assessed by the same experienced neurologist before and at 6 months after TAVR procedures, following a standardized protocol as previously described in this population[26], including(i) the severity of the neurological deficit with the NIHSS score,(ii) the level of functional dependency with the modified Rankin scale(dependence was defined by a Rankin score>1)(iii) the cognitive status with

MMSE score, and(iv) the quality of life with the EQ-5D scale.

Study Endpoints and analyses

Primary endpoint was the appearance of incident cerebral microbleed(s) on the post-procedural cerebral MRI. **Secondary endpoint** was the presence of microbleed(s) on preprocedural MRI.*Analyses* included, the identification of factors associated with the primary and secondary endpoints. As part of it, the potential relationship between presence/incidence of cerebral emboli and the incidence of cerebral microbleeds was investigated.

Additional analyses included evaluation of the impact of the primary and secondary endpoints on early outcomes described by the standardized criteria proposed by the Valve Academic Research Consortium(VARC-2)[24], but also on the neurological status evaluated at 6 months, and on the mortality at 1 year follow-up.

Statistical Analysis

Statistical analysis was performed by using commercial software(*SAS9.3; SAS Institute, Cary, NC, USA*). Results for continuous variables were expressed as means with standard deviations when data were symmetrically distributed or, otherwise, as medians with ranges. The normality of distribution was assessed using Shapiro Wilk test and normality diagrams. Results for categorical variables were expressed as frequencies and percentages. The events rates were reported as percentages. The 95% confidence interval of the events rate was estimated by the exact method(Clopper Pearson test)**.**

Comparative analyses were obtained using the chi-square test for categorical data; when not applicable because of the sample size, the Fisher's exact test was used. To compare a quantitative parameter between two groups, Student's t test or the Mann-U-Whitney test was performed. For numerical variables, we used the ANOVA test or Kruskal-Wallis test if normality of distribution was not present. The relationship between two quantitative parameters was studied by Spearman correlation coefficient.

Parameters with a level of less than 0.20 in bivariate analyses and sufficiently informed significance were introduced in a multivariate logistic regression moadel with stepwise selection.

P values less than 0.05 were considered statistically significant.

Results

Patients' characteristics

Pre-procedural MRI was performed in 90 patients with severe symptomatic aortic stenosis undergoing implantation of Edwards Balloon-Expandable valve through transfemoral access. Six patients could not undergo the postprocedural cerebral MRI because of hemodynamic instability(n=2), or necessity of permanent pacemaker implantation after TAVR procedure(n=4).

Eighty-four(93%) patients had both pre and post-procedural MRI and constituted our study group(Figure 1). The baseline demographic, clinical and echocardiographic characteristics of the study population are summarized in **Table 1**. Mean patient age was 80.6±5.6 years and 50%(n=42) were male. The mean logistic Euroscore was 20.0±4.3 %, and the predicted permanent stroke risk(STS-PROM) was 6.5±2.4%. Thirty-five percent(n=30) had a history of atrial fibrillation(AF) and 14%(n=11) had a permanent AF. Seventy-one percent(n=60) had history of hypertension, and 21%(n=18) had a previous cardiac surgery.

The mean transaortic gradient was 48±13mmHg and the mean indexed valve area 0.39±0.10 cm^2/m^2. A concomitant shear-induced acquired-VWF-defect was present in all patients as illustrated by a low mean HMW-multimer-ratio(0.66±0.21) and a high mean CT-ADP(220±65s).

Device and Procedural Outcome

According to the VARC-2 criteria, device success was observed in 84%(n=70) including no procedural mortality, no 2nd valve, and no ≥moderate aortic regurgitation and no elevated gradient(20mmHg or more)(**Supplemental Table 1**). Five patients(5%) had clinical signs of TIA/stroke after TAVI, and details about these patients are presented in **supplemental Table 2**.

Post-implantation transvalvular mean gradient decreased from 45.4±10.2 to 10.5±4.6mmHg(P<0.001), and the effective orifice area increased from 0.72±0.23 to 1.91±0.33$cm^{2(}$P<0.001). Similarly, post-implantation HMW ratio increased from 0.66±0.21 to 1.03±0.26(P<0.001) and CT-ADP decreased from 220±65s to 136±63s(P<0.001)(**Table 1**).

Post-procedural aortic regurgitation ≥grade 2 was observed in 11%(n=9)(**Supplemental Table 1**). In each of these 9 patients post-procedural VWF ratio was <0.8(mean 0.73±0.06) and post-procedural CT-ADP was>180 sec(mean 240±51 sec).

Minor vascular complications occurred in 11%(n=10) of cases involving the femoral access. There were no major vascular complications. Major bleeding was detected in 3.5%(n=3) cases with no intracranial haemorrhage, and new permanent pacemaker after the second MRI was required in 4.4%(n=4). There was 5%(n=5) of new onset atrial fibrillation(**Table 2**).

Anticoagulation management and haemostatic parameters at the end of procedure

Protamine was used to reverse heparin at time of sheath removal in 23 patients(27%). While during the procedure, peak aPTT was not different between patients who will receive Protamine and those who will not(211±26 sec vs 214±23 sec, p=0.65), final aPTT was significantly lower in patients receiving protamine(65±34 sec 116±38 sec data statview, p=0.0003).

Brain MRI findings

Pre-procedural MRI was performed at median time of 1(IQR:1-3) day before the procedure and the post-procedural MRI was performed 3(IQR:2-4) days after the procedure.

Pre-procedural brain MRI revealed at least one microbleed in 22 patients(26%, 95%CI=17-37%,) and at least one cerebral emboli(CE) in 6%(n=5) of patients(**Figure 3, Table 1 and supplemental Table 3**). Pre-procedural microbleed(s) were mostly identified in lobar regions(67%), in deep regions(26%) or in infratentorial regions(6%).

Post-procedural brain MRI revealed at least one microbleed in 34 patients(40%, 95% CI=30-52%) and at least one CE in 55 patients(65%, 95%CI=54-75%).

Incident Cerebral Microbleeds after TAVR

Between pre- and post-procedural MRI, 19 patients(23%, 95% CI=14-33%) had at least one new microbleed and 54 patients(64%, 95%CI=53-74%) had at least one new CE. Only 15%(n=13) of patients had both new microbleed and new CE, and 1.2%(n=1) new microbleed associated to pre-procedural CE. Seventy-two percent(n=61) of patients presented either new cerebral microbleed or new CE.

Most of these new cerebral microbleeds were unique(1 new microbleed n=14, 2 microbleeds n=4, 3 microbleeds n=1) and were identified in lobar regions(69%), in deep regions(18%) or in infratentorial regions(11%).

CMB and CE were independent events. No relation was found between new postprocedural microbleed and either preprocedural microbleed(p=0.23), preprocedural

CE(p=0.33) or new post-procedural CE(p=0.88)(**Table 1 and Figure 3**). Details about CE can be found in **supplemental Table 4**.

Predictors of Cerebral Microbleeds

Univariate predictors of preprocedural microbleed are listed **supplemental Table 3** and included hypertension(p=0.003), diabetes(p=0.05), and prior stroke/TIA(p=0.04).

Univariate predictors of new postprocedural microbleed are listed in **Table 1** and included a previous history of bleeding(including gastro-intestinal and cerebral bleeding)(p=0.01), and procedural parameters including valve postdilation(p=0.03), or a longer procedure(p=0.03).

A higher total dose of heparin was associated with a higher occurrence new postprocedural microbleed (p=0.02). Protamine to reverse heparin at the end of the procedure was associated with a lower occurrence of new postprocedural microbleed[8%(n=2/23) vs. 28%(n=17/61), p=0.04, Table 1] with no increased occurrence of new CE [74%(17/23) vs 61%(37/61), p=0.38] . Similarly, a lower aPTT was also observed in patients without new postprocedural microbleed(87±34sec vs. 105±38sec; p=0.05).

Platelet counts before, during or after TAVR procedure(**Table 1**), the variation of platelet count to peak(P=0.87) or to nadir(P=0.23) were not associated with the incidence of at least one new microbleed on the postprocedural MRI.

A lower HMW-multimer ratio as measured immediately at the end of the procedure was associated with the occurrence of new microbleed detected on the MRI performed 3(IQR:2-4)days after the procedure(0.90±0.14 vs. 1.06±0.27, p=0.009). Accordingly, the same observation was made with a higher CT-ADP(165±72 vs. 127±57, p=0.02)(**Table 1)**.

In multivariable analysis, a prolonged procedure(RR=1.22[1.03-1.173] for every 5 min of fluoroscopy time, p=0.02) and a post-procedural acquired-VWF-defect identified by a lower HMW-multimer ratio(RR=1.42[1.08-1.89] for every lower "0.1 unit" of the HMW-multimer-ratio, p=0.004) were the only factors associated with the occurrence of new post-procedural microbleed(s).

Cardiovascular outcome and relation to Cerebral Microbleeds

We found no influence of new post-procedural microbleed(s) on intrahospital clinical outcomes(**Supplemental Table 1**), on the occurrence of periprocedural clinical strokes or transient ischemic attack nor on 6-month mortality(**Table 2**). At 12 months, 5% of patients(n=1) with new microbleed and 12%(n=8) with no new microbleed were

dead(p=0.25).

Neurological and cognitive status: Relation to Cerebral Microbleeds

Baseline neurological examination, presented in **Table 2**, revealed that 10%(n=9) had neurological deficit(NIHSS scale: 0 n=1, 1 n=6, 2 n=2; and modified Rankin scale 0-1 n=3, 2 n=4, 3 n=2). Patients with pre-procedural CMB had a lower baseline and 6-month MMSE score than those without pre-procedural CMB(both p=0.01).

At 6 months, among the 72 survivors without periprocedural clinical stroke or TIA, an improvement of the quality of life was observed(EQ-5D 42±12 to 61±10, p<0.001) related to the success of the procedure.

Presence of pre-procedural CMB did not impact functional capacities at baseline[n=2(9%) vs. n=4(5.9%); p=0.65] and at 6 months [n=2(9.0%) vs. n=3(5.3%); p=0.32] measured by the Rankin scale. New postprocedural CMB did not affect functional capacities at 6 months [n=1(5.5%) vs. n=4(7.4%); p=0.78](**Table 2**).

Discussion

The present study including 84 patients with severe symptomatic AS undergoing transfemoral TAVR with pre and post-procedural MRI performed 3 days apart demonstrates that: 1) nearly one patient out of 4 will present new CMBs after TAVR procedure(23%, 95% CI=14-33%); 2) procedural management, including prolonged exposure to anticoagulant, or an acquired-VWF-multimer defect(in particular when this defect persists at the end of the procedure), are associated with the occurrence of those new post-procedural cerebral-microbleeds.

Cerebral microbleeds on pre-procedural MRI in elderly patients with severe symptomatic aortic stenosis

In this population, the prevalence of microbleeds(26%, 95%CI=17-37%) is at the same range of the reported prevalence of the general population at similar age[3,4](10-25%). Except for the presence of an AS and the presence of an acquired VWF multimer defect in patients with microbleeds on pre-procedural MRI, the clinical parameters associated with the presence of preprocedural microbleeds were very similar to those previously reported and included hypertension(p=0.004), diabetes(p=0.05) and previous history of TIA/stroke(p=0.01), but not oral anticoagulation(p=0.43)[6,28].

TAVR procedures as trigger of silent cerebral microbleeds

To the best of our knowledge, this study is the first to investigate the role of TAVR procedure on the incidence of new cerebral microbleeds and the key finding is that nearly one patient out of 4 experienced new microbleeds(23%, 95%CI=14-33%).

The high incidence of new microbleeds(23%) in such a short time window(3 days), contrasts with the low incidence observed over a 1-year period(4-7%)[4,3] in elderly with similar vascular risk factors receiving chronic antithrombotic medication, and clearly points out the procedure as a potential triggers for microbleeds. This observation is also very important in the context of previous attempts to link some cardiac interventions with the appearance of new cerebral microbleeds. In those previous studies, the association could not be definitely established since only one MRI was performed in most cases(**Table 4**)[29,9,10,30] or as the time elapsed between the procedure and the 2nd MRI was too long(>1-7 weeks)[11,31].

The present study also suggests that cerebral microbleeds and emboli are independent events occurring in different patients(**Figure 3**), and more importantly that the occurrence of new post-procedural CMB does not appear to be related to the presence of preprocedural

CMB(**Figure 3**). New CMB and CE are not localized in the same territories and thus it is unlikely that new postprocedural CMB are haemorrahe within microinfarction areas.

Role of anticoagulation regimen

The higher occurrence of new cerebral microbleeds with a prolonged procedure and/or a prolonged exposure to anticoagulation during the procedure is consistent with the role of anticoagulation regimen previously demonstrated for "spontaneous" cerebral-microbleeds[32] or for microbleeds associated with severe heart valve disease[11,10]. While the peak level of anticoagulation did not influence the occurrence of microbleeds, it is interesting to notice that patients receiving a higher total dose of heparin were more likely to have new cerebral microbleeds while those receiving protamine at the end of the procedure to reverse anticoagulation were less likely to have new cerebral microbleeds(p=0.04). Consistently, patients with new cerebral microbleeds had a longer aPTT value at the end of the procedure(p=0.05). This observation may extend the recently reported benefit of protamine on other bleeding complications following TAVR[33].

Acquired-VWF-defect and cerebral microbleeds(Figure 4)

Acquired-VWF-defect in patients with heart valve disease has been associated with a persistent risk of bleeding in particular gastrointestinal bleedings[17]. However, its role in the occurrence of cerebral microbleeds has never been investigated before. It is therefore an interesting new finding to suggest that acquired-VWF-defect, in particular its persistence at the end of the TAVR-procedure, may be associated with a higher risk cerebral microvascular bleeding.

The observations that 1) all cases of CMBs reported to date in patients with acute cardiovascular disease are related to situations known to be associated with a moderate(heart valve/prosthesis dysfunction; 567/608 patients; 93%, Table 4) or severe(assist device; 41/608 patients; 7%, Table 4) VWF multimer defect, and 2) that the clinical conditions with the most profound VWF multimer defect(assist device) are also those with the highest prevalence of cerebral microbleeds(**Table 4 and Figure 4**), are also highly supportive of a direct link between valve-related flow alterations, acquired VWF-defect and CMBs. Finally, in our study, CMB were mostly located in lobar areas, similar to the description in patients with heart valve disease[11,10].

Acquired-VWF-defect involvement in the blood-brain barrier permeability?

Beyond the control of primary hemostasis, several studies have emphasized the view that VWF regulates angiogenesis through multiple pathways[34] while VWF-multimer defect is promoting the appearance of angiodysplasia in the GI tract and other arteriovenous malformations[35]. VWF is also expressed abundantly in cerebral endothelial cells and could be involved in cerebral vessel remodelling[15]. VWF also modifies and damages blood-brain barrier permeability in certain pathological settings[36], and might favour cerebral vessel wall rupture with consecutive microbleeds[21].

Hemodynamic conditions and Cerebral microbleeds

The fundamental hemodynamic consequence of the acute correction of AS during TAVR is an acute shift from a narrowed pulse pressure to a normal one(or possibly a supra normal one in case of paravalvular regurgitation)[37]. This sudden hemodynamic change could trigger the appearance of microbleeds on background of the moderate/severe VWF multimer defect observed in AS patients undergoing TAVR (or SAVR[11,31]) and or in patients with acute valve dysfunction[9,10,29,30]. The report that cerebral microbleeds are observed in animal models combining VWF defect to high blood pressure[21] but not in those of VWF defect without high blood pressure[38] are consistent with this hypothesis. The role of the sudden change in hemodynamic conditions is likely explaining why, despite the presence of a VWF multimer defect, the prevalence of microbleeds observed AS-patients before the procedure is not much higher than the one observed in a general population of the same age[3].

Silent cerebral-microbleeds and neurological trajectory after TAVR

Consistent with the notion that cerebral-microbleeds are considered relatively silent[3,11], we did not observe any focal deficit in patients with cerebral-microbleeds when examining them at the time of the MRI. Similarly, there was no impact of cerebral-microbleeds on the immediate post-procedural outcomes nor on the long-term all-cause mortality(1-year follow-up). However, we found a relationship between the presence of cerebral-microbleeds at baseline and a decreased cognitive function as measured by MMSE score.

In our population, and as previously described[39], new microbleeds per se did not worsen cognitive function at 6 months.

“Spontaneous” preprocedural microbleeds may be a marker of an underlying cerebral pathology, that impact cognitive functions, as an accumulation of small hemorrhagic lesions may be a trigger to worsen a neurodegenerative process in the long term. On the other hand,

the small number of patients, the low number of new microbleeds per patient induced by the procedure, and the short follow-up may limit the impact of these lesions on cognitive functions at 6 months after TAVR. Importantly, TAVR-induced-CMB did not inflect the improvement of quality of life or autonomy at 6 months follow-up that is directly associated with the success of the procedure.

Study limitations

This is a single center study and results may have been influenced by local patient management. However, because the main purpose of the present study was not to evaluate a specific device or a specific method of management, but rather the natural history of cerebral-microbleeds during TAVR procedures and their causes, this should not have impacted our findings. Although one of the largest TAVR-MRI study population, microbleeds have been analysed on 1.5T MRI and the total number of patients with new cerebral microbleeds is small and it limits the strength of the multivariate analysis. This also limits the interpretation of the relationship between cerebral microbleeds and the neurological trajectory.

Conclusions and Clinical Perspectives

We report a high incidence(23%, 95%CI=14-33%) of new cerebral microbleeds appearing at the time of TAVR procedures. While we identified parameters related to procedural management, including anticoagulation management, and persistence of acquired-VWF-defect to be associated with the appearance of these cerebral-microbleeds, the pathophysiological mechanisms of the microbleeds needs to be better understood. The clinical impact of these procedural-related microbleed on the very long run will have to be further clarified.

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Figure titles and legends

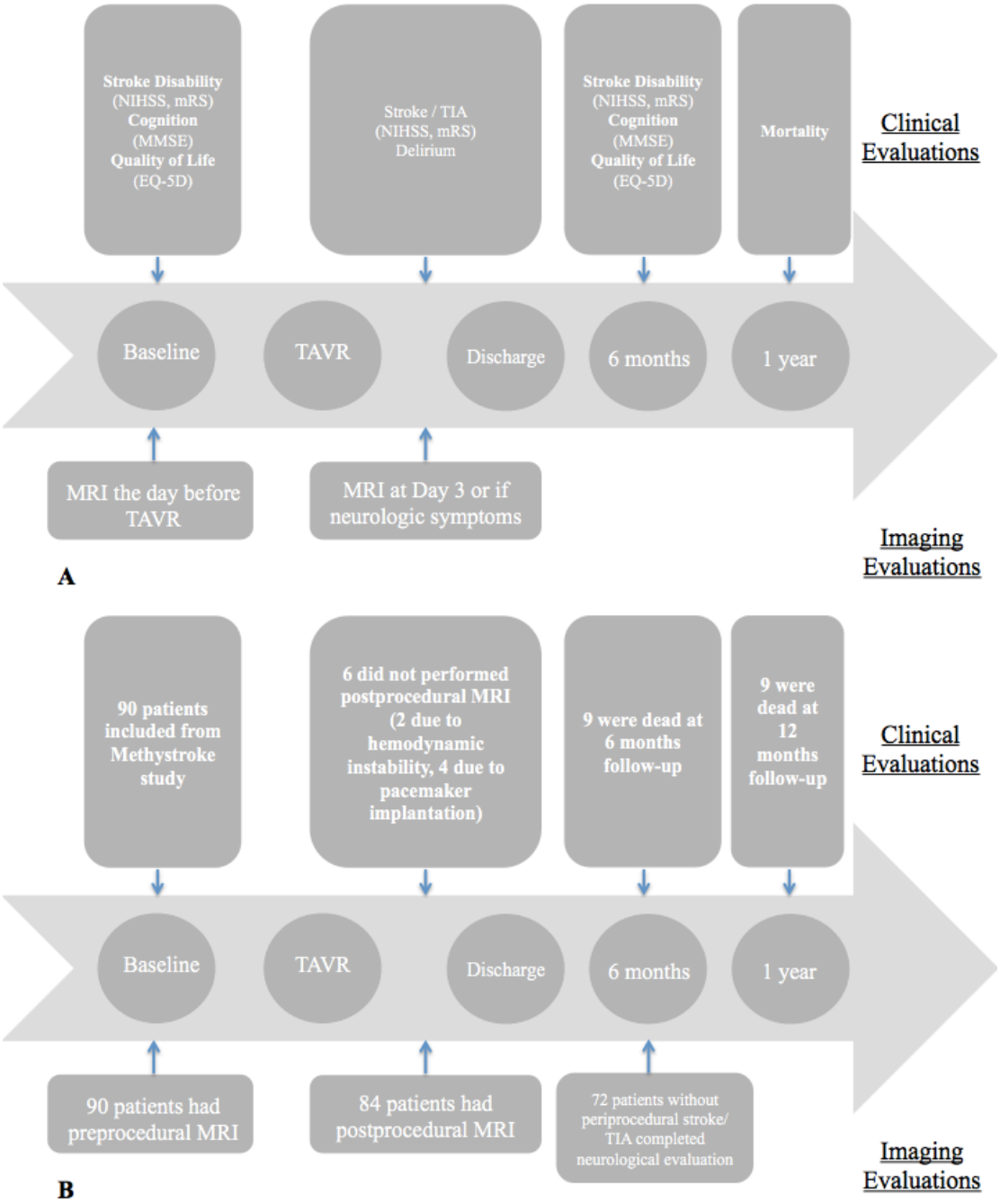
Figure 1. Standardized Timing (A) and flowchart (B) of Clinical and Imaging Evaluations (adapted from Lansky et al. JACC 2017)

Figure 2. T2*-weighted gradient-echo sequence before (A, B) and after(C, D) TAVR procedure. This patient had a unique microbleed in the right precentral gyrus before TAVR (white arrow head; B, D). Two new microbleeds were observed after TAVR, in the right frontal and temporal lobes (white arrows; C). Cerebral microbleeds were identified as homogeneous, round foci, <10 mm diameter, of low signal intensity. Flow void artifacts of the pial blood vessels(black arrows) were clearly distinguished from cerebral microbleeds by their location in the subarachnoid space and their tubular morphology on the adjacent slices.

Figure 3. Relationship between cerebral emboli (CE) and cerebral microbleeds (CMB)

Figure 4. Central Illustration: Potential role of Acquired VWF syndrome and acute cardiovascular situations on the occurrence of acute cerebral microbleeds.
The combination at various degree of 1) Acquired vWF defect (HMW proteolysis) related to heart valve disease or ECLS/LVAD, 2) prolonged anticoagulation at high level, 3) acute restauration of high systolic blood pressure (TAVR/SAVR) and 4) vascular structure alteration leading potentially to blood brain barrier disturbance could predispose to the acute appearance of new cerebral microbleeds.

Tables (separate sheets)



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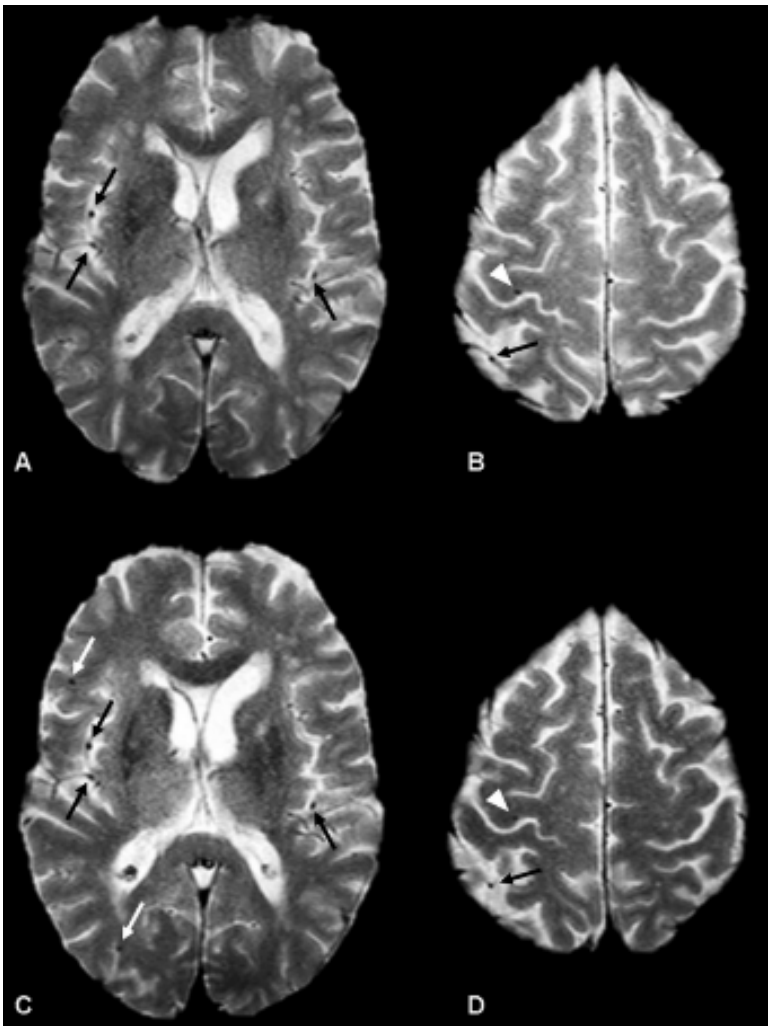

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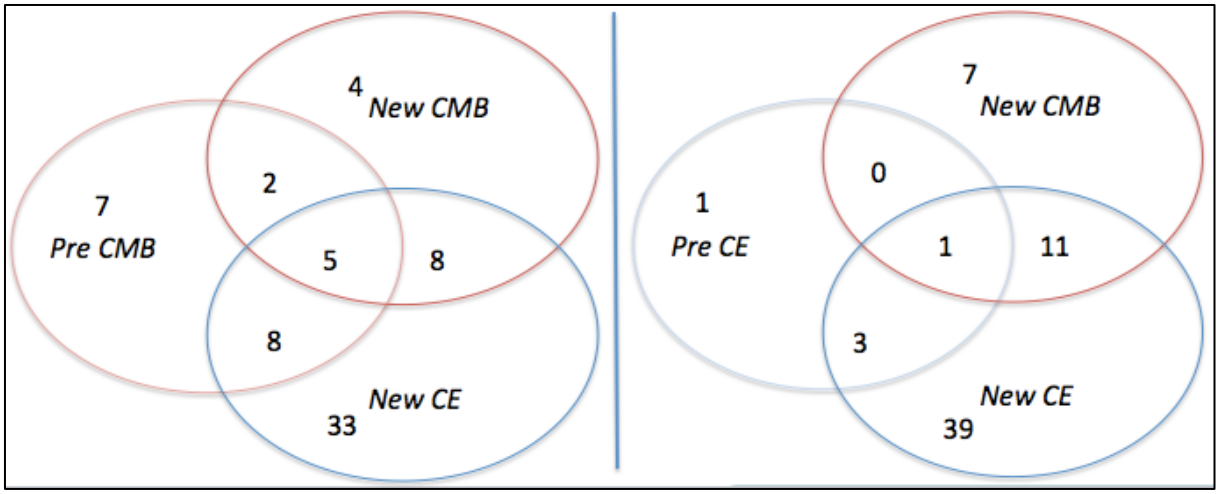
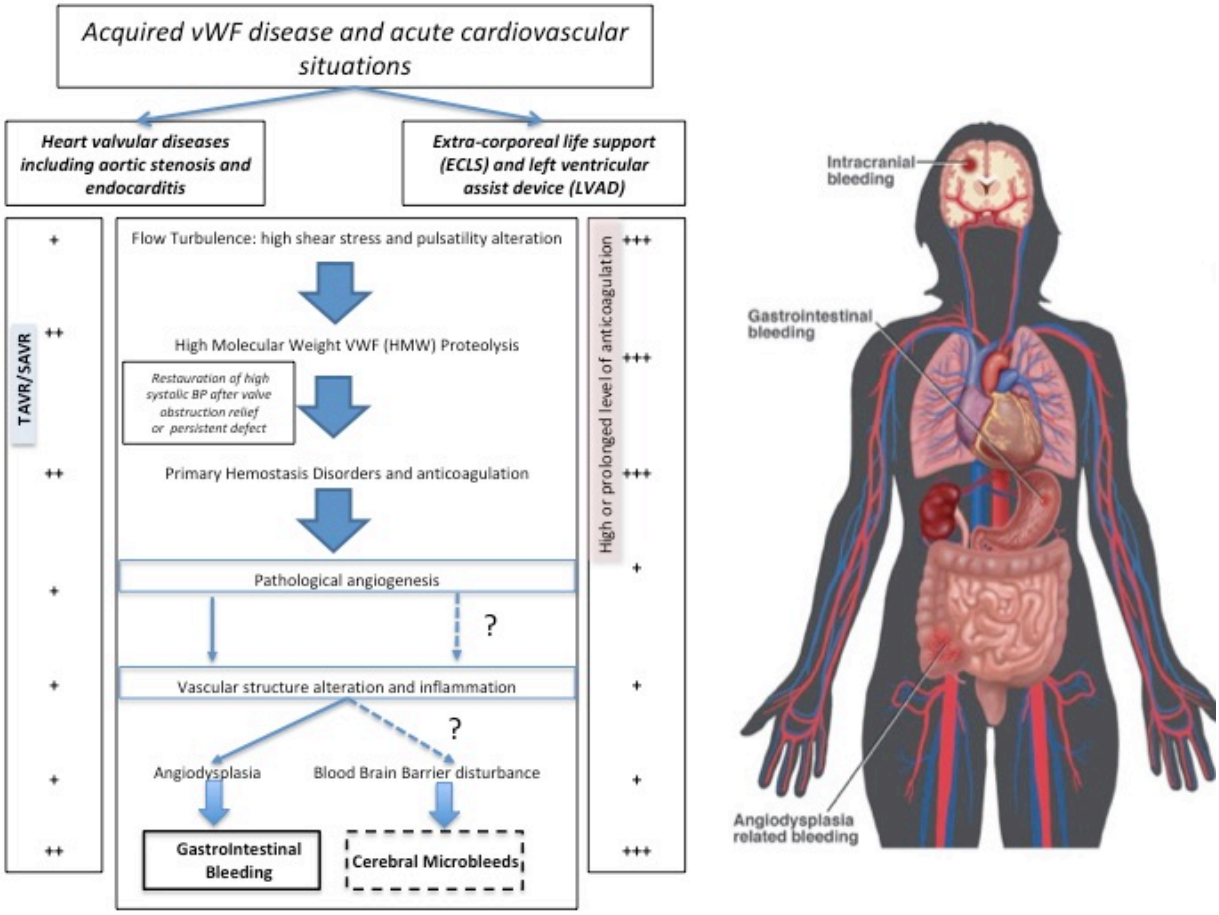


A B

Figure 3. Relationship between preprocedural lesions (CMB, A and CE, B) and new cerebral lesions (new CMB and new CE)

No relation was found between new postprocedural microbleed and either preprocedural microbleed (p=0.23), preprocedural CE (p=0.33) or new post-procedural CE (p=0.88).



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	All (n=90)	Study group (n=84)	Postprocedural ≥1 new CMB (n=19)	Postprocedural no new CMB (n=65)	P value
Clinical data	-	-	-	-	-
Age, yrs	80.9 ± 5.7	80.6 ± 5.6	79.1 ± 5.2	81.2 ± 5.3	0.35
Male n (%)	43 (47)	42 (50)	12 (63)	30 (46)	0.19
BMI (kg/m²)	27.8 ± 5.7	27.9 ± 5.9	27.9 ± 6,1	27.7 ± 5.2	0.88
Logistic Euroscore %	19.8 ± 4.5	20.0 ± 4.3	19.0 ± 5.3	20.2 ± 3.9	0.72
STS score Mortality %	12.8 ± 7.8	12.3 ± 7.6	12.8 ± 4.9	12.1 ± 8.1	0.11
STS score permanent-stroke %	6.6 ± 2.7	6.5 ± 2.4	5.7 ± 1.7	6.7 ± 2.5	0.13
Recent endovascular procedures < 1 month	11 (12)	10 (11)	3 (15)	7 (10)	0.77
Comorbidities	-	-	-	-	-
Hypertension	63 (70)	60 (71)	16 (84)	44 (67)	0.16
Diabetes	31 (34)	28 (33)	8 (42)	20 (30)	0.35
Atrial Fibrillation	33 (36)	30 (35)	9 (47)	21 (32)	0.22
Severe Renal Failure	20 (22)	19 (22)	3 (15)	16 (24)	0.41
History of bleeding	4 (4)	4 (4)	3 (15)	1 (1)	**0.01**
Coronary Artery Disease	41 (45)	40 (47)	12 (63)	28 (43)	0.12
Neurological assessment	-	-	-	-	-
MMSE <27	13 (14)	12 (14)	5 (26)	7 (10)	0.08
Prior stroke or TIA	16 (17)	16 (19)	3 (15)	13 (20)	0.68
Preoperative TTE	-	-	-	-	-
LVEF ≥ 55	70 (77)	64 (76)	14 (73)	50 (76)	0.77
Mean gradient mmHg	48 ± 13	48 ± 12	51 ± 16	47 ± 11	0.25
Indexed valve area cm²/m²	0.39 ± 0.10	0.39 ± 0.10	0.37 ± 0.12	0.40 ± 0.10	0.33
Bicuspid valve	6 (7)	5 (6)	1 (5)	4 (6)	0.88
Medication before TAVR	-	-	-	-	-
Aspirin	63 (70)	64 (76)	12 (63)	52 (80)	0.12
Clopidogrel	29 (32)	29 (38)	8 (42)	21 (32)	0.42
DAPT	20 (22)	20 (23)	5 (26)	15 (23)	0.77
Anticoagulant	28 (31)	28 (33)	9 (47)	19 (29)	0.16
APT + Anticoagulant	16 (17)	16 (19)	6 (31)	10 (15)	0.11
Preprocedural MRI	-	-	-	-	-
Microbleeds (CMB)	23 (25)	22 (26)	7 (36)	15 (23)	0.23
Cerebral emboli	5 (5)	5 (5)	2 (10)	3 (5)	0.33
Postprocedural MRI	-	-	-	-	-
New Microbleeds (CMB)	Na	19 (22)	NA	NA	NA
New Cerebral emboli	Na	54 (64)	13 (68)	41 (63)	0.66
Procedural data	-	-	-	-	-
Heparin, UI (Total dose)	5715±2402	5706±2399	6840±1878	5375±2545	**0.02**
Fluo tim, sec	1529 ± 571	1530 ± 580	1770 ± 691	1460 ± 536	**0.03**
Predilatation	62(69)	58 (69)	15 (79)	43 (66)	0.28
Postdilation	16(90)	15 (17)	5 (26)	10 (15)	**0.03**
Protamine reversion	25(28)	23 (27)	2 (10)	21 (32)	**0.04**
Haemostasis	-	-	-	-	-
Baseline	-	-	-	-	-
Hemoglobin, g/dl	12.0 ±1.7	11.9 ±1.7	12.3 ±1.4	11.7 ±1.7	0.35
Hematocrit, %	34.8±5.2	34.7±5.3	35.1±5.1	34.5±5.3	0.66
Platelet count, *10⁹/l*	183±62	181±64	172±55	183±87	0.61
aPTT, s	34.12	34±12	34±12	34±12	0.97
HMW-multimer-ratio	0.67±0.20	0.66±0.21	0.61±0.19	0.68±0.22	0.21
CT-ADP, s	221±6	220±65	235±62s	216±68	0.29
Time of valve implant	-	-	-	-	-
Platelet count, *10⁹/l*	183±80	182±81	174±58	184±107	0.83
aPTT, s	214±24	213±24	211±26	214±23	0.66
End of procedure	-	-	-	-	-
Platelet count, *10⁹/l*	170±77	172±78	165±47	175±98	0.78
aPTT, s	97±042	98±43	105±38	87±34	**0.05**
HMW-multimer-ratio	1.02±26	1.03±0.26	0.90±0.14	1.06±0.27	**0.009**
CT-ADP, s	135±62	136±63s	165±72	127±57	**0.02**
Post-procedural VARC-2 and TTE		**See Suppplemental Table 1**	**See Suppplemental Table 1**	**See Suppplemental Table 1**	**See Suppplemental Table 1**

Table 1. Baseline and procedural factors associated with new CMB.

Data are mean(SD) or n(%).

New postprocedural CMB are CMB present on post-procedural MRI which were not present on the preprocedural MRI. AF atrial fibrillation, BMI Body mass Index, TIA transient ischemic attack, TTE transthoracic echography, LVEF left ventricular ejection fraction, APT antiplatelet therapy.

		Baseline	*MRI*	*analysis*	*postTAVR*	*MRI*	*analysis*	*Evolution*	*Between*	*MRIs*
	Study group (n=84)	PREprocedural ≥1 CMB (n=22)	PREprocedural no CMB (n=62)	P value	POSTprocedural ≥1 CMB (n=30)	POSTprocedural no CMB (n=42)	P value	Postprocedural ≥1 new CMB (n=19)	Postprocedural no new CMB (n=65)	P value
Neurological examination at baseline	-	-	-	-	-	-	-	-	-	-
Modified Rankin scale>1	6 (7)	2 (9)	4(6)	0.65						
NIHss n≥1	8 (9)	3 (13)	5 (8)	0.44						
EQ-5D	42 ± 12	42 ± 18	42 ± 11	0.85						
MMSE	28 ± 2	26 ± 3	28 ± 1	**0.01**						
Neurological examination at 6 months	-	-	-	-	-	-	-	-	-	-
Modified Rankin scale>1	5 (6)	2 (9)	3 (5)	0.32	3 (10)	2 (5)	0.38	1 (5)	4 (6)	0.88
NIHss n≥1	4 (5)	2 (9)	2 (3)	0.26	3 (10)	1 (2)	0.14	1 (5)	3 (5)	0.92
EQ-5D	62 ± 10	60 ± 10	66 ± 10	0.06	62 ± 13	61 ± 8	0.86	60 ± 14	63 ± 8	0.44
MMSE	27 ± 2	26 ± 3	28 ± 1	**0.01**	27 ± 2	27 ± 1	0.11	28 ± 2	27 ± 2	0.63
Clinical events at 6 months	-	-	-	-	-	-	-	-	-	-
Death	7 (8)	2 (9)	5 (8)	0.88	2 (6)	5 (11)	0.45	0 (0)	7 (11)	0.14
MACCE	12 (15)	4 (18)	8 (12)	0.54	5 (16)	7 (16)	0.62	1 (5)	11 (17)	0.20

Table 2. Neurological evolution

Data are mean (SD) or n (%).

TIA transient ischemic accident, MACCE Major Adverse Cardiac and Cerebrovascular event. Neurological scales : NIHss, EQ-5D, MMSE as previously described.
Neurological examination at 6 months after TAVR : patients with periprocedural stroke or TIA (n=5) are excluded.

	Index Event	N	Heart Valve disease	vWF defect[a]	Detailed data on vWF[b]	Detailed data On anticoagulation[b]	Pre-operative MRI	Post-operative MRI	Days between MRIs	Post-index event CMB rate	Pre-index event CMB rate	Localisation of CMB	Standardized Neurological evaluations
Endocarditis	-	-	-	-	-	-	-	-	-	-	-	-	-
Duval et al. 2010[29]	Endocarditis	130	YES	*	NO	NO	1.5T	-	NA	57%	-	-	-
Goulenok et al. 2013[9]	Endocarditis	30	YES	*	NO	NO	1.5T	-	NA	56%	-	-	-
Iung et al. 2013[10]	Endocarditis	120	YES	*	NO	NO	1.5T	-	NA	60%	-	-	-
Hess et al. 2013[30]	Endocarditis	109	YES	*	NO	NO	1.5T	-	NA	57%	-	85% lobar	-
Total:	-	**389**	-	-			-	-	-	-	-	-	-
Cardiovascular Interventions	-	-	-	-	-	-	-	-	-	-	-	-	-
Sang-Beom Jeon et al. 2010[31]	Cardiac valve Surgery CBP	19	YES	*	NO	NO	1.5T	1.5T	7 days	63%; 95%CI 38-83%	5%; 95%CI 0.1-26%	46% lobar	-
Liebeskind et al. 2012[12]	ECLS in Children	6	NO	**	NO	NO	-	1.5T	NA	100%	-	Most lobar	-
Yoshioka et al. 2017[13]	LVAD explantation	35	NO	**	NO	Yes	-	3.0T	NA	**97%**	-	-	-
Patel et al. 2019[11]	Cardiac Surgery CBP	75	YES	*	NO	NO	1.5T	1.5T	7 weeks	76%	**36%**	70% lobar	YES
Debry et al. 2021	**TAVR**	**84**	**YES**	*	**Yes**	**Yes**	**1.5T**	**1.5T**	**3 days**	**35%; 95%CI 24-45%**	**23%; 95%CI 14-33%**	**69% lobar**	**YES**
Total:	-	**219**	-	-			-	-	-	-	-	-	-

Table 3. Summary of studies describing cerebral microbleeds in acute cardiac scenarios

- : no data; T: Tesla (MRI); NA : non applicable, CBP cardiopulmonary bypass LVAD left ventricular assist device, ECLS extra-corporeal life support,

[a]: according to published literature[17,19,40] all these clinical scenarios are known to be associated with at least moderate VWF multimer defect.
*Moderate to severe VWF multimer defect is known to be present in patients with severe aortic stenosis and severe regurgitant valve disease[17,19]
** Severe to profound VWF multimer defect is known to be present in patients with assist device (ECLS or LVAD)[40]

[b]: To describe whether these data were provided as part of the study.

Supplemental data

	Study group (n=84)	Postprocedural ≥1 new CMB (n=19)	Postprocedural no new CMB (n=65)	P value (Postprocedural)
VARC 2 criteria	**-**	-	-	-
Device success n (%)	**70 (84)**	15 (79)	55 (85)	0.73
All Bleedings n (%)	**23 (27)**	7 (36)	16 (24)	0.31
Vascular Complications n (%)	**10 (11)**	2 (10)	8 (12)	0.83
CHF n (%)	**2 (2)**	0 (0)	2 (3)	0.43
Stage 2-3 AKI n (%)	**13 (15)**	3 (15)	10 (15)	0.86
New AF episode n (%)	**4 (5)**	1 (5)	3 (5)	0.90
Clinical TIA/Stroke n (%)	**5 (5)**	0 (0)	5 (7)	0.21
IntraHospital death n (%)	**1 (1)**	1 (1)	0 (0)	0.06
TTE data	**-**	-	-	-
Aortic Regurgitation ≥2	**9 (11)**	4 (21)	5 (8)	0.15
Mean gradient mmHg mean ± SD	**10.5 ± 4.6**	11.2± 4.2	10.4 ± 4.9	0.82
Aortic valve area cm^2 mean ± SD	**1.77 ± 0.58**	1.76 ± 0.50	1.77 ± 0.60	0.97

Supplemental Table 1. Early post-procedural outcome and new post-procedural CMB
Early post-procedural outcomes at 30 days (VARC-2 criteria).
CHF congestive heart failure, AKI acute kidney injury, TTE transthoracic echography, AF atrial fibrillation, TIA transient ischemic accident.

Patient	Date of diagnostic post TAVR	NIHSS score	Ischemic Stroke or TIA	Symptoms	Lead to death	Pre procedural CE	New Post procedural CE	Pre procedural CMB	New Post procedural CMB
1	Day 1	0	TIA	Transient confusional syndrome	No	0	11	0	0
2	Day 4	0	TIA	Transient confusional syndrome	No	0	6	0	0
3	Day 1	10	Stroke	Right hemiparesis, aphasia	Yes	0	Wide range infarct	1	0
4	Day 3	3	Stroke	Aphasia	No	0	1	0	0
5	Day 2	8	Stroke	Right hemiparesis, dysarthria	No	0	8	1	0

Supplemental Table 2. Details of patients presenting new neurological deficits after TAVR procedure (n=5). TIA transient ischemic attack.

	All (n=90)	Study group (n=84)	Preprocedural ≥1 CMB (n=22)	Preprocedural no CMB (n=62)	P value
Clinical data	-	-	-	-	-
Age, yrs mean ± SD	80.9 ± 5.7	**80.6 ± 5.6**	80.0 ± 5.9	80.9 ± 5.5	0.51
Male n (%)	43 (47)	**42 (50)**	11 (50)	31 (50)	1
BMI (kg/m^2) mean ± SD	27.8 ± 5.7	**27.9 ± 5.9**	27.6 ± 6.9	28.0 ± 5.5	0.78
Logistic Euroscore % mean ± SD	19.8 ± 4,5	**20.0 ± 4.3**	19,4 ± 4.7	20.2 ± 3,6	0.80
STS score Mortality % mean ± SD	12.8 ± 7.8	**12.3 ± 7.6**	12.1 ± 5.3	12.6 ± 8.5	0.80
STS score permanent-stroke % mean ± SD	6.6 ± 2.7	**6.5 ± 2.4**	7.3 ± 2.0	6.2 ± 2.5	0.07
Recent endovascular procedures < 1 month n (%)	11 (12)	**10 (11)**	2 (9)	8 (12)	0.63
Comorbidities	-	-	-	-	-
Hypertension n (%)	63 (70)	**60 (71)**	21 (95)	39 (62)	**0.003**
Diabetes n (%)	31 (34)	**28 (33)**	11 (50)	17 (27)	**0.05**
Atrial Fibrillation n (%)	33 (36)	**30 (35)**	11 (50)	19 (30)	0.10
Severe Renal Failure n (%)	20 (22)	**19 (22)**	7 (32)	12 (19)	0.23
History of bleeding n (%)	4 (4)	**4 (4)**	2 (9)	2 (3)	0.26
Coronary Artery Disease n (%)	41 (45)	**40 (47)**	10 (45)	30 (48)	0.81
Neurological assessment	-	-	-	-	-
MMSE <27 n (%)	13 (14)	**12 (14)**	5 (23)	7 (11)	0.18
Prior stroke or TIA n (%)	16 (17)	**16 (19)**	7 (32)	8 (13)	**0.04**
Preoperative TTE	-	-	-	-	-
LVEF ≥ 55 n (%)	70 (77)	**64 (76)**	18 (81)	46 (74)	0.35
Mean gradient mmHg mean ± SD	48 ± 13	**48 ± 12**	49 ± 12	47 ± 12	0.65
Indexed valve area cm^2/m^2 mean ± SD	0.39 ± 0.10	**0.39 ± 0.10**	0.39 ± 0.13	0.40 ± 0.10	0.90
Bicuspid valve n (%)	6	**5**	2 (9)	3 (5)	0.46
Preprocedural MRI	-	-	-	-	-
Microbleeds (CMB) n (%)	23 (25)	**22 (26)**	NA	NA	NA
Cerebral emboli n (%)	5 (5)	**5 (5)**	2 (9)	3 (5)	0.46
Postprocedural MRI	-	-	-	-	-
New Microbleeds (CMB) n (%)	Na	**19 (22)**	7 (31)	12 (19)	0.23
New Cerebral emboli n (%)	Na	**54 (64)**	13 (59)	41 (66)	0.55
Medication before TAVR	-	-	-	-	-
Aspirin n (%)	63 (70)	**64 (76)**	16 (73)	48 (77)	0.65
Clopidogrel n (%)	29 (32)	**29 (38)**	7 (32)	22 (35)	0.75
DAPT n (%)	20 (22)	**20 (23)**	3 (14)	17 (27)	0.19
Anticoagulant n (%)	28 (31)	**28 (33)**	8 (36)	17 (27)	0.43
APT + Anticoagulant n (%)	16 (17)	**16 (19)**	5 (23)	11 (18)	0.60

Supplemental Table 3. Risk factors for preprocedural CMB;

BMI Body mass Index, DAPT dual antiplatelet therapy, TTE transthoracic echography, LVEF left ventricular ejection fraction, APT antiplatelet therapy.

	All (n=90)	All (n=84)	Preprocedural ≥1 CE (n=5)	Preprocedural no CE (n=79)	P value (preprocedural)	Postprocedural ≥1 new CE (n=54)	Postprocedural no new CE (n=30)	P value (Postprocedural)
Clinical data	-	-	-	-	-	-	-	-
Age, yrs mean ± SD	80.9 ± 5.7	**80.6 ± 5.6**	76.5 ± 5.6	80.9 ± 5.5	0.06	80.5 ± 6.2	80.9 ± 4.4	0.77
Male n (%)	43 (47)	**42 (50)**	3 (60)	39 (49)	0.64	30 (24)	12 (40)	0.17
BMI (kg/m^2) mean ± SD	27.8 ± 5.7	**27.9 ± 5.9**	32.8 ± 11.1	27.6 ± 5.4	0.06	27.9 ± 6.2	27.8 ± 5.3	0.93
Logistic Euroscore % mean ± SD	19.8 ± 4.5	**20.0 ± 4.3**	20.7 ± 7.2	20.0 ± 12.6	0.90	18.7 ± 8.1	22.9 ± 18.4	0.15
STS score Mortality % mean ± SD	12.8 ± 7.8	**12.3 ± 7.6**	12.3 ± 5.7	12.4 ± 7.8	0.97	12.3 ± 8.6	12.6 ± 5.5	0.87
STS score permanent-stroke % mean ± SD	6.6 ± 2.7	**6.5 ± 2.4**	7.9 ± 3.2	6.4 ± 2.4	0.17	6.5 ± 2.5	6.5 ± 2.5	0.96
Recent endovascular procedures < 1 month n (%)	11 (12)	**10 (11)**	4 (80)	6 (7)	**<0.001***	5 (9)	5 (16)	0.31
Comorbidities	-	-	-	-	-	-	-	-
Hypertension n (%)	63 (70)	**60 (71)**	3 (60)	57 (72)	0.55	36 (66)	24 (80)	0.23
Diabetes n (%)	31 (34)	**28 (33)**	4 (80)	24 (30)	**0.02***	19 (35)	9 (30)	0.62
Atrial Fibrillation n (%)	33 (36)	**30 (35)**	2 (40)	28 (35)	0.83	19 (35)	11 (36)	0.89
Severe Renal Failure n (%)	20 (22)	**19 (22)**	1 (20)	18 (22)	0.88	13 (24)	6 (20)	0.66
History of bleeding n (%)	4 (4)	**4 (4)**	0 (0)	4 (5)	0.60	2 (3)	2 (6)	0.54
Coronary Artery Disease n (%)	41 (45)	**40 (47)**	3 (60)	37 (46)	0.55	25 (46)	15 (50)	0.74
Neurological assessment	-	-	-	-	-	-	-	-
MMSE <27 n (%)	13 (14)	**12 (14)**	1 (20)	11 (13)	0.70	9 (16)	3 (10)	0.40
Prior stroke or TIA n (%)	16 (17)	**16 (19)**	3 (60)	37 (46)	**0.01***	11 (20)	5 (16)	0.67
Preoperative TTE	-	-	-	-	-	-	-	-
LVEF ≥ 55 n (%)	70 (77)	**64 (76)**	5 (100)	59 (74)	0.19	41 (75)	23 (76)	0.82
Mean gradient mmHg mean ± SD	48 ± 13	**48 ± 12**	46.2 ± 15.3	48.4 ± 12.5	0.70	48.2 ± 12.5	48.3 ± 12.9	0.99
Indexed valve area cm^2/m^2 mean ± SD	0.39 ± 0.10	**0.39 ± 0.10**	0.43 ± 0.10	0.39 ± 0.04	0.50	0.40 ± 0.09	0.37 ± 0.12	0.27
Bicuspid valve n (%)	6 (7)	**5 (6)**	0 (0)	6 (7)	0.52	4 (7)	2 (7)	0.90
Preprocedural MRI	-	-	-	-	-	-	-	-
Microbleeds (CMB) n (%)	23 (25)	**22 (26)**	2 (40)	20 (25)	0.46	13 (24)	9 (30)	0.55
Cerebral emboli n (%)	5 (5)	**5 (5)**	NA	NA	NA	4 (7)	1 (1)	0.44
Postprocedural MRI	-	-	-	-	-	-	-	-
Microbleeds (CMB) n (%)	Na	**19 (22)**	1 (20)	18 (22)	0.88	9 (16)	10 (34)	0.05
Cerebral emboli n (%)	Na	**54 (64)**	4 (80)	50 (63)	0.44	NA	NA	NA
Medication before TAVR	-	-	-	-	-	-	-	-
Aspirin n (%)	63 (70)	**64 (76)**	2 (40)	62 (78)	0.05	41 (75)	23 (76)	0.82
Clopidogrel n (%)	29 (32)	**29 (38)**	3 (60)	26 (32)	0.21	16 (29)	13 (43)	0.07
DAPT n (%)	20 (22)	**20 (23)**	0 (0)	20 (25)	0.19	10 (18)	10 (33)	0.12
Anticoagulant n (%)	28 (31)	**28 (33)**	1 (20)	27 (34)	0.51	18 (33)	10 (33)	1
APT + Anticoagulant n (%)	16 (17)	**16 (19)**	0 (0)	16 (20)	0.26	12 (22)	4 (13)	0.32

Supplemental Table 4. Risk factors for CE; # P<0.05 on preprocedural MRI, * P<0.05 on postprocedural MRI. New postprocedural CE weren't present on the preprocedural MRI.
BMI Body mass Index, DAPT dual antiplatelet therapy, TIA transient ischemic attack, TTE transthoracic echography, LVEF left ventricular ejection fraction, APT antiplatelet therapy.

Discussion générale et Perspectives

CHAPITRE 1: Situations cliniques d'urgence et traitement percutané du RA

Rétrécissement aortique serré et choc cardiogénique

Cette première étude incluant 44 patients et menée dans 2 centres est l'une des plus importantes cohortes publiées de patients traités par valvuloplastie aortique (BAV) pour un choc cardiogénique (CC) lié à une RA sévère. Il révèle 4 résultats clés : (1) de nos jours la mortalité à 1 an reste élevée (70 %), (2) la mortalité est directement reliée à la durée du choc avant la réalisation du BAV, (3) réaliser une BAV après un laps de temps trop long après l'initiation des agents inotropes (>48H) est associée à une issue désastreuse, (4) la situation la plus favorable pour effectuer le BAV semble être avant l'introduction des catécholamines, car elle permet d'amener 50 % des patients au TAVI ou au remplacement chirurgical. Par ailleurs il y'a 2 complications majeures liées à la BAV : les AVC et la tamponnade.

Nous ne voyons aucune amélioration concernant la mortalité précoce depuis 1994. À l'ère moderne du TAVI, nous confirmons que la BAV lors d'un CC reste associé à un mauvais pronostic avec seulement 27% des patients pouvant être traités par TAVI ou chirurgie dans l'année, et 70% de mortalité à un an.

Pour la première fois, nous rapportons que les patients avec un choc cardiogénique non-hypotensif ont un risque plus faible de décès ou de récidive de choc cardiogénique à 1 an que le sous-groupe choc cardiogénique hypotensif ($p = 0,03$) et qu'il existe une tendance à une mortalité plus faible dans cette population à un mois ($p = 0,14$) et à un an ($p=0,09$). La BAV peut être utile pour les patients avec choc cardiogénique non-hypotensif car il permet d'effectuer une chirurgie ou un TAVI à distance dans la moitié des cas.

Les anciennes études incluaient une plus petite cohorte de patients et les détails sur la surveillance hémodynamique étaient rares. En particulier, les données biologiques concernant l'insuffisance rénale ou hépatique, ou les doses de catécholamines au moment de la valvuloplastie font toujours défaut. Même une étude récente ne donne pas beaucoup d'informations sur la gestion médical du choc et les résultats après la BAV. Les essais explorant les résultats du TAVI d'urgence pour le choc cardiogénique lié au RA semblent avoir la même faiblesse. Néanmoins, nous rapportons un taux de mortalité à 1 mois de 47%, qui est cohérent avec les études précédentes avec une mortalité à l'hôpital ou à 1 mois variant de 43% à 71%.

Nos résultats illustrent la difficulté d'améliorer les résultats des patients en choc cardiogénique secondaires à un RA serré. La durée des symptômes de choc avant la tentative de traitement causal (pour soulager l'obstruction valvulaire) semble déterminer l'issue. Nous

montrons que le timing d'introduction des agents inotropes est crucial, puisque les patients sans amines ont un meilleur pronostic à 1 an. La valvuloplastie doit être réalisée avant ou lors de l'apparition des signes d'altération de la perfusion des organes cibles, au lieu de débuter les agents inotropes.

Lorsque les catécholamines ont été initiées, un retard dans l'exécution de la BAV peut être mortel. Réaliser une BAV précoce, pendant les premières 48h du diagnostic du CC, avant par exemple d'augmenter la dose de dobutamine au-delà de 5 microgrammes/kg/min pour maintenir une pression systolique supérieure à 90 mmHg pourrait être la réponse à une détérioration rapide de l'état hémodynamique. Une BAV retardée après 48h peut être inutile, car l'insuffisance hépatique et rénale s'aggrave. *Buchwald et al*. ont également suggéré dans une série beaucoup plus petite (n=14) un effet bénéfique d'une BAV précoce dans les 48 premières heures suivant le diagnostic de choc.

La mortalité à 1 an restant élevée chez les patients atteints de RA sévère avec choc cardiogénique traités par une BAV, 47 % dans la présente étude, on peut légitimement s'interroger sur l'intérêt d'un TAVI d'urgence dans la prise en charge de ces patients. Cependant, une étude rétrospective de patients (n=27) atteints de RA et de CC traités par TAVI d'urgence rapporte un taux de mortalité à 30 jours et à 1 an de 33 % et 41 %, respectivement. Une autre étude multicentrique récente portant sur les TAVI et les BAV réalisés en situation urgente (n=118) ont également montré des mortalités procédurales immédiates et à 30 jours élevées (33 %), avec plus d'AVC et de complications vasculaires pour le groupe TAVI par rapport au groupe BAV.

Dans l'ensemble, cela peut soulever le fait que le TAVI urgent n'est pas l'option idéale chez les patients atteints de RA avec un choc cardiogénique. Nos données peuvent néanmoins suggérer que l'organisation de centres pour effectuer des BAV urgentes chez ces patients atteints de CC pourrait sauver des vies.

Malgré le succès initial de la BAV urgente, la morbidité et la mortalité du CC liées à un RA sévère restent considérablement élevées et sont directement liées à la durée du choc. La réalisation d'une BAV avant de commencer les agents inotropes ou dans les 48 heures suivant leur initiation semble être la clé de la survie.

Avec l'amélioration des résultats du TAVI, il est nécessaire de réaliser un essai randomisé comparant la BAV urgente suivi du TAVI comparé au TAVI urgent seul pour ces patients instables. Notre équipe a rédigé un protocole de recherche PHRC soumis au GIRCI qui n'a pas eu de financement pour le moment.

Rétrécissement aortique serré et chirurgie extracardiaque urgente

La meilleure prise en charge préopératoire des patients avec RA serré avant une chirurgie extracardiaque (CEC) urgente est inconnue. Cette étude est la première (i) à présenter le plus grand nombre de patients avec RA serré nécessitant une chirurgie extracardiaque urgente, et à inclure une grande proportion (> 60 %) de chirurgie extracardiaque impérieuse (<48h), et (ii) à comparer stratégie médicale conservatrice et invasive (avec BAV) avant chirurgie extracardiaque urgente en utilisant une analyse en IPTW. Globalement, cet essai reflète la réalité de la prise en charge de patients âgés atteints de RA serré qui souffrent, par exemple, d'une fracture de la hanche qui nécessite une intervention chirurgicale en urgence pour préserver leur autonomie.

Les principaux résultats de cette analyse en IPTW sont les suivants : (i) Les patients atteints de RA serré pris en charge de manière conservatrice avant CEC présentent un risque élevé d'événements cardiovasculaires (MACE) (20,0%), et de mortalité à 1 mois (10,0%), (ii) la réalisation d'une BAV dans cette population n'est pas « bénigne » et est associée à 7 jours à une mortalité de 3,2 %, et à 9,6 % de complications non mortelles, (iii) alors que la mortalité « immédiate » à un mois après la CEC pourrait être plus faible chez les « survivants » de la stratégie invasive par rapport à la stratégie médicale, le MACE global à un mois et la survie à 3 mois sont similaires chez les patients traités avec ou sans BAV, (iv) un score ASA ≥ 3 ou une hypertension pulmonaire préopératoire > 35 mm Hg semblent avoir un impact sur le pronostic après chirurgie extracardiaque. Nous rapportons par ailleurs un taux de 3,2% de saignement menacant le pronostic vital ainsi qu'un taux de 1,1% d'AVC après BAV.

Certaines études ont précédemment décrit les résultats des patients atteints de RA par rapport aux patients non atteints de RA subissant une CEC. Il n'a pas été démontré que les patients atteints de RA subissant une chirurgie non cardiaque présentent un risque accru de mortalité, mais présentent des taux significativement plus élevés d'événements cardiovasculaires graves par rapport aux patients sans RA, en particulier ceux présentant un RA serré symptomatique ont plus de MACE (infarctus aigu du myocarde, insuffisance cardiaque, arythmie) que le RA serré asymptomatique (36 % contre 16 % respectivement) et des taux de mortalité plus élevés que le RA modérée (16 % contre 4 %).

Nous rapportons des taux de mortalité à 1 mois (10,0%) et de MACE (20,0%) plus élevés avec une stratégie conservatrice après chirurgie extracardiaque urgent, que *Tashiro et al.* de la Mayo Clinic, mais cette étude n'a exploré que les patients asymptomatiques atteints de RA après chirurgie extracardiaque programmée (mortalité à 1 mois 3,3% et MACE 12%).

Aucune étude randomisée comparant les résultats des patients atteints de RA serré subissant une CEC urgente sous une approche conservatrice ou invasive n'a été menée à ce jour. La stratégie invasive réduit le taux de mortalité « immédiate » à 1 mois après NCS (3,2% vs 10,0% ; P=0,04) mais pas si l'on prend en compte la mortalité induite par la BAV elle-même (5,4% et 10,0% ; P=0,33). En partie à cause du « bénéfice hémodynamique » insuffisant et des complications liées à la stratégie invasive du BAV, les deux attitudes thérapeutiques donnent un taux de MACE similaire à un mois après chirurgie extracardiaque. Bien que nous confirmions que l'utilisation d'une stratégie invasive de routine ne soit pas recommandée pour les patients atteints de RA serré, elle peut être bénéfique pour certains patients sélectionnés.

Les patients avec RA serré asymptomatiques, ou les patients nécessitant une chirurgie extracardiaque à faible risque/intermédiaire pourraient être pris en charge de manière conservatrice. Comme le rappelle l'étude de *Tashiro et al*, les CEC programmées n'ont pas la même morbidité que les CEC urgentes et sont également un bon prédicteur de mortalité à 30 jours. Des résultats publiés indiquent que les événements indésirables se sont produits principalement chez les patients atteints de RA très serrés avec une AVA ≤ 0,7 cm2 et un gradient moyen ≥ 50 mm Hg. Dans notre étude, en raison d'une petite cohorte et de la présence de RA sévère dans les deux groupes, nous n'avons pas été en mesure d'identifier les critères anatomiques qui devraient nous inciter à réaliser une BAV avant chirurgie extracardiaque. Cependant, une hypertension pulmonaire préopératoire > 35 mmHg et un score ASA ≥ 3 sont associés à des taux plus élevés de MACE et de mortalité à court terme. Une stratégie invasive chez les patients présentant ces critères pourrait être discutée pour améliorer le pronostic après CEC.

La première façon de diminuer la morbi-mortalité après CEC peut être de réduire la morbidité liée à la procédure de BAV. L'utilisation d'un plus petit accès transradial unilatéral ou bilatéral pour la BAV est sûre et faisable. La BAV avec des ballons semi-compliants avec profil optimisé, sans nécessité de stimulation ventriculaire gauche, ou avec stimulation sur le guide rigide ventriculaire gauche a également été récemment décrit.

La deuxième voie peut être d'améliorer le résultat hémodynamique de la procédure. Dans notre étude, 30% des patients n'ont pas connu d'amélioration significative des paramètres hémodynamiques après la BAV. De plus, dans les 70 % restants avec une amélioration, le gradient résiduel moyen était de 30,0 +/- 0,4 mmHg et donc encore élevé. La seule façon d'obtenir une nette amélioration hémodynamique, et éventuellement une

diminution de la morbi-mortalité après NCS, pourrait être d'effectuer un TAVI d'emblée chez certains patients très sélectionnés. La correction du RA serré avec le TAVI est évidente par rapport à la BAV en termes d'hémodynamique, de symptômes, de récidive et de mortalité. Mais dans cette situation préopératoire particulière, le TAVI peut être difficile à réaliser car il nécessite un plateau technique dédié avec scanner multicoupe et une salle de cathétérisme disponible sur site. Elle nécessite au moins un accès vasculaire 14F, plus large que pour une BAV transradiale (9F), et peut être associée à plus de complications. Dans notre étude, seulement 25% de la cohorte de RA serré a eu une procédure TAVI dans les 3 mois après chirurgie extracardiaque mettant en évidence que cette population présente moins de symptômes, une combinaison de fragilité et de comorbidités multiples dont le cancer, des handicaps, qui au final peuvent retarder voire annuler la procédure TAVI. Cependant, d'autres études ont rapporté que les patients cancéreux atteints de RA sévère ayant subi une chirurgie avaient une survie améliorée, quel que soit le statut cancéreux. Enfin, le TAVI direct peut être contre-indiqué en cas de bactériémie par exemple avant une chirurgie digestive, ou une chirurgie orthopédique septique urgente avec un risque élevé d'endocardite. D'autre part, par rapport à la chirurgie valvulaire aortique, le TAVI sous anesthésie locale est moins invasif et peut éviter la possibilité de dissémination du cancer liée à la circulation extracorporelle chez les patients cancéreux.

Enfin nous insistons sur l'importance cruciale de la discussion pluridisciplinaire pour chaque patient au sein de la Heart-Team avant CEC. Des études de cohorte prospectives à grande échelle sont nécessaires pour clarifier nos interrogations et délimiter le rôle de la procédure BAV mini-invasive ou du TAVI « direct » chez certains patients à haut risque opératoire.

CHAPITRE 2: TAVI et voies d'abord alternatives à la voie fémorale

Nous décrivons dans ce 3e travail l'une des plus grandes séries de patients traités via un accès vasculaire transcarotide (TC) ou transaxillaire (TAx). Les principaux résultats de cette étude avec appariement par score de propensité sont les suivants : (i) les TAVI TC et TAx ont un taux similaire de mortalité et d'AVC/AIT à 1 mois, une sécurité et une efficacité cliniques satisfaisantes avec des valves auto ou expansibles au ballon, (ii) il y'a moins de saignements mineurs et d'hématomes de l'accès principal dans le groupe transaxillaire.

Il n'y a pas de données comparatives sur ces deux voies alternatives les plus couramment utilisées pour le TAVI. De nombreux articles ont déjà décrit ces voies par rapport au TAVI par voie transthoracique (transapical et transaortique) avec des résultats favorables.

Un registre français récent dans une cohorte de TAVI périphérique non fémoral a retrouvé un taux d'AVC similaire (3,35 %), moins de complications vasculaires majeures (0,68 %) et plus d'hémorragies majeures (8,56 %) que dans notre analyse. Nous rapportons également des taux de succès élevés de ces dispositifs (95,4 %) et des faibles taux de mortalité à 1 mois (5,0 %) similaires à ceux de *Dahle et al.* Cependant ce registre STS/ACC analysait uniquement des valves expansibles au ballon et rapporte des taux extrêmement faibles de complications vasculaires majeures (1,1 %) et d'hémorragie menaçant le pronostic vital (0,1 %). Dans ces registres, l'évaluation des critères VARC-2 n'a pas été adjudiqué de façon indépendante, et il ne peut être exclu que certains événements cliniques, en particulier l'AIT aient pu être en partie sous-déclarés, car ils sont également significativement inférieurs à ceux rapportés dans les autres essais cliniques. Nous rapportons des taux similaires de complications vasculaires majeures (9,0 % contre 11,9 %) et des plus faibles taux de saignements menaçant le pronostic vital (3,6 % contre 11,4 %) que les autres études plus anciennes sur le TAx; avec uniquement les valves auto-expansibles. Une des explications potentielles de ce résultat défavorable avec TAVI non fémoral est la courbe d'apprentissage nécessaire. Les accès transaxillaires ou transcarotides peuvent être plus délicats à manipuler que les axes ilio-fémoraux et sujets à la dissection, à la sténose ou à la thrombose, et ne sont pas accessibles à une compression manuelle efficace.

Notre étude suggère que les deux approches sont également sûres sans différence de mortalité précoce (30 jours) et tardive (1 an) et de taux similaires d'AVC/AIT précoces. Dans le cas du TAVI transcarotidien, même s'il offre un accès plus direct, un chemin moins tortueux pour atteindre la valve aortique, avec moins d'interaction vasculaire et aortique, les

complications comprenant hématomes locaux et saignements mineurs, l'embolisation de débris et la baisse transitoire du débit sanguin cérébral au cours de l'intervention peuvent expliquer l'augmentation non significative du taux d'AVC/AIT à 1 mois (6,8 % vs 3,2 %) avec la voie TC. Le taux d'AIT/AVC avec la voie TC n'a pas diminué significativement entre la période précoce (2010-2015 et l'utilisation de prothèse de première génération) et après 2015 (7,0 % vs 5,4 %, p=0,53). Le taux d'AVC/AIT à 30 jours que nous rapportons se situe dans la zone supérieure de ceux précédemment rapportés par *Amer et al.* (3 %), et *Mylotte et al.* qui avaient également un taux de 3,2 % d'AVC/AIT à 30 jours. Ces chiffres sont cohérents avec ceux d'un précédent essai qui a rapporté un taux de 5,7 % d'événements cérébrovasculaires périopératoires et un taux de 11,4 % de complications globales de l'accès vasculaire avec TAVI transcarotide. La perfusion carotidienne antérograde passive utilisant un shunt fémoro-carotide temporaire a été utilisée pour les premiers patients TC (2010) et désormais n'est plus utilisée.

L'accès plus direct depuis l'artère carotide permet un positionnement plus précis de la prothèse, en particulier pour les valves auto-expansibles, ce qui aurait pu entraîner une réduction de la régurgitation périprothétique postprocédurale. Ceci peut ne pas être le cas car l'angle d'arrivée du cathéter via la voie carotide par rapport au plan de l'anneau est moins favorable que pour l'artère axillaire gauche ce qui permet au cathéter de se positionner sur la paroi latérale de l'aorte et enfin de traverser le plan de l'anneau plus perpendiculairement qu'à partir de l'artère carotide.

Nous préférons également l'artère axillaire/carotide gauche à la voie droite car elle évite les lésions ou l'occlusion de l'artère innominée qui alimente la distribution carotide et vertébrale droite. De plus, une lésion isolée de l'artère axillaire/carotide gauche est plus facile à réparer qu'une lésion de l'artère innominée. L'incidence élevée des complications vasculaires et hémorragiques dans les deux groupes souligne la nécessité d'une évaluation multidisciplinaire préopératoire attentive de l'anatomie vasculaire pour déterminer la meilleure approche non fémorale.

Les TAVI par voie TC et TAx ont des taux similaires de mortalité et d'AVC/AIT à 1 mois et une sécurité et une efficacité cliniques semblables avec des valves expansibles au ballon ou auto-expansibles. Les taux de saignements mineurs et les hématomes de l'accès principal sont plus faibles dans le groupe d'accès transaxillaire. Des études randomisées sont nécessaires pour déterminer si le TAVI transcarotide ou transaxillaire donnent des résultats équivalents lorsque la voie fémorale est inutilisable.

CHAPITRE 3: TAVI et lésions cérébrales hémorragiques

Cette 4e étude, ancillaire du PHRC Méthystroke, avec 84 patients atteints de rétrécissement aortique (RA) symptomatique sévère traité par TAVI par voie transfémorale avec une IRM pré et post-opératoire réalisée à 3 jours d'intervalle démontre que : 1) près d'un patient sur 4 présentera des nouveaux microbleeds (MCB) après la procédure TAVI (23 %, IC à 95 % = 14-33%); 2) la procédure, avec l'exposition prolongée au traitement anticoagulant, et un défaut acquis du facteur Willebrand vWF (en particulier lorsque ce défaut persiste à la fin de la procédure) sont associés à la survenue de ces micro-hémorragies cérébrales post-procédurales.

Dans cette population, la prévalence des micro-hémorragies (26 %, IC 95 % = 17-37 %) se situe dans la même zone que la prévalence rapportée dans la population générale au même âge (10-25 %). À l'exception de la présence du RA serré et d'un défaut acquis en multimère du vWF chez les patients présentant des MCB à l'IRM préopératoire, les paramètres cliniques associés à la présence de MCB préopératoires étaient très similaires à ceux précédemment rapportés dans la littérature et incluaient l'hypertension (p=0,004), le diabète (p=0,05), des antécédents d'AIT/AVC (p=0,01), mais pas l'anticoagulation orale (p=0,43).

À notre connaissance, cette étude est la première à étudier le rôle de la procédure TAVI sur l'incidence de nouveaux MCB, et la principale conclusion est que près d'un patient sur 4 a présenté de nouveaux MCB (23 %, 95 % IC = 14 -33%).
L'incidence élevée de nouveaux micro-hémorragies (23 %) dans un laps de temps aussi court (3 jours) contraste avec la faible incidence observée sur une période d'un an (4 à 7 %) chez les personnes âgées présentant des facteurs de risque vasculaire similaires, recevant également un antithrombotique de façon chronique, et indique clairement que la procédure est un déclencheur potentiel de MCB. Cette observation est également très importante dans le cadre des tentatives précédentes de relier certaines interventions cardiaques avec l'apparition de nouveaux microsaignements cérébraux. Dans les études antérieures, l'association n'a pu être définitivement établie puisqu'une seule IRM a été réalisée dans la plupart des cas ou que le temps écoulé entre l'intervention et la 2ème IRM était trop long (>1 -7 semaines).
La présente étude suggère également que les MCB et les infarctus cérébraux (ICS) sont des événements indépendants survenant chez différents patients, et plus important encore, que la survenue d'un nouveau MCB post-opératoire ne semble pas être liée à la présence de MCB pré-opératoire. Les nouveaux MCB et ICS ne sont pas localisés dans les mêmes territoires et

il est donc peu probable qu'il s'agisse de micro-infarctus, lié par exemple au débris d'embolisation, avec transformation hémorragique.
La fréquence plus élevée de nouveaux microsaignements cérébraux avec une durée prolongée de procédure et/ou une exposition prolongée à l'anticoagulation pendant la procédure est cohérente avec le rôle de la gestion de l'anticoagulation précédemment démontré pour les MCB cérébraux « spontanés » ou pour les MCB associés à une valvulopathie grave.

L'anomalie acquise du vWF chez les patients atteints d'une valvulopathie cardiaque a été associée à un risque persistant d'hémorragie, en particulier d'hémorragies gastro-intestinales. Cependant, son rôle dans la survenue de MCB n'a jamais été étudié auparavant. C'est donc une nouvelle découverte intéressante de suggérer que le défaut acquis-vWF, en particulier sa persistance à la fin de la procédure TAVI, peut être associé à un risque plus élevé d'hémorragie microvasculaire cérébrale.
Les observations selon lesquelles 1) tous les cas de MCB signalés à ce jour chez les patients atteints de maladie cardiovasculaire aiguë sont liés à des situations connues pour être associées à un dysfonctionnement modéré du multimère du vWF (valve cardiaque/prothèse ; 567/608 patients ; 93 %,) ou sévère (dispositif d'assistance ; 41/608 patients ; 7 %), et 2) que les conditions cliniques avec un défaut plus profond du multimère vWF (dispositif d'assistance circulatoire) sont également celles avec la prévalence la plus élevée de micro-hémorragies cérébrales ; sont donc très évocatrices d'un lien direct entre les perturbations du débit liées à la maladie valvulaire, d'un défaut acquis en vWF et l'apparition de MCB. Enfin, dans notre étude, les MCB étaient principalement localisés dans les zones lobaires, similaires à la description des patients atteints de valvulopathie cardiaque aiguë.

Au-delà du contrôle de l'hémostase primaire, plusieurs études ont souligné l'idée que le vWF régule l'angiogenèse par de multiples voies, tandis que le défaut acquis en vWF favorise l'apparition d'angiodysplasie dans le tractus gastro-intestinal et d'autres malformations artérioveineuses. Le vWF est également exprimé abondamment dans l'endothélium cérébral et pourrait être impliqué dans le remodelage des vaisseaux cérébraux. Le vWF modifie et endommage également la perméabilité de la barrière hémato-encéphalique dans certains contextes pathologiques, et pourrait favoriser la rupture de la paroi des vaisseaux cérébraux avec pour conséquence des micro-hémorragies.

La conséquence hémodynamique fondamentale de la correction aiguë du RA serré au cours du TAVI est le passage aigu d'une pression artérielle différentielle abaissée à une pression normale (ou éventuellement supra normale en cas de régurgitation paravalvulaire). Ce changement hémodynamique soudain pourrait déclencher l'apparition de micro-

hémorragies sur un fond de défaut modéré/sévère du multimère du vWF observé chez les patients atteints de RA subissant une réparation aortique et/ou chez des patients présentant un dysfonctionnement valvulaire aigu. Les études rapportant des MCB observés chez des modèles animaux combinant un défaut du vWF et une pression artérielle élevée mais pas chez ceux avec un seul défaut du vWF sont cohérents avec cette hypothèse. Le rôle du changement soudain des conditions hémodynamiques explique probablement pourquoi, malgré la présence d'un défaut du vWF, la prévalence des micro-hémorragies observées chez les patients avec RA avant l'intervention n'est pas beaucoup plus élevée que celle observée dans une population générale du même âge.

Conformément à l'idée que les MCB sont considérés comme relativement silencieux, nous n'avons observé aucun déficit neurologique focalisé chez les patients présentant des MCB lors de leur examen neurologique au moment de l'IRM. De même, il n'y avait pas d'impact de ces micro-hémorragies cérébrales sur les résultats post-opératoires immédiats ni sur la mortalité toutes causes confondues à long terme (suivi à 1 an). Cependant, nous avons trouvé une relation entre la présence initiale de micro-hémorragies cérébrales (avant TAVI) et une diminution de la fonction cognitive telle que mesurée par le score MMSE.
Dans notre population, et comme décrit précédemment, les nouveaux MCB n'ont pas aggravé la fonction cognitive à 6 mois.

Les MCB préopératoires « spontanés » peuvent être un marqueur d'une pathologie cérébrale sous-jacente, qui impacte les fonctions cognitives, car l'accumulation de petites lésions hémorragiques peut être un élément déclencheur pour aggraver un processus neurodégénératif à long terme. En revanche, le faible nombre de patients, le faible nombre de nouveaux MCB par patient engendrés par l'intervention, et le suivi trop court peuvent limiter l'impact de ces lésions sur les fonctions cognitives à 6 mois après TAVI. Il est important de noter que les CMB engendrés par le TAVI n'ont pas infléchi l'amélioration de la qualité de vie ou de l'autonomie au suivi de 6 mois qui est directement associée au succès de la procédure.

Nous rapportons donc une incidence élevée (23 %, IC 95 % = 14-33 %) de nouveaux MCB apparaissant au moment des procédures TAVI. Alors que nous avons identifié des paramètres liés à la procédure, comprenant la durée d'anticoagulation, et la persistance du défaut acquis-vWF qui sont associés à l'apparition de ces micro-hémorragies cérébrales, les mécanismes physiopathologiques des micro-hémorragies doivent être encore mieux compris. L'impact clinique de ces micro-hémorragies liées à la procédure à très long terme devra être également clarifié.

Une étude issue du PHRC méthystroke est en cours de réalisation étudiant l'impact du régime antiagrégant plaquettaire préopératoire sur la survenue de microbleeds au cours de la procédure TAVI.

L'étude Witecmo analyse également les modifications du vWF lors de l'implantation de système d'assistance circulatoire –ECLS et la survenue de microbleeds.

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Annexes

Chapitre 1. Situations cliniques d'urgence et traitement percutané du RA

EDITORIAL

Urgent balloon aortic valvuloplasty in cardiogenic shock patients: still state of the art in the TAVI era?

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For a decade, percutaneous balloon aortic valvuloplasty (BAV) was a treatment option for high surgical risk and inoperable patients with severe aortic stenosis (AS). It was first described by Cribier et al in 1986 (1). Six years later, in 1992, Cribier et al reported the results of 10 patients treated by BAV as a life-saving procedure in an emergency setting due to cardiogenic shock (CS) (2). In 2012, BAV was regarded as a bridge to surgery or transcatheter aortic valve implantation (TAVI) in haemodynamically unstable patients at high surgical risk, and as a palliative treatment alternative in patients for whom neither surgery nor TAVI was an option (3).

In this issue of EuroIntervention, *Debry and co-workers* focus on the periprocedural and one-year outcomes of urgent BAV as a rescue therapy in patients with CS due to severe AS (4). The authors studied 44 patients with acutely decompensated severe AS who were treated by BAV at two centres. They divided the patients into two groups according to their blood pressure, hypotensive (n=31) and non-hypotensive CS (n=13). Hypotensive CS patients were classified as "classic" shock patients with a systolic blood pressure <90 mmHg and catecholamine dependency. Non-hypotensive CS patients had a systolic blood pressure >90 mmHg without vasopressor therapy but a combination of low cardiac index (<2.2 l/min/m²) and peripheral hypoperfusion. All patients were at extremely high surgical risk with a mean EuroSCORE II of 41.6±13.7%. The BAV procedure was performed 1.2±0.5 and 4.1±2.9 days after admission to the intensive care unit in patients with non-hypotensive CS and hypotensive CS, respectively. In 88.6% of the procedures, BAV was considered successful, defined as a reduction in transaortic pressure gradient of at least 50% and without moderate-to-severe aortic regurgitation (AR).

One-month and one-year mortality was 47% and 70%, respectively. Patients with a successful procedure had significantly lower in-hospital mortality (33% versus 80%; p=0.04). Furthermore, surviving patients had a lower post-procedural mean transaortic pressure gradient (22.5±9.7 vs. 30.5±12.6 mmHg; p=0.03). Univariate analysis identified a preoperative dose of dobutamine >5 µg/kg/min and a BAV delayed for >48 hrs as predictive of the primary endpoint of mortality or recurrent CS at one year.

The authors concluded that "despite initial success of urgent BAV, morbidity and mortality of CS related to severe AS remains dramatically high and is directly related to the duration of shock. Performing BAV before starting inotropic agents or within 48 hours of their initiation appears to be key to survival".
So, should every patient in CS secondary to severe AS undergo a BAV procedure today? And what is the role of TAVI in this setting? The first TAVI procedure described by *Cribier et al* was performed in 2002 in a patient with CS due to severe AS (5). This patient was declined cardiac surgery because of severe comorbidities and a haemodynamically unstable condition. He had undergone emergency BAV one week earlier, which was initially successful. However, the patient's condition deteriorated with recurrent CS within one week. TAVI was then successfully performed (5).

The key question here is: why not perform TAVI directly instead of BAV in patients with CS? We know from the literature that BAV has a high rate of recurrent AS. Patients in this study even had severe AS despite a successful procedure. The mean aortic valve area after BAV was 0.82±0.20 cm^2, corresponding to severe AS in the majority of patients. One could argue that particularly patients in CS should be treated optimally with respect to the correction of AS. The lower the transaortic pressure gradient in a patient with CS and severely reduced left ventricular ejection fraction the better the outcome. This was also shown by *Debry et al* in the lower post-procedural mean transaortic pressure gradients in surviving patients. When performing TAVI, the transaortic pressure gradient is going to be much lower than after BAV. One could argue that after TAVI patients will have a better outcome.

The second argument in favour of TAVI is the lower risk of significant post-procedural AR. A meta-analysis of more than 15,000 TAVI patients showed a 2.12-fold increase in overall (≥1 year) all-cause mortality in cases with ≥moderate AR (6).

Third, transfemoral TAVI with the latest-generation devices can be performed via 14-16 Fr access. The mean French size for BAV in the current analysis was 11.6±0.9. This difference versus a TAVI procedure is rather low; thus, TAVI can be performed safely in most cases. Despite these arguments favouring TAVI there are also arguments against TAVI. First, TAVI is not available at every hospital. Unstable patients in CS should not be transferred to another hospital because of the risk of further deterioration during transportation. Second, the size of the required transcatheter valve prosthesis can, in most cases, only be measured via echocardiography and angiography. A computed tomography scan of the aortic valve and the access vessels – which is the current state of the art – cannot be readily carried out in every patient without the risk of further clinical deterioration.

In summary, the paper by *Debry et al* underlines the need for a discussion on the best treatment option for patients with CS secondary to severe AS. In this author's opinion, in experienced centres TAVI should be carried out as a first-line therapy provided this option is available and the aortic annulus can be measured safely and reliably, e.g., with 3D echocardiography. In all other centres and situations, BAV should be discussed as a treatment option, especially as a bridge to TAVI or surgical aortic valve replacement **(Figure 1)**.

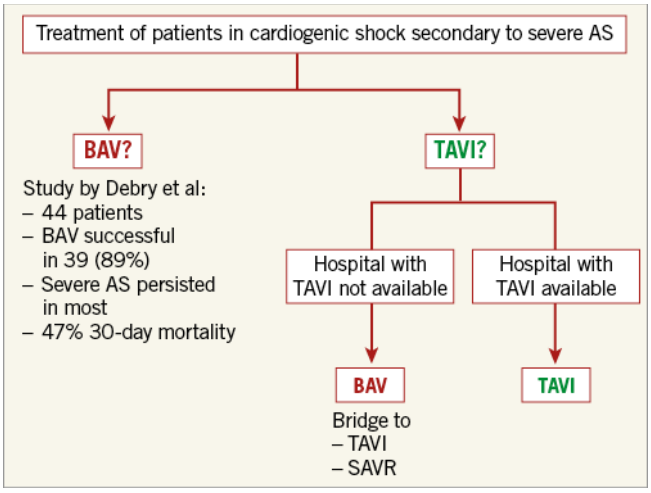

Figure 1. Decision tree for the emergency treatment of patients in cardiogenic shock secondary to severe aortic stenosis (AS). BAV: balloon aortic valvuloplasty; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation

Conflict of interest statement

C. Frerker received lecture honoraria and travel support from Medtronic, Edwards Lifesciences and Abbott Vascular.

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EDITORIAL

Balloon Aortic Valvuloplasty for Severe Aortic Stenosis Before Urgent Noncardiac Surgery.

Expected to be published on the 1st october 2021 (Eurointervention)

EDITORIAL

Special focus on valvular interventions with the PCR Valves e-Course: patient-centring the Heart Team, COVID and clinical trials; mitral valve leaflet repair today; PASCAL, a novel mitral repair device; gender-related outcomes from the SURTAVI trial; differences in access-site outcomes in TAVI; the FORWARD PRO study and more… EuroIntervention 2020;16:. Davide Capodanno

Could a transcarotid (TC) or transaxillary (TAx) access site affect TAVI outcomes? This is the question examined by **Nicolas Debry, Eric Van Belle and colleagues** in a propensity-matched comparison of a French multicentre prospective registry which included 502 patients, with 374 undergoing TC-TAVI and 128 undergoing TAx-TAVI for symptomatic AS. Patients treated through the TAx access were matched 1:2 with patients treated through the TC route with a propensity score involving 20 clinical, anatomical and procedural variables, as well as by date of the procedure. While the two access sites provided similar outcomes in terms of mortality, stroke or TIA, the TAx access group showed less minor bleeding and fewer main access haematomas than the TC group. They conclude that randomised studies would be of interest.

Résumé

Complications ischémiques et hémorragiques des procédures de réparation valvulaire aortique percutanée

La réparation valvulaire aortique percutanée a connu d'immense progrès depuis une vingtaine d'années permettant au patient atteint de rétrécissement aortique (RA) serré de bénéficier d'un traitement curatif, le plus souvent avec une approche minimaliste sous anesthésie locale associée à une diminution des complications procédurales. Cependant la prise en charge de certaines situations cliniques d'urgence ou de certains patients à haut risque opératoire est encore mal définie et nécessite une évaluation précise des complications ischémiques et hémorragiques de la procédure percutanée.

Dans la première partie de la thèse nous avons confirmé que certaines situations cliniques complexes urgentes telles qu'un état de choc cardiogénique secondaire à un RA serré, ou la nécessité d'une chirurgie extracardiaque urgente constituent encore une zone grise où le traitement optimal du RA n'est pas clair et nécessite de plus amples investigations. Dans le choc cardiogénique ou la chirurgie extracardiaque urgente, le risque de complications hémorragiques et surtout ischémiques et la mortalité à court terme restent très élevés. En cas de choc cardiogénique, les complications sont principalement reliées au timing de la valvuloplastie aortique (BAV). En cas de chirurgie extracardiaque urgente, la BAV systématique n'améliore pas le pronostic par rapport au traitement médical.

Dans la deuxième partie de la thèse, chez des patients à risque intermédiaire ou élevé contre indiqué à l'accès transfémoral pour un TAVI, nous avons comparé les deux voies alternatives extrathoraciques les plus utilisées : axillaire et carotidienne. Celles ci font jeu égal en terme de complications ischémiques et de mortalité mais l'accès carotidien semble avoir plus de complications hémorragiques en particulier locales.

La troisième et dernière partie de la thèse nous a permis d'apprécier l'incidence importante de microbleeds au cours de la procédure TAVI. Leur apparition semble être reliée avec la durée de la procédure et l'absence de correction du déficit en facteur Willebrand acquis lors du RA ; ces lésions n'ont pas de retentissement sur l'évolution neurologique à court terme (6mois). Des études sont en cours pour mieux préciser le lien entre risque hémorragique cérébral, anomalie du facteur vWF et dispositif cardiaque valvulaire ou d'assistance.

Mots clés : rétrécissement aortique, valvuloplastie aortique, TAVI, choc cardiogénique, chirurgie extracardiaque, voies alternatives carotidienne et axillaire, microbleeds, hémorragie
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