INCIDENCE, PREDICTORS AND OUTCOMES OF MYOCARDIAL INJURY FOLLOWING TRANSCATHETER AORTIC VALVE REPLACEMENT

Thèse

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RÉSUMÉ

L'implantation de valve aortique par cathéter (TAVI) a été développée comme une alternative thérapeutique pour les patients avec une sténose aortique sévère et ayant un risque opératoire élevé ou extrême en cas de chirurgie de remplacement valvulaire standard.

Par rapport à la chirurgie à cœur ouvert classique, les procédures de TAVI sont moins invasives, parce qu'elles ne sont pas associées au clampage aortique et à la cardioplégie. Toutefois, la procédure implique un certain degré de dommage myocardique dû à la compression du tissu par le ballonnet et la prothèse transcathéter, ainsi que plusieurs courts épisodes d'hypotension extrême et d'ischémie myocardique globale, au cours de la stimulation ventriculaire rapide et du déploiement de la prothèse. De plus, l'approche transapicale, qui est réalisée lorsque l'approche transfémorale n'est pas possible, comprend la ponction de l'apex du ventricule gauche et l'introduction de larges cathéters ce qui augmente vraisemblablement encore les dommages myocardiques. En conséquence, presque tous les patients subissant un TAVI présentent un certain degré de dommage myocardique, défini par une augmentation des enzymes cardiaques, telles que la créatine kinase-MB (CK-MB), la troponine ou le peptide natriurétique de type B (BNP). Néanmoins, les données sur l'incidence exacte des dommages myocardiques, leur étendue, leurs prédicteurs, ainsi que les résultats échocardiographiques et cliniques associés, en fonction des différentes approches et prothèses sont limitées.

Les objectifs généraux de mon projet de doctorat sont d'évaluer l'incidence, les facteurs prédictifs et les résultats des dommages myocardiques après TAVI pour le traitement des patients symptomatiques avec sténose aortique sévère ou bioprothèse dysfonctionnelle et à haut risque chirurgical.

SUMMARY

Transcatheter aortic valve replacement (TAVR) has emerged as a less invasive therapeutic alternative to surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis at very high-risk or prohibitive perioperative risk. Compared to conventional open-heart surgery, TAVR procedures are less invasive, because they are not associated with aortic cross-clamping and cardioplegia. Even so, the procedure involves some degree of myocardial injury due to tissue compression, caused by the balloon and valve prosthesis, as well as several short episodes of extreme hypotension and global ischemia, during rapid ventricular pacing and valve deployment. Also, the transapical approach, which is an alternative to the transfemoral approach, involves the puncture of the ventricular apex and the introduction of large catheters through it. Accordingly, nearly all patients undergoing TAVR present some degree of myocardial injury, as defined by any increase in cardiac biomarkers, including creatine kinase-MB (CK-MB), troponin or B-type natriuretic peptides (BNP). Nonetheless, data on the exact incidence of myocardial injury, extent, predictors, as well as the associated echocardiographic and clinical outcomes, according to the different type of TAVR procedures and transcatheter valves, have been limited.

The general objectives of my PhD project are to evaluate the incidence, predictors and outcomes of myocardial injury following TAVR for the treatment of high-risk patients with severe symptomatic AS or dysfunctional aortic bioprosthesis.

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LIST OF ABBREVIATIONS

ACC/AHA: American College of Cardiology/American Heart Association

ANOVA: analysis of variance

Ao: aorta

AF: atrial fibrillation

AR: aortic regurgitation

AS: aortic stenosis

AVR: aortic valve replacement

BAV: balloon aortic valvuloplasty

BMI: body mass index

BSA: body surface area

CABG: coronary artery bypass graft

CAD: coronary artery disease

CK-MB: creatinine kinase-MB

CMR: cardiovascular magnetic resonance

COPD: chronic obstructive pulmonary disease

CT: computed tomography

cTnT: cardiac troponin T

ECG : electrocardiogram

IL: interleukin

eGFR: estimated glomerular filtration rate

EOA: effective orifice area

EOAi: effective orifice area index

GLS: global longitudinal strain

LCA: left coronary artery

LGE: late gadolinium enhancement

logEuroSCORE: logistic EuroSCORE

LV: left ventricle

LVEF: left ventricular ejection fraction

LVM: left ventricular mass
LVMi: left ventricular mass index
LVOT: left ventricular outflow tract
MR: mitral regurgitation
NP: natriuretic peptides
NT-proBNP: N-Terminal-proBNP
ROC: receiver-operating characteristic
NYHA: New York Heart Association
PCI: percutaneous coronary intervention
PSAP: pulmonary systolic arterial pressure
RCA: right coronary artery
SAVR: surgical aortic valve replacement
SD: standard deviation
SE: standard error
SOV: sinus of Valsalva
STS: Society of Thoracic Surgeons
STS-PROM: Society of Thoracic Surgeons predicted risk of mortality
SV: stroke volume
SVi: stroke volume index
TA: transapical
TAo: transaortic
TAVI: transcatheter aortic valve implantation
TAVR: transcatheter aortic valve replacement
THV: transcatheter heart valve
TF: transfemoral
VARC: Valve Academic Research Consortium

To my wife, Ana Paula

To my daughters, Laura and Maria Luisa

To my parents, Expedito and Cida

To my sister Maíra

Love and family are the essence of life…

« It had long since come to my attention that people of accomplishment rarely sat back and let things happen to them. They went out and happened to things»

Leonardo da Vinci (1452-1519)

ACKNOWLEDGMENTS

Defending a PhD has always been one of my dreams and great objectives in life, and accomplishing this important step is an honor and a privilege that must be shared with so many special people surrounding me. Although being a personal accomplishment, pursuing a PhD is much of a "Heart Team" work composed of numerous individuals that I was fortunate to interact, learn and work together, but more importantly I was profoundly supported and encouraged in order to succeed.

Therefore, I would like first to thank all the committee members that have promptly accepted the task of reviewing and correcting my PhD thesis, as well as attending the defense. My sincere thanks to: **Dr. Rebecca T. Hahn**, director of interventional echocardiography at the New York Presbyterian Hospital, from Columbia University College of Physicians and Surgeons (USA); **Dr. Pierre Voisine**, cardiac surgeon and great researcher at the Quebec Heart & Lung Institute; and **Dr. Mathieu Bernier**, director of the echocardiography lab at the Quebec Heart & Lung Institute.

Likewise, I would like to express my deep appreciation and thanks to **Dr. Josep Rodés-Cabau**, director of interventional cardiology at the Quebec Heart & Lung Institute, that has been a tremendous mentor for me. First, you have opened this marvelous opportunity of spending such amazing years in Canada to perform both a fellowship in interventional cardiology and a PhD. In addition, since the first day at the Quebec Heart & Lung Institute you spare no efforts to teach and support me in this undertaking. I would like to thank you for encouraging my research and for trusting in my potential, ultimately supporting my growth as a researcher and as a physician. Your advices on research as well as on my career have been invaluable. You have now became more than a colleague and a mentor, but also a dear friend.

My gratitude also extends to **Dr. Philippe Pibarot**, my PhD director, for his enthusiasm and willingness to provide both data and research expertise, which were essential in my journey. You have paved my away to achieve and succeed in my PhD. You are an

extraordinary person with such a nice character, enthusiasm and research experience, yet humble, humorous and supportive. Our numerous meetings and discussions together, with really intense and novel ideas and insights, will always inspire my future research life.

* * *

During these years of research the interaction with patients was incredible and especially because most of the subjects undergoing transcatheter aortic valve procedures are frail, with advanced age and numerous comorbidities. Therefore, among thousands of patients included in all of my work I was able to learn many of the challenges in dealing with this population. Thus, I would sincerely address my warmest thanks to all of the patients, their time and motivation in participating in our clinical research.

I would kindly thank **Dr. Robert De Larochellière**, chief of the multidisciplinary department of cardiology at the Quebec Heart & Lung Institute, with whom I was able to learn more than interventional cardiology but also ascertain insightful allusions on being a physician, father, brother and friend. Thanks to him I was even able to start loving hockey!!!

I must also acknowledge the exceptional "Heart Team" at the Quebec Heart & Lung Institute that since the very beginning have helped, supported and taught me so much. This includes **Drs. Daniel Doyle and Éric Dumont**, two magnificent cardiac surgeons at the Quebec Heart & Lung Institute. Additionally, my regards goes to **Dr. Jean-Michel Paradis**, interventional cardiologist, and **Dr. Siamak Mohammadi**, cardiac surgeon and clinical researcher. Both have more recently joined and certainly enhanced this wonderful "Heart Team".

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I would kindly thank my dear friends and partners that spent time with me during all of these years as fellow. For sure I was able to interact with so many different cultures, from all of the continents around the globe, what has been a fantastic personal experience. Therefore I recall my dear friends: **Luis Nombela-Franco**, **Marina Urena**, **Ignacio Amat-Santos** and **Omar Altisent** from the Spanish squad; **Ricardo Allende** from Mexico; **Michael Mok** and **Rishi Puri** from Australia.

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My warmest thanks to my family that have supported me for all of these years, and has really furnished me with education, character, respect, curiosity and humility, but more importantly with love and joy, both the essence of life. Thank you very much for my father Dr. **Expedito Ribeiro**, great friend, example and mentor in life, my dear mother **Cida Ribeiro**, a constant shoulder and support, and my sister **Maíra Ribeiro**, great love and partner. The unit of our family has been the most important support and happiness that guided me through difficult times and in the ensuing love and joy.

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PREFACE

The research work included in this PhD project was conceived in the research center of the Quebec Heart and Lung Institute (IUCPQ) from Laval University, both in the research group of Structural Heart Diseases directed by Dr. Josep Rodès-Cabau and in the Research Laboratory of Valvulopathies directed by Dr. Philippe Pibarot. The present PhD thesis includes 10 chapters, all of them written by Dr. Henrique B. Ribeiro, being 6 scientific articles (chapters 4 to 9) that have been published in peer-review cardiovascular journals.

During this research project, the student received a PhD grant (246860/2012-0) from "CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico - Brasil", effective from 01-01-2013 until 31-12-2014).

The first paper included in this thesis of doctorate is entitled: «**Predictors and Clinical Impact of Myocardial Injury Following Transcatheter Aortic Valve Replacement: Insights from a Large Multicenter Registry**». It has been published in the «***Journal of the American College of Cardiology***» and the student is the first author. It has also been presented at the Transcatheter Cardiovascular Therapeutics meeting in October 2015 (TCT – San Francisco, USA) as a poster abstract. This study included a worldwide collaboration network in TAVR, with 13 included centers from North America, South America and Europe. The student was responsible for developing a databank for the study, managing the data from the worldwide centers, collection of the data at the Quebec Heart & Lung Institute, analysis and interpretation of the data, and drafting the manuscript. Dr. Josep Rodès-Cabau and Dr. Philippe Pibarot supervised each of these stages. All of the other co-authors contributed with comments and constructive suggestions that have improved the final version of the manuscript.

The second article presented in this doctorate thesis is entitled: **«Long-Term Prognostic Value And Serial Changes Of Plasma N-terminal Pro B-type Natriuretic Peptide In Patients Undergoing Transcatheter Aortic Valve Implantation»**. It has been published in the

«***American Journal of Cardiology***» and the student is the first author. It has also been presented at the American Heart Association Scientific Session 2013 (Dallas, USA) as a poster abstract. This study included consecutive patients from the Quebec Heart & Lung Institute. The student was responsible for developing a databank for the study, collection of the data at the Quebec Heart & Lung Institute, analysis and interpretation of the data, and drafting the manuscript. Dr. Josep Rodès-Cabau supervised each of these stages and Dr. Philippe Pibarot was responsible for all of the Echocardiography analysis performed at the Central Core Laboratory under his direction. All of the other co-authors from the Quebec Heart & Lung Institute contributed with comments and constructive suggestions that have improved the final version of the manuscript.

The third article presented in this doctorate thesis is entitled: **«Myocardial Injury Following Transaortic Versus Transapical Transcatheter Aortic Valve Replacement»**. It has been published in the «***The Annals of Thoracic Surgery***» and the student is the first author. It has also been presented at the Transcatheter Cardiovascular Therapeutics meeting in October 2015 (TCT – San Francisco, USA) as a poster abstract, at the meeting from the Brazilian Society of Interventional Cardiology (SBHCI, Brasilia, june 2015) where it was awarded with the prize of one of the best oral abstracts. This study included consecutive patients from the Quebec Heart & Lung Institute. The student was responsible for developing a databank for the study, collection of the data at the Quebec Heart & Lung Institute, analysis and interpretation of the data, and drafting the manuscript. Dr. Josep Rodès-Cabau supervised each of these stages. The Echocardiography analyses were performed in the Central Core Laboratory at the Quebec Heart & Lung Institute directed by Dr. Philippe Pibarot, with the supervision of Dr. Abdellaziz Dahou. All of the other co-authors from the Quebec Heart & Lung Institute contributed with comments and constructive suggestions that have improved the final version of the manuscript.

The fourth article presented in this doctorate thesis is entitled: **«Myocardial Injury Following Transcatheter Aortic Valve Implantation: Insights from Delayed-Enhancement Cardiovascular Magnetic Resonance»**. It has been published in the «***Eurointervention***» and the student is the first author. It has also been presented at the Transcatheter Cardiovascular Therapeutics meeting in October 2014 (TCT – Washington-DC, EUA) as a poster abstract. This study included consecutive patients from the Quebec

Heart & Lung Institute. The student was responsible for developing a databank for the study, collection of the data at the Quebec Heart & Lung Institute, analysis and interpretation of the data, and drafting the manuscript. Dr. Josep Rodès-Cabau supervised each of these stages. The CMR analyses were performed in the Central Core Laboratory at the Quebec Heart & Lung Institute directed by Dr. Éric Larose, with the supervision of Dr. Maria de la Paz Ricapito. The Echocardiography analyses were performed in the Central Core Laboratory at the Quebec Heart & Lung Institute directed by Dr. Philippe Pibarot, with the supervision of Dr. Florent Le Ven. All of the other co-authors from the Quebec Heart & Lung Institute contributed with comments and constructive suggestions that have improved the final version of the manuscript.

The fifth article presented in this doctorate thesis is entitled: **«Coronary Obstruction Following Transcatheter Aortic Valve Implantation: A Systematic Review»**. It has been published in the «***JACC: Cardiovascular Interventions***» and the student is the first author. Of note, this article has been selected as the issue's Continuing Medical Education (CME) activity by accreditation and designation statement of the American College of Cardiology Foundation, accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. It has also been presented at the Scientific Session of the American College of Cardiology in March 2013, and at the meeting of the Latin American Society of Interventional Cardiology (SBHCI, Sao Paulo, June 2013), where it was awarded with the prize of one of the best oral abstracts. The student was responsible for developing a databank for the study, performing the systematic review of the literature (together with Dr. Luis Nombela-Franco), analysis and interpretation of the data, and drafting the manuscript. Dr. Josep Rodès-Cabau supervised each of these stages. All of the other co-authors from the Quebec Heart & Lung Institute contributed with comments and constructive suggestions that have improved the final version of the manuscript.

The sixth article presented in this doctorate thesis is entitled: **«Predictive Factors, Management and Clinical Outcomes of Coronary Obstruction Following Transcatheter Aortic Valve Implantation: Insights from a Large Multicenter Registry»**. It has been published in the «***Journal of the American College of Cardiology***»

and the student is the first author. It has also been presented at the meeting of the European Association of Percutaneous Cardiovascular Interventions (EuroPCR, Paris, May 2013), as an oral abstract in the session: “Hot Line - Registries and first-in-man for structural heart disease". This study included a worldwide collaboration network in TAVR, with 81 included centers from North America, Europe, South America, and Asia, from January 2007 to January 2013. The student was responsible for developing a databank for the study, managing the data from the worldwide centers, collection of the data at the Quebec Heart & Lung Institute, analysis and interpretation of the data, and drafting the manuscript. Dr. Josep Rodès-Cabau supervised each of these stages. The CT analyses were performed in the Central Core Laboratory at the Quebec Heart & Lung Institute directed by Dr. Éric Larose, also with the aid of Dr. Sergio Pasian. All of the other co-authors contributed with comments and constructive suggestions that have contributed improved the final version of the manuscript.

INTRODUCTION

The heart is a cone-shaped muscular organ that pumps blood throughout the vessels of the circulatory system, what generates a cardiac output of ~5 liters/minute. The heart is located in the middle compartment of the mediastinum, behind the breastbone of the chest (Figure 0-1), and is enclosed in a double-membrane protective sac, the pericardium.

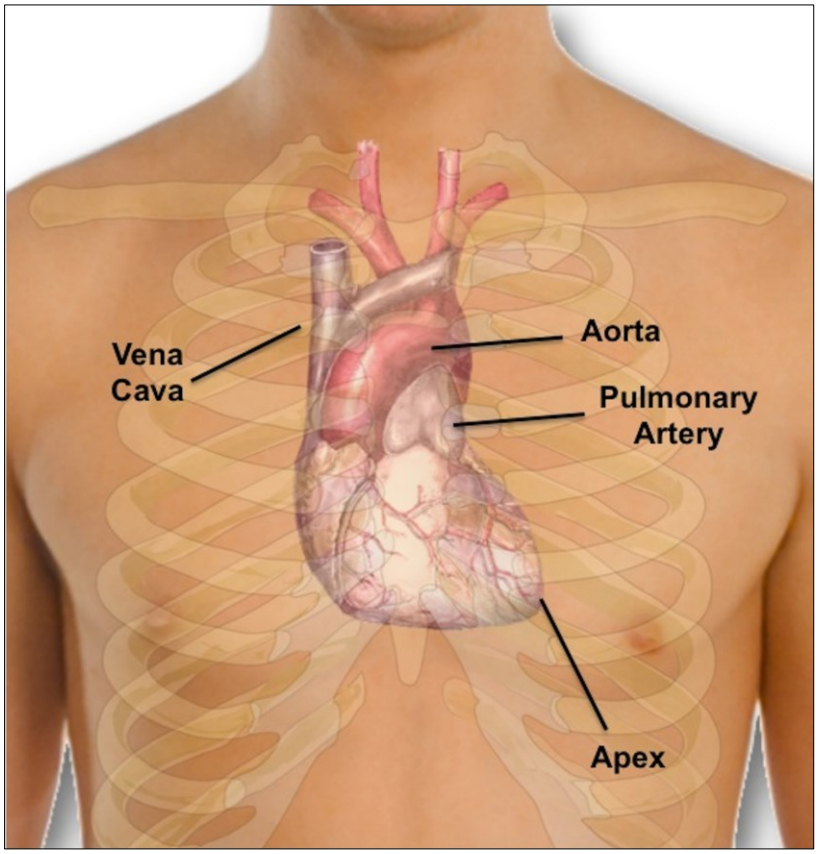


Figure 0-1: Location of the heart in the mediastinum

(Source: Adapted from WikiMedia Commons, by Mikael Häggström)

The pericardium attaches to the mediastinum, providing anchorage for the heart, and it also contains a small amount of fluid that lubricates the surface of the heart. The posterior surface of the heart lies close to the vertebral column, and the anterior surface sits deep to

the sternum and costal cartilages. The great veins – the vena cava, and the great arteries, the aorta and pulmonary artery, are attached to the upper part of the heart, and this location is also called the base, which is found at the level of the third costal cartilage. The lower tip of the heart, the apex, lies just to the left of the sternum between the junction of the fourth and fifth ribs near their articulation with the costal cartilages. The right side of the heart is deflected forward, and the left deflected backward.

The wall of the heart is comprised of three layers: epicardium, myocardium, and endocardium (Figure 0-2). The innermost layer of the heart is the endocardium, and is made up of a lining of simple squamous epithelium, and covers heart chambers and valves. It is continuous with the endothelium of the veins and arteries of the heart, and is joined to the myocardium with a thin layer of connective tissue. The middle layer is called myocardium, and is constituted of a layer of involuntary striated muscle tissue surrounded by a skeleton of collagen. The outermost layer of the heart is the epicardium, which consists of the inner (or visceral) serous membrane of the pericardium that together with the outer membrane (or parietal serous pericardium) encloses the pericardial cavity, surrounding the heart.

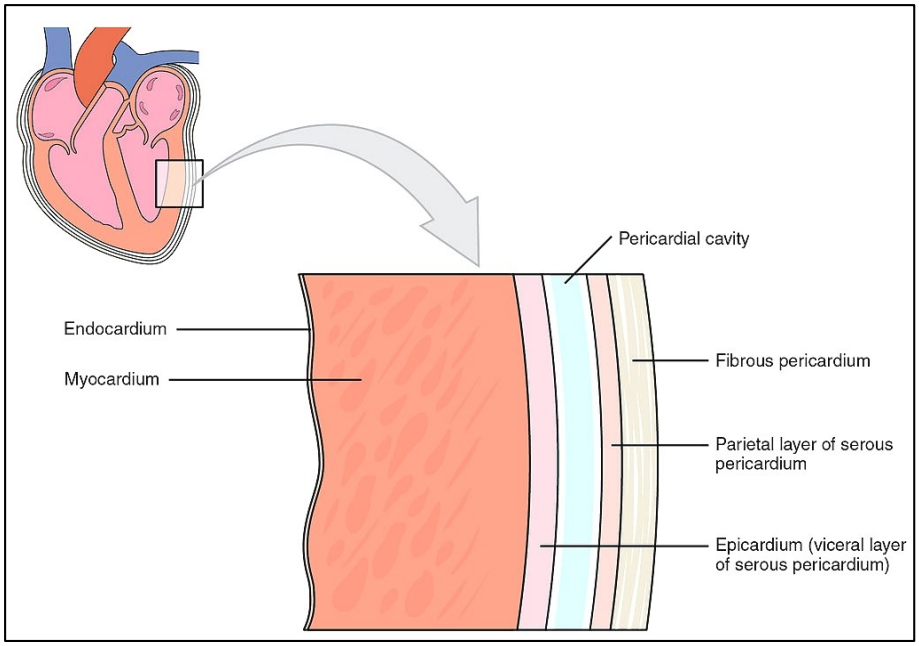


Figure 0-2: Heart wall layers

(Source: Adapted from Anatomy & Physiology, Connexions Website)

The heart has four chambers, two upper atria, the receiving chambers, and two lower ventricles, the discharging chambers (Figure 0-3). The right atrium and the right ventricle are connected by the tricuspid valve, and together are sometimes referred to as the right heart. Likewise, the left atrium and the left ventricle (LV) are connected by the mitral valve, and together are referred to as the left heart. Importantly, the cardiac skeleton, made of dense connective tissue, gives structure to the heart. The cardiac skeleton separates and partitions the atria from the ventricles, and through its fibrous rings, serves as a base for the four heart valves (Figure 0-3). The cardiac skeleton also provides an important boundary in the heart's electrical conduction system since collagen cannot conduct electricity. The interatrial septum separates the atria and the interventricular septum separates the ventricles. The interventricular septum is much thicker than the interatrial septum, since the ventricles need to generate greater pressure when they contract.

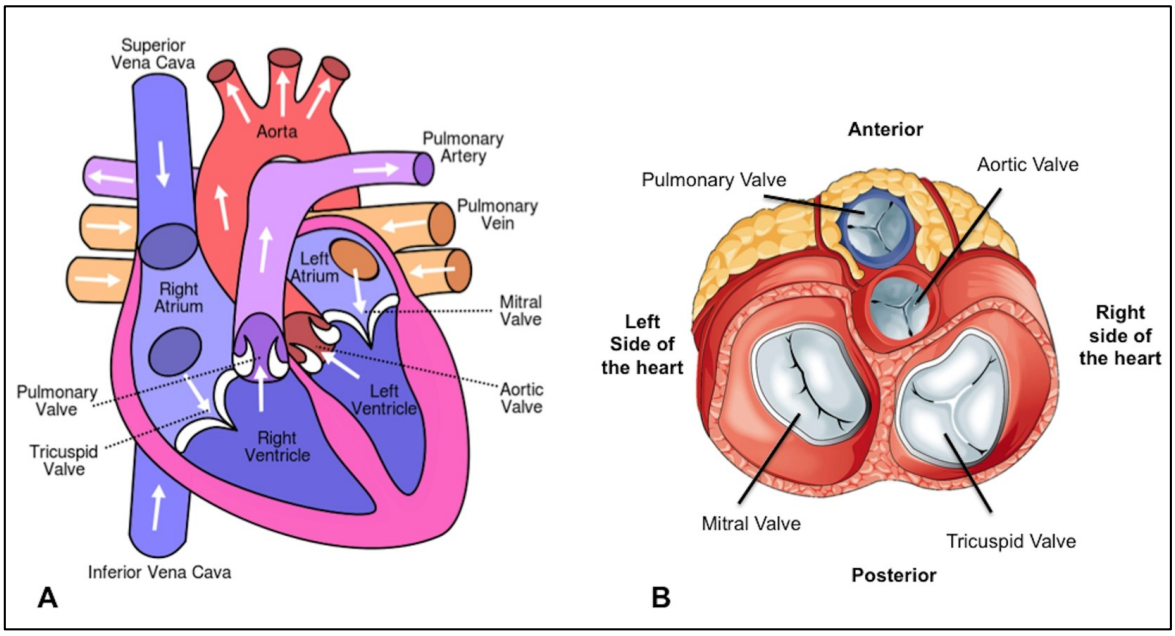


Figure 0-3: A) Anatomy of the heart (the white arrows show the normal direction of blood flow). B) Base of the heart showing all four valves

(Source: Adapted from www.wikipedia.org)

All four heart valves (tricuspid, pulmonary, mitral and aortic) lie along the same plane. The valves ensure unidirectional blood flow through the heart, preventing the backflow. Between the right atrium and the right ventricle there is the tricuspid valve, which consists

of three cusps (leaflets), made of endocardium reinforced with additional connective tissue. Each of the three valve-cusps is attached to several strands of connective tissue, the chordae tendineae (tendinous cords). They are composed of approximately 80 percent collagenous fibers with the remainder consisting of elastic fibers and endothelium. They connect each of the cusps to a papillary muscle that extends from the lower ventricular surface. These muscles control the opening and closing of the valves. The three papillary muscles in the right ventricle are called the anterior, posterior, and septal muscles, which correspond to the three positions of the valve cusps. Between the left atrium and LV there is the mitral valve that is rather bicuspid, as it has only two cusps, one anterior whereas the other cusp is posterior and medial. These cusps are also attached via chordae tendinae to two papillary muscles projecting from the ventricular wall.

The pulmonary valve is the semilunar valve of the heart that lies between the right ventricle and the pulmonary artery. It has three cusps that open during ventricular systole, when the pressure in the right ventricle rises above the pressure in the pulmonary artery. At the end of ventricular systole, when the pressure in the right ventricle falls rapidly, the pressure in the pulmonary artery will close the pulmonary valve.

The aortic valve is the semilunar valve of the heart that lies between the LV and the aorta. During ventricular systole, pressure rises in the LV above the pressure in the aorta, so that the aortic valve opens, allowing blood to exit the LV into the aorta. When ventricular systole ends, pressure in the LV rapidly drops, so that the aortic pressure forces the aortic valve to close.

There are two pathological processes that can affect the aortic valve - aortic stenosis in which the valve fails to open fully, thereby obstructing blood flow out from the heart, and aortic insufficiency, also called aortic regurgitation, in which the aortic valve is incompetent and blood flows passively back to LV cavity.

In the present PhD project I will focus in the study of aortic stenosis, and specifically I will concentrate in transcatheter aortic valve replacement (TAVR), one of the treatment options for those patients with severe symptomatic aortic stenosis deemed at high-risk for conventional surgical aortic valve replacement (SAVR). Compared to conventional open-heart surgery, TAVR procedures are less invasive, because they are not associated with

aortic cross-clamping and cardioplegia. Even so, the procedure involves some degree of myocardial injury, and in the present thesis I will evaluate the incidence, predictors and outcomes of myocardial injury following TAVR. This thesis is composed of 10 chapters, being 6 original publications on this theme (Chapters 4-9). The chapters 1 to 3 comprise an introduction to aortic stenosis (chapter 1) and to the TAVR procedures (chapter 2), as well as the main hypothesis and objectives (chapter 3). Finally, in the chapter 10 a brief discussion of the main results and future perspectives are pursued.

CHAPTER 1:

AORTIC STENOSIS

1.1 EPIDEMIOLOGY

Aortic stenosis (AS) is the most frequent valvular heart disease in developed countries,[1,2] and is the third most prevalent cardiac disorder after coronary artery disease and systemic hypertension.[2-4] AS is frequently preceded by aortic valve sclerosis, which courses with aortic valve leaflet thickening and calcification, in patients with a congenital uni- or bicuspid valve or an anatomically normal trileaflet valve (Figure 1-1).[2,5,6] Degenerative AS is the most prevalent form present in 84% of the patients, whereas congenital AS is present in ~5% of the patients. Other etiologies include rheumatic disease (11%), endocarditis (1%), as well as rarer causes (<1%) such as infectious and inflammatory diseases, actinic and drug induced AS.[2]

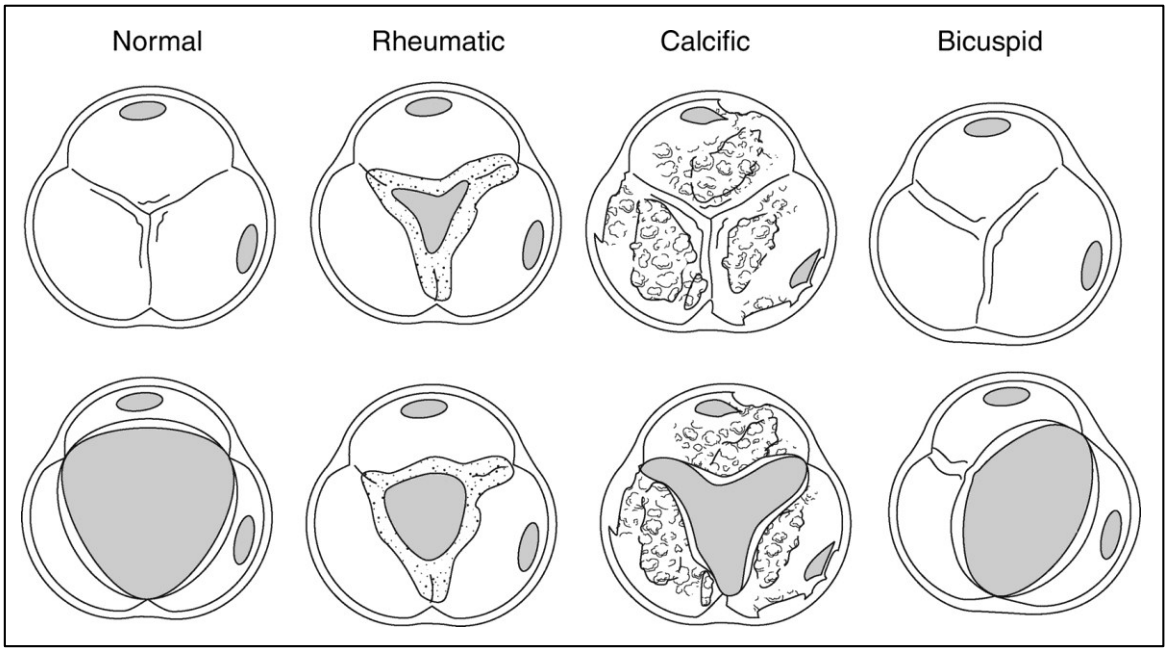


Figure 1-1: Most prevalent forms of aortic stenosis[7]

Aortic sclerosis is common in the elderly, being found in 26 to 29 percent of individuals ≥ 65 years of age, and may reach up to half of those with age >80 years.[8-10] Even in the absence of obstruction to blood flow, aortic sclerosis is associated with an increase of 50% in the risk of myocardial infarction and death from cardiovascular causes during the next 5 years.[9] Aortic sclerosis will eventually progress to clinical aortic stenosis in 1.8% to 1.9% of the patients per year.[11-13] Therefore, a recent meta-analysis including 6 studies, has found

a prevalence of AS, either mild, moderate or severe, ranging from 2.6% to 22% in ages > 75 years. The overall pooled prevalence was 12.4% (95% CI: 6.6% to 18.2%). Of note, the prevalence of severe AS in the elderly ranged from 1.2% to 6.1%, with a pooled prevalence of 3.4% (Figure 1-2).[4]

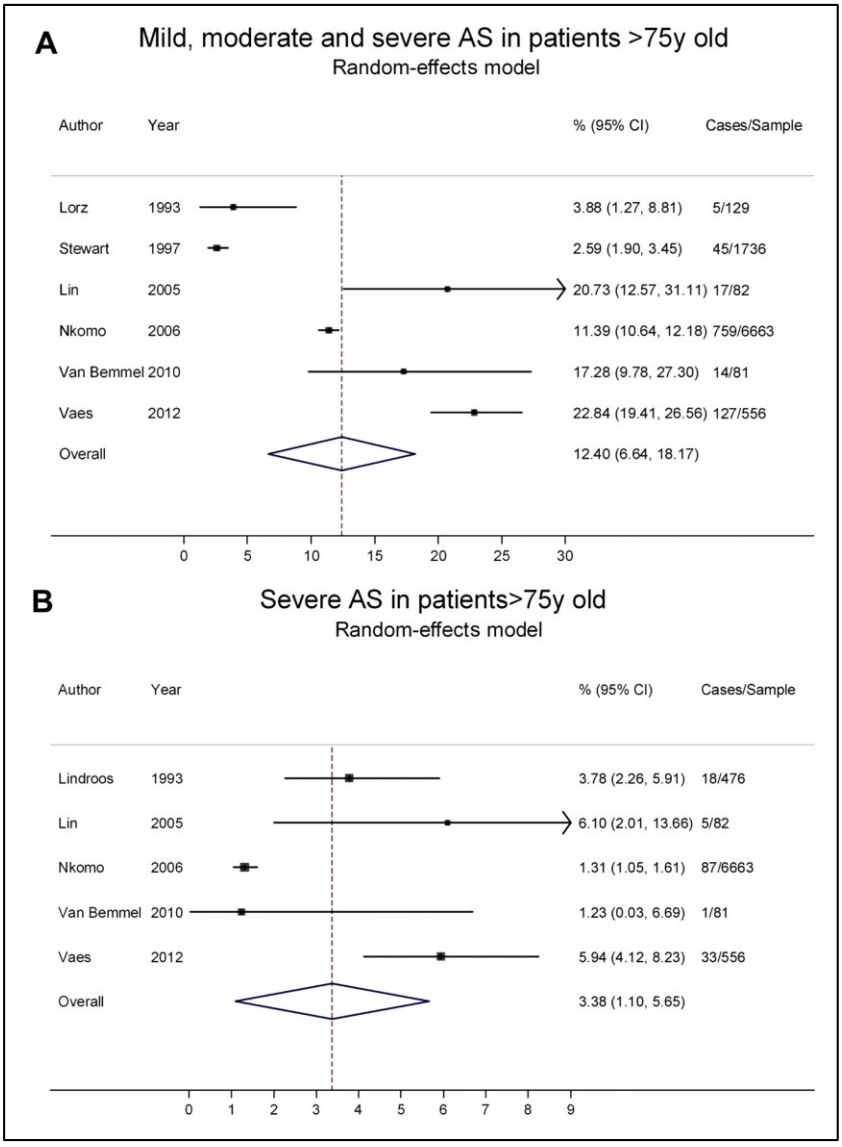


Figure 1-2: Forest plots on the prevalence of aortic stenosis[4]

These estimates of the prevalence of AS in patients ≥ 75 years old correspond to approximately 2.7 million elderly patients with AS in North America and 4.9 million in the European countries. Similarly, if only symptomatic severe AS is evaluated, this translates to 540,000 elderly patients in North America and 1.0 million in the European countries.

These numbers represent the estimates for 2011 when the population with ≥75 years of age reached 8.5% in the 19 European countries evaluated. Nonetheless, this will strike 10.7% in 2025 and 16.6% in 2050, corresponding to approximately 1.3 million and 2.1 million patients with symptomatic severe AS, respectively.[4] In North America, similar increases in the population demographics of the elderly are expected (2025, 8.3%, and 2050, 11.8%).[4] These estimates correspond to approximately 0.8 million and 1.4 million patients with symptomatic severe AS in North America, respectively. These numbers undertake the major societal and economic burden of AS for the healthcare systems worldwide, linked with the dramatic increase in life expectancy and corresponding growth in AS prevalence.[4]

1.2 PATHOGENESIS AND RISK FACTORS

Aortic valve leaflet thickening and calcification is generally the common pathway for the development of severe AS. Yet, calcific aortic valve disease is not simply due to age-related degeneration of the valve but, rather, it is an active and progressive disease. It is initiated by genetic, anatomical, and hemodynamic factors, that together with age, sex, and cardiovascular risk factors may lead to different biochemical and metabolic processes that ultimately lead to calcification of the aortic valve, reducing leaflet mobility and resulting in obstruction of the flow (Figure 1-3). This active and dynamic concept has emerged over the past three decades, based on: (1) epidemiologic studies underscoring the specific relationship between risk factors with the increased prevalence or rate of progression of aortic valve disease; (2) identification of histopathologic features of chronic inflammation, lipoprotein deposition, renin-angiotensin system components, and molecular mediators of calcification in heart valve tissues; and (3) identification of cell-signaling pathways and genetic factors that may contribute to valve disease pathogenesis.

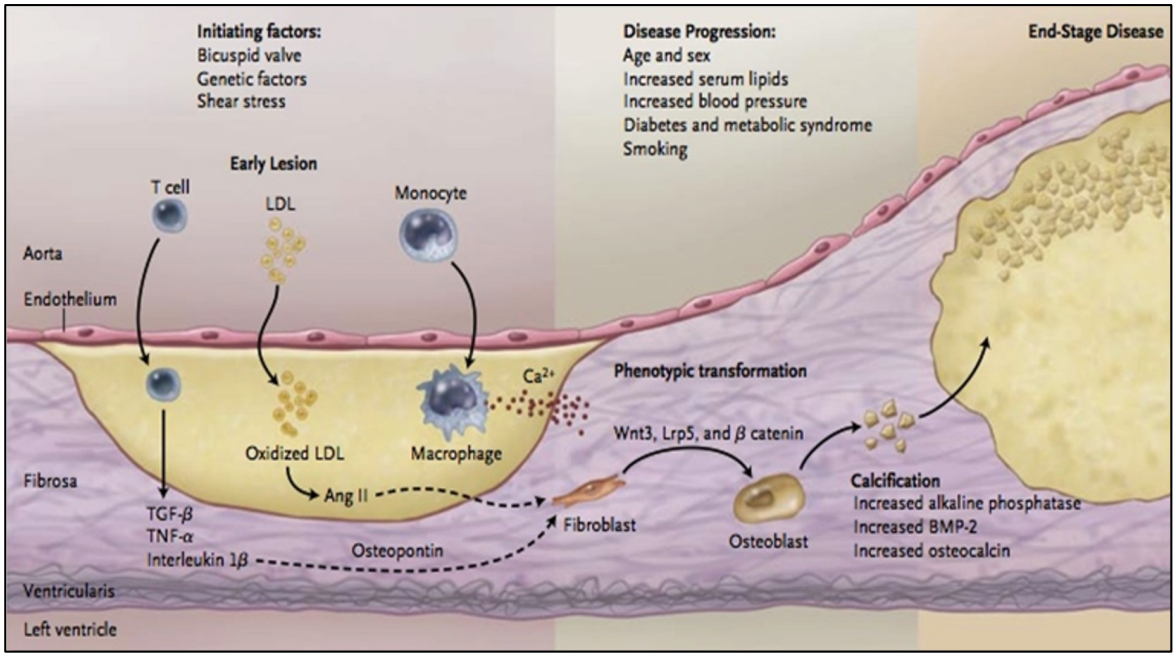


Figure 1-3: Disease progression in calcific aortic stenosis, showing changes in aortic-valve histologic features[14]

1.2.1 Aortic valve sclerosis - Early phase

Aortic valve sclerosis is the precursor of calcific AS, and it seems that mechanical stress is one of the key initiating factors. Specifically, a congenitally bicuspid valve, which is present in about 0.5 to 0.8% of the population, is the underlying anatomy in a great proportion of patients. Blood-flow dynamics may also play a role, since early lesions are located on the aortic side of the valve in regions with low shear stress.[5] Importantly, apart from these initiating hemodynamic and genetic factors, there is also an active process with some similarities with atherosclerosis, including three primary components in its pathobiology: lipid accumulation, inflammation, and calcification (Table 1-1).[8,9,15-20]

Table 1-1: Pathobiology of calcific aortic valve

• Focal areas of accumulation of apolipoproteins B, (a), and E, consistent with accumulation of low density lipoprotein (LDL) and lipoprotein(a) with evidence of lipoprotein oxidation.[18,21]
• Inflammation as evidenced by macrophage and T lymphocyte infiltration on histology,[17,18] inflammatory mediators such as interleukin-1-beta and transforming growth factor beta-1,[22,23] and increased fluorodeoxyglucose uptake on positron emission tomography (PET) scanning.[16]
• Local production of proteins that promote tissue calcification, suggesting that valve calcification is actively regulated rather than being an unregulated degenerative process.[15,19,24,25]
• Production and activity of angiotensin converting enzyme.[26,27]
• Upregulation of adhesion molecules and alterations in matrix metalloproteinase activity.[28,29]

1.2.2 Lipid mediated inflammation

1.2.2.1 Lipid infiltration and oxydation

There are innumerous evidences associating AS to atherosclerosis. Early lesions of the aortic valve consist of leaflet infiltration by apolipoprotein B containing lipids in the fibrosal layer.[30] Moreover, excised AS valves have shown the infiltration of apolipoprotein B and oxidized low-density lipoprotein (ox-LDL), suggesting that along with tissue infiltration by LDL, an active oxidative process takes place.[21] Ox-LDLs are subsequently phagocytosized by macrophages to become foam cells; comparable to what happens in atherosclerotic lesions.[31,32] Lipoprotein-associated phospholipase A2 (Lp-PLA2) uses oxidized LDL as substrate and produces free fatty acids and lysophosphatidylcholine, a powerful pro-inflammatory and pro-calcifying factor,[33] that also induces mineralization of valvular interstitial cells in vitro.[34] Lp-PLA2 is highly expressed within stenotic aortic valves and elevated Lp-PLA2 activity was associated with significantly faster AS progression rate.[35] Likewise, Mendelian randomization studies have highlighted that lipoprotein(a) [Lp(a)] was indeed associated with calcific aortic valve disease.[36] Lp(a) transports oxidized phospholipids (OxPL) with a high content in lysophosphatidylcholine. Autotaxin (ATX) transforms lysophosphatidylcholine into lysophosphatidic acid. ATX is transported in the aortic valve by Lp(a) and is also secreted by valve interstitial cells. Of

note, ATX-lysophosphatidic acid promotes inflammation and mineralization of the aortic valve.[37] Hence, this implies that innumerous lipoproteins may participate in the process of aortic valve tissue inflammation and calcification.

In addition to the above histopathologic observations, aortic sclerosis and AS have been correlated with clinical risk factors for atherosclerosis, such as smoking, hypertension, hyperlipidemia, diabetes, and metabolic syndrome.[38-48] The array of association among them are illustrated for instance in some echocardiographic studies. In the *Cardiovascular Health Study* (CHS) evaluating 5176 patients with age ≥ 65 years, 26 percent had aortic valve sclerosis with visually apparent leaflet thickening and/or calcification; and 2 percent had AS.[38] Multivariate analysis found significant correlations of aortic valve disease with age, male gender, lipoprotein(a), LDL cholesterol, hypertension, and smoking. Furthermore, in the *Framingham Heart Study* offspring cohort (n = 2683; mean age 61 years), 8 percent had at least one calcified valve, 5 percent had aortic sclerosis, and 1 percent had AS.[46] Valvular calcification was also associated with age, hypertension, and diabetes.

Similar findings have been noted when aortic valve calcification was assessed by computed tomography (CT). In the *Multi-Ethnic Study of Atherosclerosis* (MESA) study, among 6780 individuals (mean age of 63 years) the prevalence of aortic valve calcification was higher among those with metabolic syndrome (12 percent in women, 22 percent in men) or diabetes (17 percent in women, 24 percent in men) compared with those with neither risk factor (8 percent in women, 14 percent in men).[49] Metabolic syndrome and diabetes were also related with greater number of new cases of aortic valve calcification (odds ratio [OR] 1.67 [95% CI 1.21-2.31] for metabolic syndrome and 2.06 [1.39-3.06] for diabetes).[50] Of note, in contrast to the CHS findings, in the MESA cohort among the 5801 non-statin using participants, LDL cholesterol levels were only correlated with the presence of aortic valve calcification in participants younger than 65 years, although the total cholesterol to HDL ratio was associated with a slight increase in the risk for calcific disease across all ages.[51]

Factors that predict incident aortic valve calcification overlap but differ from factors that predict the disease progression. In the CHS study, 9% of 5621 subjects progressed from aortic sclerosis to aortic stenosis at 5-year follow-up. Older age, male gender, and LDL

cholesterol were associated with disease progression, whereas taller height and black race were associated with a lower likelihood of disease progression.[11] Finally, although calcific AS shares many similarities with atherosclerosis, there are also meaningful differences (Table 1-2).[8,21] This is underscored by the fact that no convincing evidence supports statin therapy to slow disease progression once even mild valve obstruction is present, in contrast to its widely known benefits in atherosclerotic disease.[52-54]

Table 1-2: Comparison of the histopathological, clinical and genetic factors of the aortic stenosis and atherosclerosis[8]

	Aortic stenosis	Atherosclerosis
Histopathological characteristics		
Lipoprotein accumulation	++++	++++
Lipids oxidation	++++	++++
Calcification	+++++	++
Inflammatory changes	++++	++++
Systemic inflammatory markers	+	++
Infectious agents	+	+
Predominant cell type	Fibroblasts	Smooth muscle cells
Clinical risk factors		
Renal dysfunction	++++	++++
Smoking	+++	++++
Hypertension	++	++++
Elevated plasmatic lipoproteins	+++	++++
Diabetes	+	+++++
Endothelial dysfunction	++	++++
Genetic Factors		
Genetic polymorphisms	++	+++

1.2.2.2 Inflammation

Inflammation also has an important role in the pathogenesis of calcific AS, inflammatory cells being predominant early in the process (Figure 1-3).[8,17,18,21,55] A positron electron imaging study in a series of adults with a range of calcific aortic valve severity demonstrated inflammation in early disease and progressive calcification with more severe disease *in vivo*.[16,56,57]

Monocytes infiltrate the aortic valve via adhesion molecules and differentiate into macrophages that produce tumor necrosis factor α (TNF-α), an important inflammatory mediator with pro-calcific activity.[28,58] Similarly, T cells activation may also participate in

the disease progression. Activated T lymphocytes within atherosclerotic lesion release Th-l cytokines, such as the macrophage-activating cytokine interferon y (IFN-γ). IFN- γ increases the synthesis of TNF-α and interleukin-1β (IL-1β), thus, acting synergistically to promote the inflammatory cascade and the development of atherosclerosis.[59,60] TNF-α, TGF-1β, and IL-1β may all contribute to extracellular matrix formation, remodeling, and local calcification.[23] In addition, changes in tissue matrix, including the accumulation of tenascin C, and up-regulation of matrix metalloproteinase 2 and alkaline phosphatase activity may take place.[29] Finally, leaflet fibroblasts undergo phenotypic transformation into osteoblasts, regulated by the Wnt3–Lrp5–β catenin and Runx2 signaling pathways. Tenascin C, which has been involved in growth promotion, stimulation of bone formation and mineralization, is present in calcified aortic leaflets and is both co-expressed and overexpressed with matrix metalloproteinase.[29]

1.2.3 ***Dysregulation of mineral metabolism***

Disturbances of mineral metabolism might also contribute to the development of aortic valve sclerosis and mitral annular calcification. This has been supported by studies such as the MESA, within the participants with chronic kidney disease. It was shown that each 1 mg/dL increase in serum phosphate within the normal range (2.5 to 4.5 mg/dL) was associated with 25 and 62 percent greater incidences of aortic and mitral valve calcification, respectively. This was confirmed after adjustment for traditional risk factors for atherosclerosis, as well as PTH and 1,25 dihydroxyvitamin D levels.[61] Likewise, in the CHS cohort of older adults, each 0.5 mg/dL higher serum phosphate concentration was associated with 17, 12, and 12 percent higher adjusted prevalences of aortic sclerosis, mitral annular calcification, and aortic annular calcification, respectively.[62] Other markers of mineral metabolism, including serum calcium, parathyroid hormone, and 25-hydroxyvitamin D concentrations, were neither associated with aortic or mitral calcification. There is still a lack of data with respect to the association between calcium supplementation in adults with osteoporosis or osteopenia and the possible link to the increased risk of aortic valve leaflet calcification.

1.2.4 ***Genetic factors***

Genetic factors contribute to the risk of aortic sclerosis and aortic valve calcification as well as the risk of development of calcific aortic stenosis.[36,63-67] Genetic contributions to calcific aortic valve disease were suggested by studies of community-based populations including the *Cohorts for Heart and Aging Research in Genomic Epidemiology* (CHARGE) consortium (including participants from the Framingham Heart Study [FHS], MESA study, and the Age, Gene/Environment Susceptibility-Reykjavik Study [AGES-RS]).[36,68]

A genome-wide association study in 6942 CHARGE participants identified a single-nucleotide polymorphism (SNP) located in an intron of the lipoprotein(a) (LPA) gene (rs10455872) that was significantly associated with the presence of aortic valve calcification (odds ratio per allele, 2.05).[36] The association was also confirmed in three additional cohorts of diverse ancestry. The same polymorphism was associated with circulating LPA levels, and with the development of AS. Furthermore, in the CHARGE consortium, a Mendelian randomization study has shown an association between the weighted genetic risk score (GRS, a measure of the genetic predisposition to elevations in plasma lipids) for low-density lipoprotein cholesterol (LDL-C) and aortic valve calcium in 6942 participants.[68] The LDL-C GRS was also associated with incident AS identified by national registry in the *Malmo Diet and Cancer Study* (MDCS) population-based cohort.

Other risk factors for calcific aortic valve disease include specific polymorphisms in the genes for apolipoprotein E, interleukin-10, the vitamin D receptor, and angiotensin-converting enzyme.[65-67] Patients with familial hypercholesterolemia are at risk for developing severe premature calcific valvular AS, as well as supravalvular AS and premature atherosclerosis.[36,68]

Mutations in the signaling and transcriptional regulator NOTCH1 are associated with a variety of aortic valve anomalies (such as bicuspid aortic valve with or without thoracic aortic aneurysm) and with severe aortic valve calcification in human pedigrees in a nonsyndromic autosomal dominant pattern.[63,69] NOTCH1 transcripts are abundant in the developing aortic valve in mice and may promote valve calcification by diminishing the activity of Runx2, an important transcriptional regulator of the fate of osteoblast cells. This observation is consistent with the suggestion that aortic valve calcification is an active process mediated by the differentiation of valvular cells into osteoblast-like cells.[19,69]

1.3 CLINICAL MANIFESTATIONS

Patients with AS are generally asymptomatic for a prolonged period of time despite the obstruction and increased pressure load on the LV. Indeed, there is wide variability in the degree of outflow obstruction that causes symptoms, depending in part upon size of the patient, degree of physical activity and LV loading conditions. As a result, there is no single value of maximum aortic transvalvular velocity, mean transvalvular gradient, or aortic valve area to determine whether symptoms will occur. In general, symptoms in patients with AS and normal LV systolic function rarely occur until stenosis is severe (defined as valve area <1.0 cm^2, peak jet velocity ≥ 4.0 m/sec, and/or mean transvalvular gradient ≥40 mmHg).[1] When severe AS is present, even mild cardiac symptoms should prompt for intervention, since survival is significantly jeopardized if left untreated, with an average survival of only two to three years, and a high risk of sudden death (figure 1-4).[1]

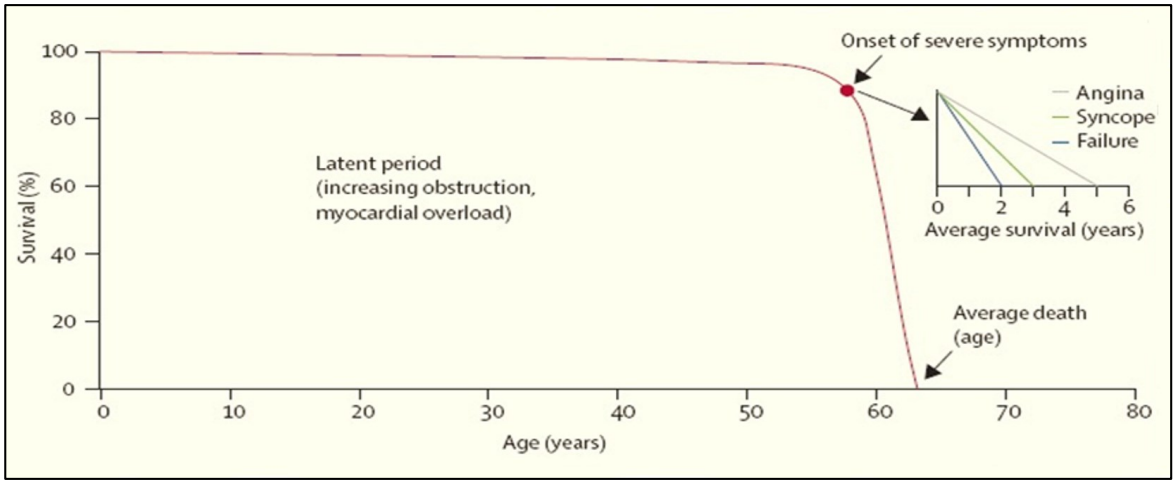


Figure 1-4: Survival of the patients with aortic stenosis over time[70]

The classic symptoms due to severe AS are heart failure, syncope, and angina. Nonetheless, those symptoms reflect the end-stage disease since there is a long latent period (Figure 1-4).[70] Nowadays, with the advent of earlier diagnosis by echocardiography and further prospective follow-up of the patients, the most common presenting symptoms are dyspnea on exertion or decreased exercise tolerance, exertional dizziness (presyncope) or syncope, and exertional angina.

The most common symptom of AS is therefore dyspnea, generally associated with the decreased exercise tolerance. Most important contributing factors are diastolic dysfunction with an increase in LV filling pressures with exercise, and failure of the LV to increase the cardiac output throughout exercise. Likewise, systolic LV dysfunction is rare, and overt heart failure is often an end-stage finding, usually in patients who have not received regular medical care. When evident heart failure occurs, the patient may complain from shortness of breath, easy fatigability, debilitation, and other signs and symptoms of a low cardiac output state.

Angina with effort is also a common complaint in patients with severe AS, present in ~75% of patients with severe AS, and in approximately half of those without significant coronary artery disease (CAD).[71-73] Of note, approximately one-half of the patients have underlying CAD, and the absence of angina does not reliably exclude the presence of severe CAD.[71] Angina in patients with AS without significant obstructive coronary artery disease has been attributed to left ventricular hypertrophy, which can cause coronary ischemia in function of different mechanisms:[74] increased LV oxygen demand as a result of increased LV mass; compression of intramyocardial coronary arteries from prolonged contraction and impaired myocardial relaxation; reduced diastolic coronary perfusion time during tachycardia; reduced coronary flow reserve.

Finally, exertional dizziness (presyncope) or syncope in patients with AS may reflect decreased cerebral perfusion, with also different underlying mechanisms, including: exercise-induced vasodilation in the presence of an obstruction with fixed cardiac output, resulting in hypotension; abnormalities in the baroreceptor response with an ensuing failure to appropriately increase blood pressure; transient bradyarrhythmia that can occur during or immediately after exertion; various arrhythmias, including more frequently atrial fibrillation rather than ventricular arrhythmias that are uncommon.

1.3.1 Physical examination

The presence of those aforementioned symptoms should prompt a careful physical examination that will likely provide evidence to the presence of AS. The physical examination may correlate with the severity of AS, despite the fact that no combination of physical findings has both a high sensitivity and high specificity for identifying severe AS, especially in asymptomatic patients.[75] In reviewing most of the studies in the context of

AS, assessing the precision and accuracy of clinical examination for abnormal systolic murmurs has shown that there are four more useful findings for the diagnosis AS:[76,77] 1) slow rate of rise in the carotid pulse; 2) mid to late peak intensity of the murmur; 3) reduced intensity of the second heart sound; and 4) maximal murmur intensity at the second right intercostal space. Any combination with three of these four findings was very likely to be associated with AS.[77] Likewise, the most useful finding for ruling out AS was the absence of a systolic murmur radiating to the right carotid artery or right clavicle.[76,77]

The quality of the pulse, murmur intensity and timing, and abnormalities in S2 may correlate with the severity of AS. In one report, carotid upstroke delay, carotid pulse amplitude, murmur intensity, murmur peak, and a single second heart sound correlated with AS severity.[75] While the classic findings of severe AS are accurate for corroborating the existence of severe valve obstruction, the physical examination is less useful for excluding the presence of severe AS in patients with symptoms and a systolic murmur. Hence, echocardiography is still necessary to confirm the presence of severe AS, since none of the physical findings has both a high sensitivity and high specificity for severe valvular obstruction.[75-77]

1.4 APPROACH TO THE DIAGNOSIS AND EVALUATION

The diagnosis of AS is usually suspected on physical examination (including a typical systolic ejection murmur) or when AS is detected on an echocardiogram performed for other indications.[1] Symptoms such as dyspnea and decreased exercise tolerance, dizziness, syncope, and angina pectoris may or may not be present in patients with severe AS. Echocardiography is the primary test in diagnosis and evaluation of AS. Echocardiography has largely replaced cardiac catheterization for hemodynamic measurements to assess the severity of AS. An electrocardiogram is not indicated in the diagnosis of AS but is generally performed as a component of the initial evaluation. Exercise testing is suggested in selected patients with asymptomatic severe AS or equivocal symptoms and severe AS (peak aortic jet velocity $\geq$ 4.0 m/s or mean transvalvular gradient $\geq$ 40 mmHg) to confirm asymptomatic status. Exercise testing should be avoided in patients with symptomatic severe AS. Other diagnostic approaches may include: dobutamine stress-echocardiography,

computed tomography (CT), which allows for quantitative evaluation of the amount of valve calcification; cardiovascular magnetic resonance (CMR), that although helpful may be limited due to costs and availability of the technique; and cardiac catheterization that is recommended if the noninvasive evaluation is nondiagnostic.

1.4.1 ***Echocardiography***

A transthoracic echocardiogram is indicated to diagnose and assess patients with signs or symptoms suggestive of AS. The echocardiographic exam in such patients should comprise the evaluation of valve anatomy and structure, valve hemodynamics, hemodynamic consequences (LV size and function and pulmonary artery pressure), and associated aortic regurgitation, as well as other concomitant valve diseases. In patients with AS, the aortic leaflets are generally thickened and calcified, and have a reduced excursion with a small or barely discernible aortic orifice during systole. Of note, a semi-quantitative score has been developed in order to determine different degrees of aortic valve calcification: 1) no calcification; 2) mildly calcified (small isolated spots); 3) moderately calcified (multiple larger spots); and 4) heavily calcified (extensive thickening and calcification of all cusps) (Figure 1-5).[78]

In contrast to degenerative calcific AS, in children or young adults with congenital AS, the leaflets may be severely fibrotic and immobile without calcification. When a bicuspid aortic valve is present, systolic images show the two leaflets (and two commissures) of the open valve. A bicuspid valve may appear trileaflet on diastolic images if a raphe is present. In patients with bicuspid aortic valve, the risk of associated aortic root involvement is related to the specific bicuspid valve phenotype (congenital fusion of the right and left versus the right and noncoronary cusps).

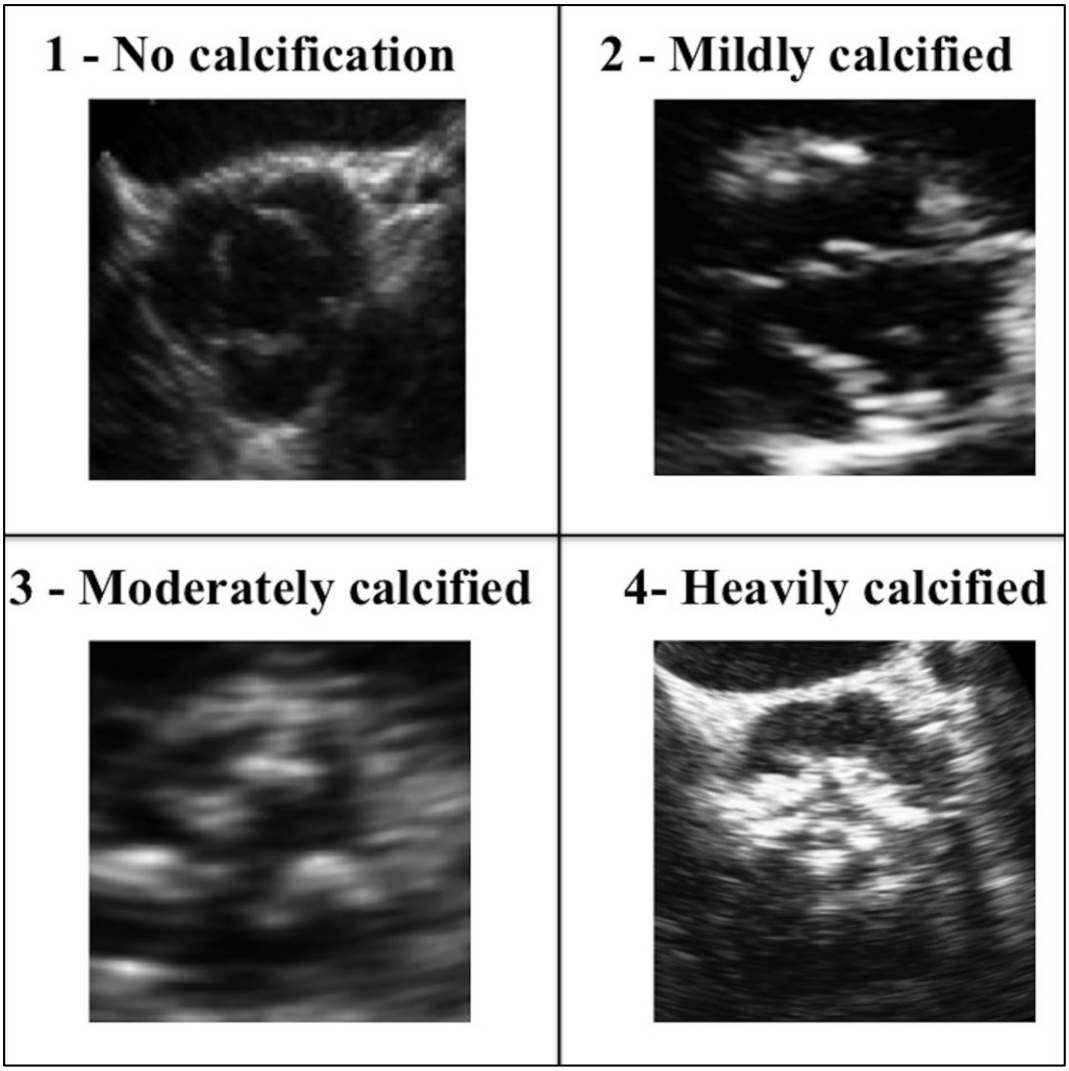


Figure 1-5: Evaluation of the degree of aortic valve calcification by echocardiography

Doppler echocardiography allows measurement of peak aortic jet velocity and calculation of the LV aortic gradient and valve area, which are the standard parameters used for evaluation of stenosis severity. This may also include a number of different parameters that together may help in determining the severity of AS (Table 1-3). The principle underlying the Doppler evaluation of valve function consists of an acceleration of the transvalvular blood flow when the valve narrows (Figure 1-6).

Table 1-3: Recommendations for classification of aortic stenosis severity[79]

	Aortic sclerosis	Mild	Moderate	Severe
Aortic jet velocity (m/s)	≤2.5 m/s	2.6–2.9	3.0–4.0*	>4.0
Mean gradient (mmHg)	—	<20	20–40*	>40
AVA (cm^2)	—	>1.5	1.0–1.5	<1.0
Indexed AVA (cm^2/m^2)		>0.85	0.60–0.85	<0.6
Velocity ratio		>0.50	0.25–0.50	<0.25

*In patients with normal cardiac output/transvalvular flow.

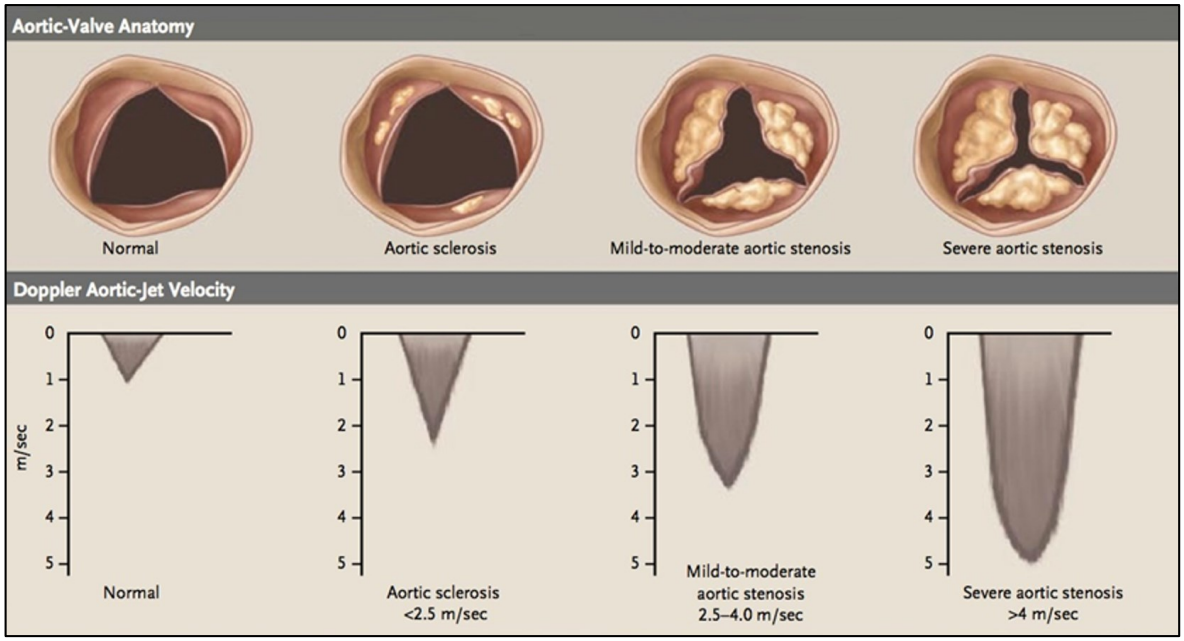


Figure 1-6: Disease progression in calcific aortic stenosis, showing changes in leaflet opening in systole and Doppler velocities[14]

The Doppler beam is positioned in the aortic valve, parallel to the direction of the blood flow, so that maximal velocity is determined (V_{max}), that allows for the determination of the severity of the AS. This V_{max} also permits the calculation of the pressure gradient (ΔP in mmHg) according to the Bernoulli simplified formula:[80]

$$\Delta P = 4 \times (V_{max})^2$$

For the determination of the aortic valve area, Doppler velocities may also be directly applied to an estimation by the continuity principle. Simply stated, flow volume (Q) measurements at proximate sites in a closed system (such as the heart) should be identical:

$$Q = A_{OT} \times V_{OT} = AVA \times V_{AV}$$

$$AVA = (A_{OT} \times V_{OT}) \div V_{AV}$$

A_{OT} = Area of the LV outflow tract; VOT = peak velocity in the outflow tract, AVA = area of the stenotic aortic valve, and V_{AV} = maximum velocity across the aortic valve

Some experts prefer to use of the left ventricular and aortic time-velocity integrals rather than the peak velocities:[81]

$$AVA = (A_{OT} \times TVI_{OT}) \div TVI_{AV}$$

AVA = area of the stenotic aortic valve; A_{OT} = Area of the LV outflow tract; TVI_{OT} = time velocity integral across the outflow tract and TVI_{AV} = time velocity integral across the aortic valve

The LV chamber is generally normal in size with normal systolic function. Yet, the LV wall is concentrically and uniformly hypertrophied. Doppler echocardiography provides the most reliable noninvasive estimation of the pulmonary artery pressure. The pulmonary artery pressure may be increased in AS because of the chronic elevation in LV diastolic filling pressure. A severe elevation in pulmonary artery pressure (systolic pressure >50 mmHg) occurs in ~15 percent of patients.[82] In some cases, pulmonary hypertension is due to coexisting lung disease rather than to the effects of aortic valve obstruction. Concurrent aortic regurgitation is present in ~80% of patients with AS although usually mild. Mitral regurgitation is also common due to mitral annular calcification and leaflet thickening. The severity of mitral regurgitation is usually mild to moderate and may be exacerbated by the high systolic LV pressure resulting from the outflow obstruction.

1.4.2 Electrocardiogram

An electrocardiogram (ECG) is generally performed in patients undergoing evaluation for AS, although its findings are generally non-specific. Hence, the main value of the electrocardiogram in this setting is for detection of concomitant conditions such as atrial fibrillation and coronary disease, although similar repolarization abnormalities are caused either by LV hypertrophy or ischemia. The primary electrocardiographic findings in AS are therefore related to the presence of LV hypertrophy, so that voltage of the QRS complex is markedly increased, with common associated ST-T wave changes that reflect chronic subendocardial ischemia, and eventually left atrial hypertrophy.[83] Importantly, such findings may confer a worse clinical prognosis in patients with AS.[84] Nonetheless, the absence of hypertrophy on the ECG does not exclude the presence of severe AS.[83]

Atrial fibrillation is unusual in patients with AS. Risk factors associated with atrial fibrillation include older age, more severe AS, LV hypertrophy, and LV systolic dysfunction.[85,86] Intraventricular or atrioventricular conduction abnormalities are also infrequent and may underscore severe hypertrophy, extension of calcium from the valve and valve ring into the interventricular septum, or concomitant heart disease if present. Similarly, ventricular and supraventricular arrhythmias are unusual and may reflect underlying LV dysfunction.

1.4.3 Stress testing

Exercise testing is indicated in selected patients with asymptomatic severe AS or equivocal symptoms (maximum aortic valve velocity of ≥4.0 m/s or mean transvalvular aortic valve pressure gradient ≥40 mm) to confirm the asymptomatic status. Such evaluation is particularly helpful when a patient's functional capacity is unclear or low. Patients with severe AS who develop typical symptoms of AS (e.g., exertional dyspnea) during low level exercise testing should be considered symptomatic even if the clinical history is uncertain.[1] Exercise testing should be avoided in those patients with symptomatic severe AS.

Low-flow, low-gradient AS is characterized by a small aortic valve area (≤ 1.0 cm^2 or ≤ 0.6 cm^2/m^2 when indexed for body surface area), a low transvalvular gradient (e.g. mean gradient < 40 mmHg), and a low LV ejection fraction [LVEF] (≤ 40 %).[87] While this

clinical entity occurs in 5% to 10% of the patients with AS, it represents one of the most challenging subset of patients both in terms of diagnosis and treatment.[87] Stress testing, especially with low-dose dobutamine stress testing in patients with suspected low flow/low gradient AS and reduced ejection fraction can be very important to confirm the true severity of AS vs. those patients with rather pseudo-severe AS.[88-90] Also, dobutamine stress echocardiography might help in determining the contractile reserve and risk stratifying such patients.[89,90]

1.4.4 B-type natriuretic peptide

B-type natriuretic peptide (BNP) and its prohormone NT-proBNP are released in response to myocardial wall stress and have a diagnostic and prognostic role in patients with heart failure. In addition, BNP and NT-proBNP have also been intensively studied in the whole spectrum of AS, including asymptomatic and symptomatic patients, as well as those with low-flow and low-gradient AS, with reduced LV function.[91] In a patient with equivocal symptoms and severe valve obstruction an elevated BNP or NT-proBNP level suggests that close follow-up is needed. Thus, observation of the patient for symptoms and signs of LV deterioration, together with the natriuretic peptides evaluation may be helpful to define the optimal timing of aortic valve replacement.

Among patients with severe AS, plasma BNP and NT-proBNP concentrations are higher in symptomatic vs. asymptomatic patients,[92,93] decrease after aortic valve replacement,[94] and higher values are independently predictive of reduced symptom-free survival[95] and overall survival.[96] Regarding the prognosis, in a prospective study of 1953 patients with at least moderate AS with mean 3.8-year follow-up, a BNP ratio (measured BNP/maximal normal BNP value specific to age and sex) >1 was defined as BNP clinical activation.[96] BNP clinical activation independently predicted excess long-term mortality in the population as a whole (adjusted HR 1.91; 95% CI 1.55 to 2.35) as well as in asymptomatic patients with normal LV ejection fraction (adjusted HR 2.35; 95% CI 1.57 to 3.56). Higher BNP ratios were associated with higher mortality risk. Aortic valve replacement was associated with similar improvement in survival in patients with BNP ratio of <2 (HR 0.68; 95% CI 0.52 to 0.89) or BNP ratio of ≥2 (HR 0.56; 95% CI 0.47 to 0.66).

1.4.5 Cardiac catheterization

Cardiac catheterization is indicated in patients with suspected severe AS when noninvasive data (including echocardiographic findings) are nondiagnostic or if there is a discrepancy between the clinical evaluation and the echocardiogram.[1] There is some risk of cerebral embolization associated with crossing the aortic valve for the invasive measurement of aortic valve gradients (Figure 1-7), therefore this approach should be undertaken only when absolutely needed.[97,98]

Significant CAD is present in ~50% of adults with severe symptomatic AS. Unfortunately, stress testing with perfusion imaging and echocardiography have a low accuracy for diagnosis of CAD and are contraindicated if any cardiac symptoms are present, so that coronary angiography is recommended when CAD is a concern.[1] Coronary angiography is also recommended in patients with apparently mild to moderate AS who have one or more of the general indications for coronary angiography such as progressive angina, objective evidence of ischemia, or either asymptomatic or symptomatic left ventricular dysfunction.

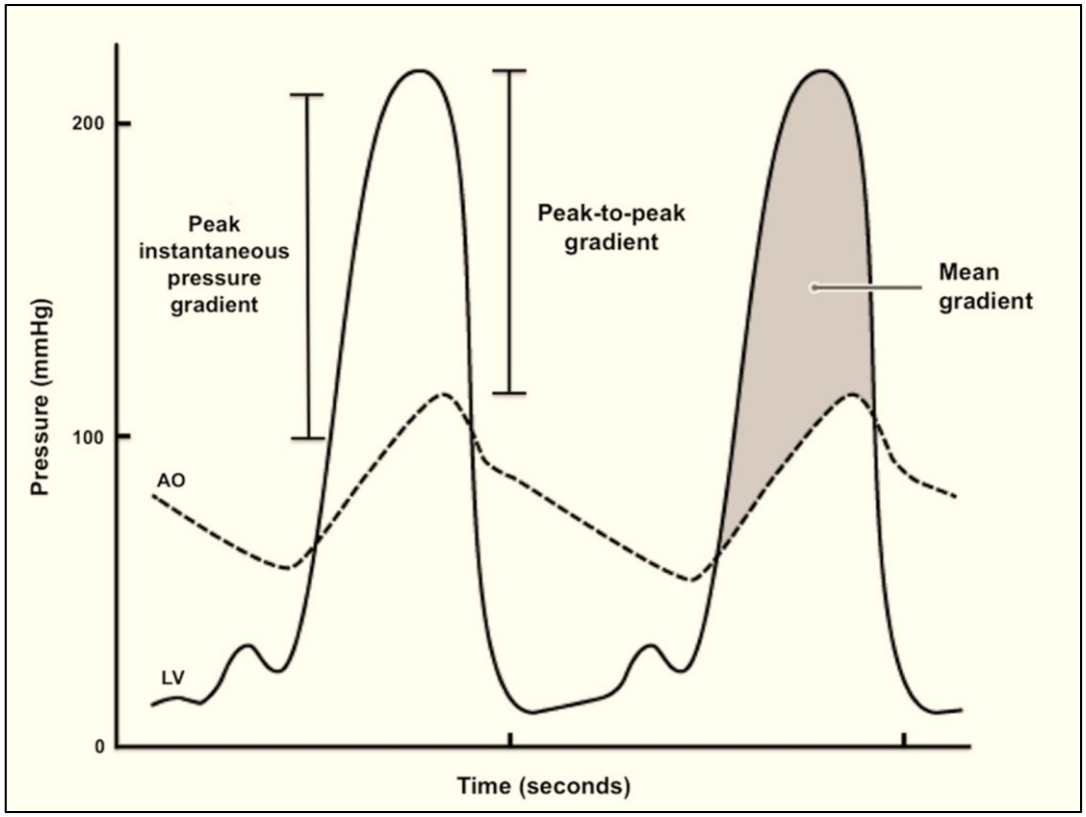


Figure 1-7: Invasive measurement of aortic valve gradients in the catheterization

1.4.6 Computed tomography

CT can provide a subjective (Figure 1-8) and a quantitative evaluation of the amount of valve calcification,[99,100] what may also importantly correlate with the severity of AS (Table 1-4).[101] In addition, a recent large-scale, multicenter outcomes study with quantitative Doppler echocardiographic and CT assessment of AS, has shown that measuring aortic valve calcification load provides incremental prognostic value for survival beyond clinical and Doppler echocardiographic assessment.[101] Severe aortic valve calcification (Table 1-4) independently predicts excess mortality after AS diagnosis, which is greatly alleviated by aortic valve replacement. Accordingly, measurement of aortic valve calcification by CT can be considered in the sake of decision-making in patients with AS, as well as for risk-stratification purposes. The experience with CT quantification of aortic valve area is limited.[102]

Table 1-4: Recommendations thresholds used to define severe aortic stenosis and its impact on survival[101]

		Definition of severe AS	
		Area under curve	**Individual value**
Women	Agatston score, UA	0.91	1.274
	Calcium density, UA/cm^2	0.93	292
Men	Agatston score, UA	0.90	2065
	Calcium density, UA/cm^2	0.92	476

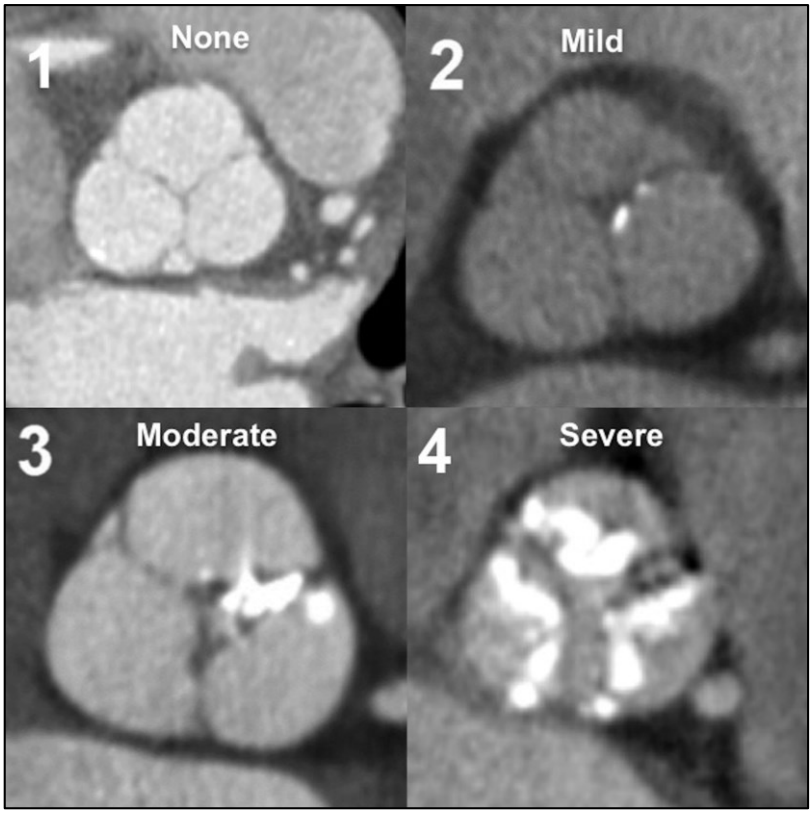


Figure 1-8: Evaluation of the aortic valve calcification by computed tomography

1.4.7 Cardiovascular magnetic resonance

Although CMR imaging methods enable assessment of aortic valve area and may aid in risk stratification, experience with these methods and the availability of this technique are limited. The anatomic aortic valve area can be evaluated from CMR short axis views of the valve.[103-106] In addition, CMR velocity-encoded imaging can accurately measure the antegrade velocity through the stenotic valve without angle dependence, an advantage compared with echocardiography.[107]

Furthermore, studies from a few centers have found that the presence of late gadolinium enhancement (LGE) by CMR is an independent predictor of mortality in patients with severe AS (Figure 1-9).[108-111] As an example, in a CMR study of 143 patients with moderate or severe AS followed for a mean of two years, midwall fibrosis (hazard ratio 5.35; 95% CI 1.16-24.56) and LVEF (hazard ratio 0.96; 95% CI 0.94-0.99) were independent predictors of mortality.[108] Hence, CMR may also play a role in risk stratifying such patients.

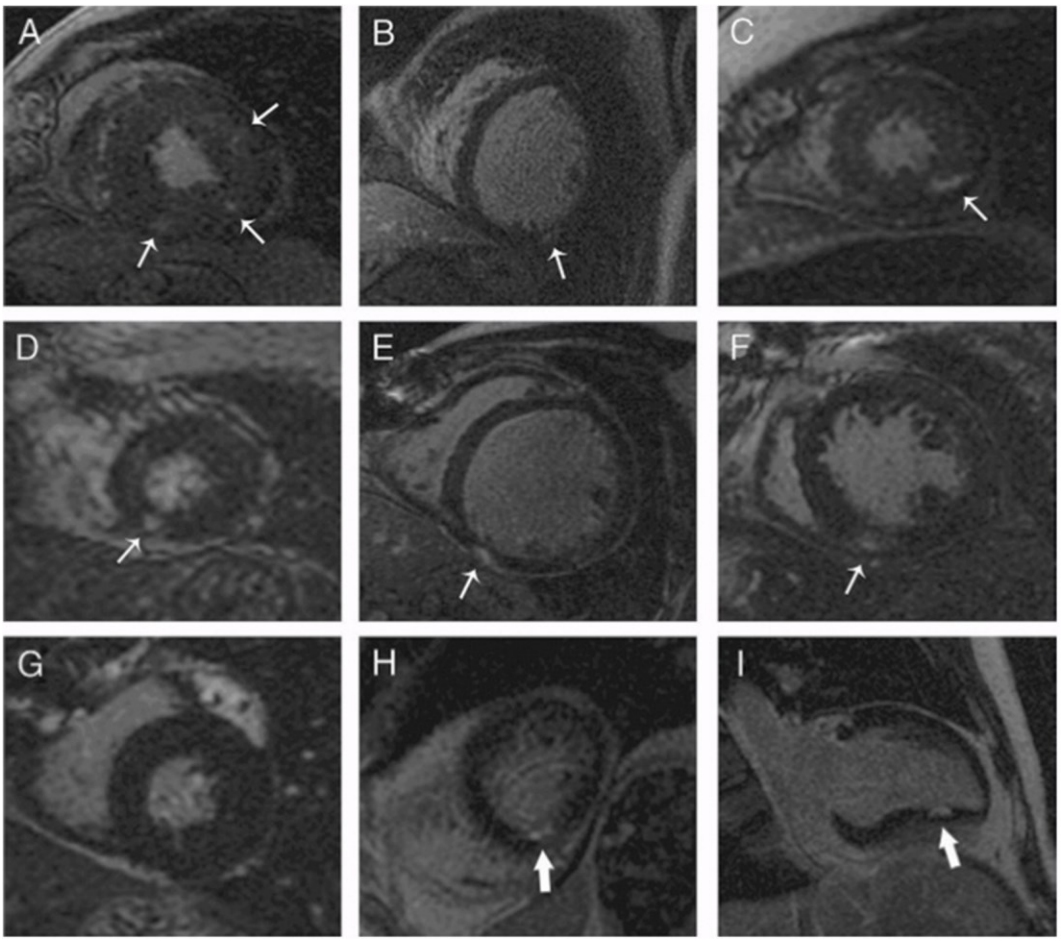


Figure 1-9: Delayed-enhanced MRI from different patients with severe AS[112]

*Examples from patients with aortic stenosis **(A, C, D)** and aortic regurgitation **(B, E, F)** showing several foci of myocardial fibrosis (MF) accumulation **(thin arrows)**. **(G)** Example from a patient with aortic stenosis that did not have any region of identifiable MF by contrast-enhanced magnetic resonance imaging (MRI). Illustrative images showing that the regions of MF identified on the short-axis images **(H)** could also be visualized on the orthogonal long-axis views **(I) (thick arrows)**.*

1.5 TREATMENT OPTIONS

Numerous studies have confirmed the concept of Ross and Braunwald[70] that the onset of symptoms entails in a significant decline in survival, with roughly 50% of patients dying within the next 3 to 5 years.[113,114] It is therefore of utmost importance to assess precisely the AS severity and associated comorbidities in order to pursue an accurate clinical decision-making and proper management of the patients. In Table 1-5, the aortic valve stenosis stages are underlined according to the 2014 AHA/ACC valvular heart disease (VHD) guidelines. Following the evaluation of the stage of the disease an algorithm is proposed for the management of these patients (Figure 1-10).[1] Also, in those patients at higher risk for AVR, a new risk assessment is proposed, including frailty and major organ failure (Table 1-6).[1] Therefore, according to these algorithms and the heart team evaluation, alternative treatment options may be proposed (Figure 1-11).[1]

Table 1-5: Stages of progression of valvular heart disease[1]

Stage	Definition	Description
A	At risk	Patients with risk factors for the development of VHD
B	Progressive	Patients with progressive VHD (mild-to-moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who have reached the criteria for severe VHD
		C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated
		C2: Asymptomatic patients who have severe VHD, with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

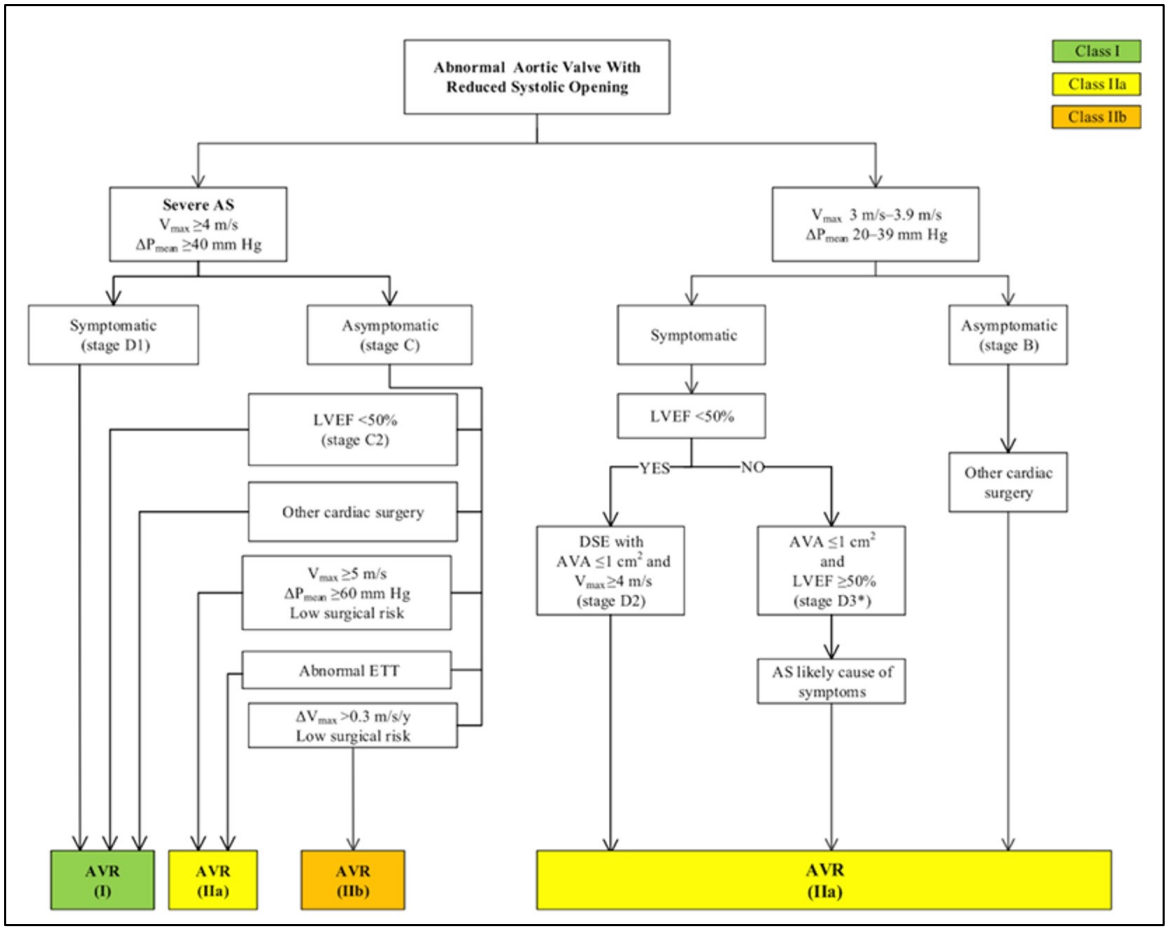


Figure 1-10: Approach to the diagnosis and management of aortic stenosis[1]

*Arrows show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage D or C) and those with low-gradient AS (stage D2 or D3) who do not meet the criteria for intervention. *AVR should be considered with stage D3 AS only if valve obstruction is the most likely cause of symptoms, stroke volume index is <35 mL/m^2, indexed AVA is 0.6 cm^2/m^2, and data are recorded when the patient is normotensive (systolic BP <140 mm Hg).*

AS indicates: aortic stenosis; AVA: aortic valve area; AVR: aortic valve replacement by either surgical or transcatheter approach; BP: blood pressure; DSE: dobutamine stress echocardiography; ETT: exercise treadmill test; LVEF: left ventricular ejection fraction; ΔP_{mean}: mean pressure gradient; and V_{max}: maximum velocity.

Table 1-6: Risk assessment combining STS risk estimate, frailty, major organ system dysfunction, and procedure-specific impediments[1]

	Low Risk (Must Meet ALL Criteria in This Column)	Intermediate Risk (Any 1 Criterion in This Column)	High Risk (Any 1 Criterion in This Column)	Prohibitive Risk (Any 1 Criterion in This Column)
STS-PROM sore*	<4% **AND**	4% to 8% **OR**	>8% **OR**	Predicted risk with surgery of death or major morbidity (all-cause) >50% at 1 y **OR**
Frailty	None **AND**	1 Index (mild) **OR**	≥2 Indices (moderate to severe) **OR**	
Major organ system compromise not to be improved postoperatively	None **AND**	1 Organ system **OR**	No more than 2 organ systems **OR**	≥3 Organ systems **OR**
Procedure-specific impediment	None	Possible procedure-specific impediment	Possible procedure- specific impediment	Severe procedure-specific impediment

*Use of the STS PROM to predict risk in a given institution with reasonable reliability is appropriate only if institutional outcomes are within 1 standard deviation of STS average observed/expected ratio for the procedure in question.

†Seven frailty indices: Katz Activities of Daily Living (independence in feeding, bathing, dressing, transferring, toileting, and urinary continence) and independence in ambulation (no walking aid or assist required or 5-meter walk in <6 s). Other scoring systems can be applied to calculate no, mild-, or moderate-to-severe frailty.

‡Examples of major organ system compromise: Cardiac—severe LV systolic or diastolic dysfunction or RV dysfunction, fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV1 <50% or DLCO2 <50% of predicted; CNS dysfunction (dementia, Alzheimer's disease, Parkinson's disease, CVA with persistent physical limitation); GI dysfunction—Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0; cancer—active malignancy; and liver—any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy. §Examples: tracheostomy present, heavily calcified ascending aorta, chest malformation, arterial coronary graft adherent to posterior chest wall, or radiation damage.

CKD indicate: chronic kidney disease; CNS: central nervous system; CVA: stroke; DLCO2: diffusion capacity for carbon dioxide; FEV1: forced expiratory volume in 1 s; GI: gastrointestinal; INR: international normalized ratio; LV: left ventricular; PROM: predicted risk of mortality; RV: right ventricular; STS: Society of Thoracic Surgeons; and VKA: vitamin K antagonist.

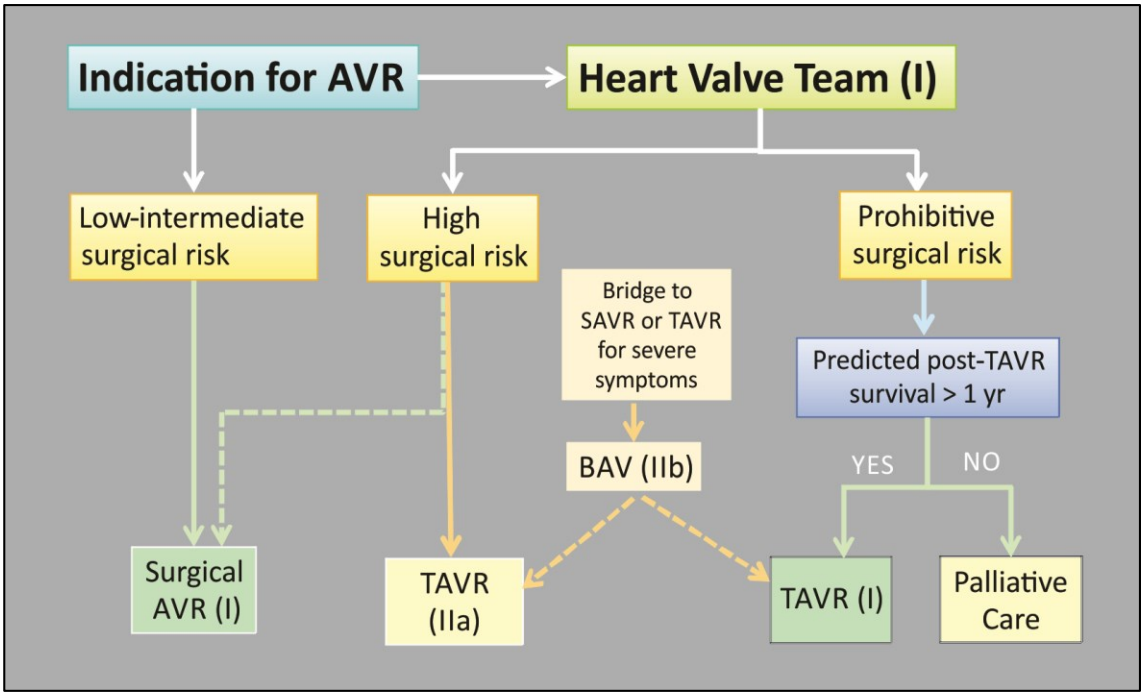


Figure 1-11: Approach to the management of aortic stenosis after risk stratification[1]

BAV: balloon aortic valvuloplasty; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement.

1.5.1 Medical therapy

Severe AS is primarily a mechanical problem (ie, a fixed obstruction to flow), and therefore, definitive management is directed to relief the obstruction either by surgical or transcatheter therapies. Medically managed symptomatic AS has a dismal prognosis, [115] and there are no medical therapies that can slow the progression of AS. Despite the claimed role of atherogenesis in the development and progression of calcific AS, statin therapy has not been shown to slow or halt worsening of valvular AS.[52,53]

Owing to the inefficacy of medical therapy in AS, the non-operative management of severe AS is directed at optimizing comorbidities while avoiding medications that may adversely impact hemodynamics. Medications that reduce preload, including nitroglycerin, and that decrease afterload, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), hydralazine, and non-selective beta-blockers, are contraindicated in severe AS, especially in those patients that are symptomatic. Still, patients with mild or moderate AS and a depressed LVEF should receive standard evidence-based heart failure therapies, which may include ACE inhibitors, ARBs, beta-blockers, and aldosterone

receptor antagonists. In addition, patients with mild or moderate AS should have their comorbid conditions, including hypertension, managed appropriately.[1]

1.5.2 Aortic valve replacement

AVR is clearly indicated in patients with symptomatic severe AS,[1,116] and surgery in such patients improves symptoms and increases life expectancy.[113,117,118] TAVR can be an alternative to SAVR in high-risk patients and a definitive treatment in those deemed inoperable (discussed in the next chapter).[1]

1.5.2.1 Surgical aortic valve replacement (SAVR)

SAVR was first introduced in the early 1960s and has considerably improved the outcome of patients with valvular heart disease. SAVR for the treatment of AS represents 50% of all operations for valvular heart disease in North America,[119] and approximately 90,000 valve substitutes are now implanted in the United States and 280,000 worldwide each year; nearly half are mechanical valves (Figure 1-12) and half are bioprosthetic valves (1-13).[120] Over the recent decades, there has been an increasing use of bioprosthetic valves compared with mechanical valves.[121] Isolated AVR can now be accomplished with a mini-sternotomy, although a full sternotomy is often required if extensive concomitant coronary artery bypass grafting is required.

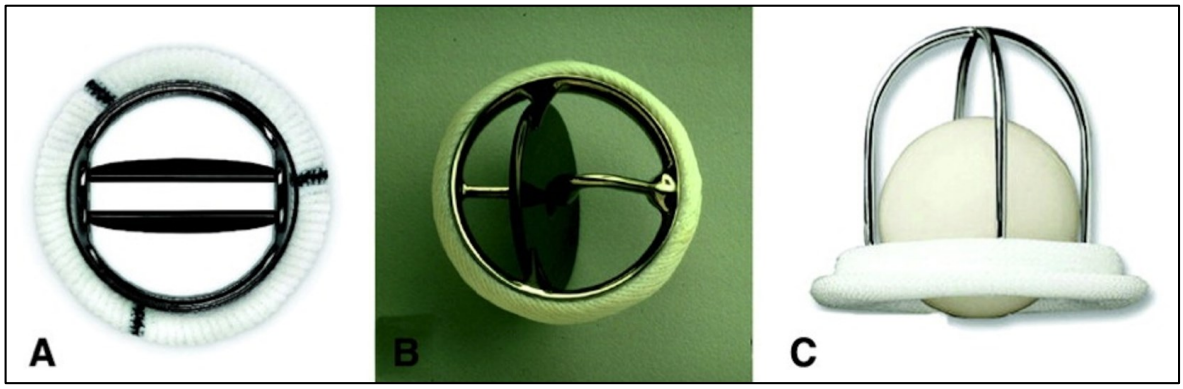


Figure 1-12: Different types of mechanical prostheses

A) Bileaflet mechanical valve (St Jude); B) monoleaflet mechanical valve (Medtronic Hall); C) caged ball valve (Starr-Edwards)[120]

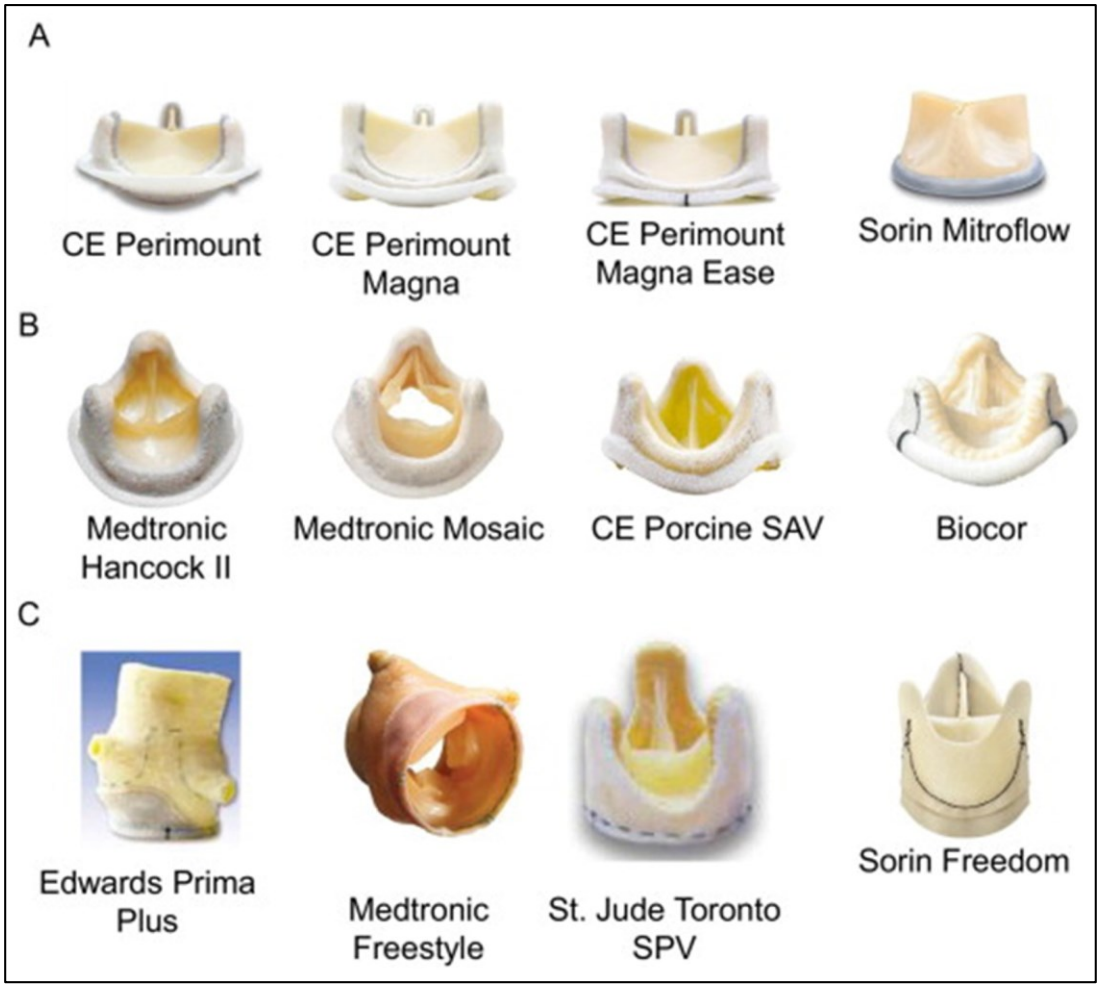


Figure 1-13: Different types of bioprostheses

(A) Stented pericardial bovine bioprosthetic valves. (B) Stented porcine aortic valve bioprostheses. (C) Stentless bioprosthetic valves. These lists are nonexhaustive. (CE: Carpentier-Edwards; SPV: stentless porcine valve)[122]

Bioprosthetic valves are normally recommended for patients aged >65 years because of greater durability in older individuals, as evidenced by the decrease in lifetime risk of reoperation with increasing patient age, at the time of implantation (Figure 1-14).[122] Still, there is growing adoption of bioprostheses in younger patients due to lifestyle issues and lack of necessity for chronic oral anticoagulation. There are no definitive data favoring one bioprosthetic valve (porcine heterograft, bovine pericardial heterograft, or homograft) compared with mechanical valves (Figure 1-12).

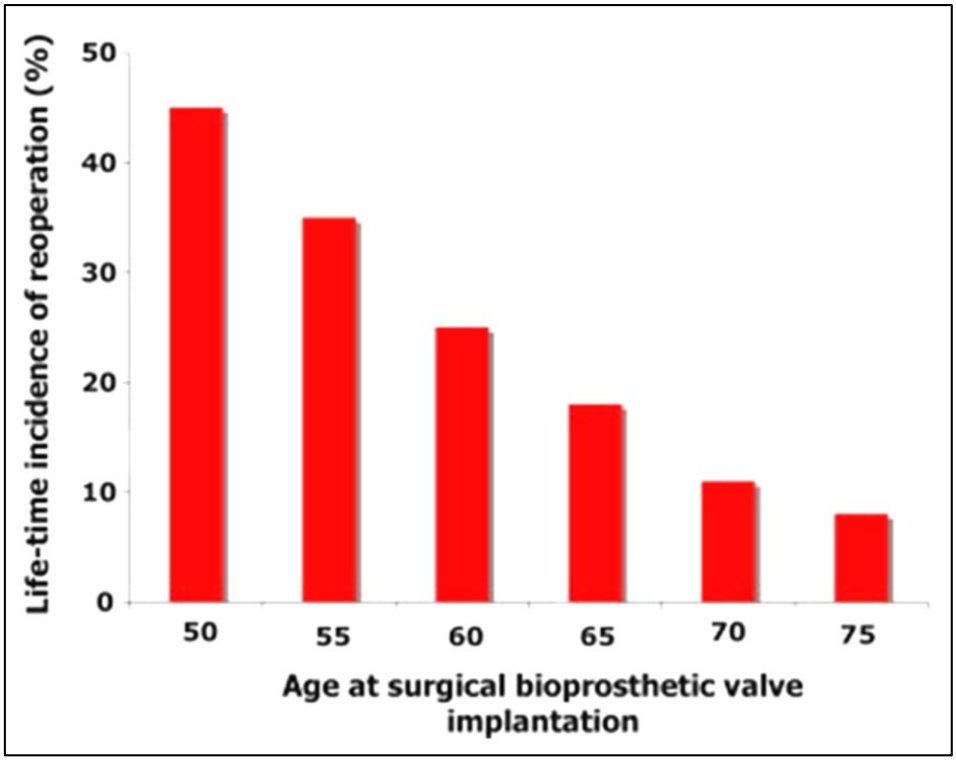


Figure 1-14: Lifetime risk of reoperation as a function of age at surgical aortic valve replacement[122]

The operative mortality associated with SAVR is generally between 1-3%, but this can reach up to 5-10% of those with age > 80 years and a great burden of comorbidities, as well as according to the skill and experience of the surgical team.[121,123,124] Comorbidities associated with higher 30-day mortality include age, LV dysfunction, concomitant CAD, previous coronary artery bypass grafting, renal insufficiency, and chronic pulmonary disease.[125] A number of readily available risk scores, including the EuroSCORE, the Society of Thoracic Surgeons (STS) risk calculator, and the valve-specific risk calculator of Ambler et al., provide an estimate of surgical risk, although none of these scores is optimal because other important variables, such as frailty and cognitive capacity, are not included.[126] These same factors may also impact long-term survival after AVR.[127]

There is also a great proportion of symptomatic patients, with severe AS, that would otherwise fulfill class I indications for AVR, but that are ultimately not referred for surgery in Europe and the United States. In a recent meta-analysis involving more than 2,000 patients, 40.5% of the patients (95% CI: 35.8% to 45.1%) with symptomatic severe AS, did not undergo SAVR despite having a formal indication (Figure 1-15).[4]

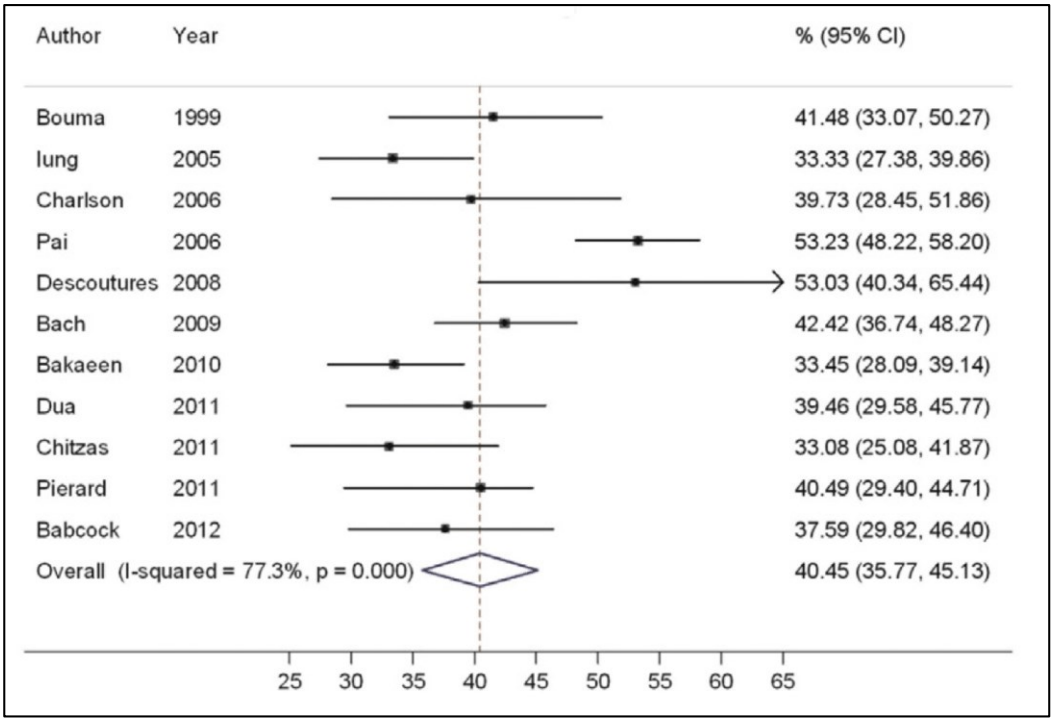


Figure 1-15: Patients with severe AS not treated with SAVR but potentially treatable with TAVR[4]

Although this treatment gap could be explained by the reluctance of internists and cardiologists to recommend surgery in elderly patients with much comorbidity, even low-risk symptomatic patients are often not referred for surgery. Bach et al.[128] have previsouly demonstrated that 22% of symptomatic patients with severe AS and an operative mortality risk <10% as estimated by the EuroSCORE were not referred for surgery. It is widely understood that the EuroSCORE overestimates actual observed operative mortality, and these were indeed relatively low-risk patients for surgery. The mortality of the symptomatic patients in that series that did not undergo SAVR was 53% at 36 months, in keeping the concept of Ross and Braunwald[70] of 40 years ago that severe symptomatic AS has a dismal prognosis.

1.5.3 Balloon aortic valvuloplasty

Balloon aortic valvuloplasty (BAV) is a transcatheter procedure by which a balloon is passed in a retrograde fashion through a severely stenotic aortic valve. The balloon is positioned within the valve orifice, and subsequent balloon inflation results in a fracturing of the calcific deposits on the aortic valve, improved leaflet mobility, and a modest improvement in aortic valve area. Therefore, BAV improves cardiac index and is associated

with an immediate relief in the symptoms. Following original description, and its rapid widespread adoption, subsequent clinical studies with longer-term follow-up have been deceiving, as the duration of this benefit was generally limited to a few months after successful procedure. [129,130] Therefore, restenosis occurs almost invariably after a mean of 6-12 months.[129-132] Repeated BAV can still be performed, despite lower achieved valve area with the redo procedure. Likewise, there are the associated complications including stroke, annulus rupture, and vascular access injury that have posed BAV as an exception procedure.[131-133] Therefore, BAV is used for palliation in those patients who cannot undergo either SAVR or TAVR, because of serious comorbid conditions, or as a bridge to either definitive treatment.[1,133]

CHAPTER 2:

TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR)

2.1 INTRODUCTION

The concept of a transcatheter heart valve (THV) was first tested *in vivo* in the early 90s, in a porcine model[134] followed a decade later by the first percutaneous implantation of a prosthetic valve in a pulmonary conduit.[135] The first human TAVR for the treatment of symptomatic severe stenosis was performed in 2002, and was followed by several single center and small multicenter registries/series showing the feasibility of this new approach for the treatment of patients considered at very high or prohibitive risk for standard SAVR.[136,137] Therefore, in the recent years the technology has experienced a very rapid development, stimulated by the large proportion of severe AS patients not undergoing SAVR and given the limited effect of BAV. To date >150,000 transcatheter valves have already been implanted worldwide. The results of several recent large multicenter registries[138-144] and the prospective randomized *Placement of Aortic Transcatheter Valves* (PARTNER)[145,146] and the US-CoreValve[147,148] trials have provided definitive data confirming this treatment as an alternative to SAVR in non-operable and high-risk surgical candidates.

2.2 PROSTHETIC VALVE SYSTEMS

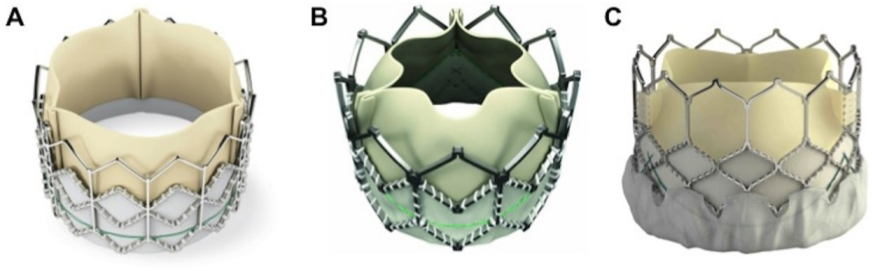
Despite the great iterations to the current transcatheter systems and the large number of new valves under development or being evaluated in trials, the clinical experience with TAVR has been based upon the use of two types of transcatheter aortic valves: i) the balloon-expandable Edwards valve - Cribier-Edwards, Edwards SAPIEN, SAPIEN XT and the new generation the SAPIEN 3 (Edwards Lifesciences Inc., Irvine, CA); ii) the self-expanding CoreValve Revalving system, and its newer generation the CoreValve Evolut-R (Medtronic, Minneapolis, MN).

2.2.1 ***Balloon-expandable valves (Adapted from Ribeiro et al.[137])***

The clinical experience with balloon-expandable THV commenced with the Cribier-Edwards balloon-expandable aortic stent valve (Edwards Lifesciences, Irvine, CA), which consisted of a trileaflet tissue valve of equine pericardium mounted in a stainless steel frame.[149] This was the first THV prototype implanted in humans[149,150] and subsequent

improvements in the valve and delivery systems resulted in the second generation of balloon-expandable THVs, the Edwards-SAPIEN THV (Edwards Lifesciences, Irvine, CA) (Figure 2-1). This valve also consists of a tubular slotted stainless-steel stent frame, but it integrates a unidirectional trileaflet tissue valve made of bovine pericardium, which is pretreated to decrease valve calcification. Moreover, the fabric skirt, made of poly-ethylene terephthalate, extends further to improve sealing and potentially reduce paravalvular regurgitation. This valve is available in two sizes, with expanded external diameters of 23 and 26 mm, requiring 22F and 24F delivery catheters for transfemoral approach implantation, respectively.

The SAPIEN XT valve (Edwards Lifesciences, Irvine, CA) is the 3rd generation of balloon-expandable Edwards valves, which also consists of a trileaflet pericardial bovine valve, but unlike those of the previous generation, it is mounted in a cobalt chromium stent frame (Figure 2-1). The stent frame design of the SAPIEN XT valve has fewer rows, columns and vertical struts between commissure pots, which in addition to the scallop shape design of the leaflets, contributes to decreasing the profile of the valve. Also, the leaflets are in a partially closed configuration even when opened, which may reduce the likelihood of interaction between native and prosthetic leaflets.[151,152] The SAPIEN XT valve is available in 20-, 23-, 26- and 29-mm sizes, and is implanted through the transfemoral approach using the NovaFlex delivery system implanted through 16Fr (20-, 23-mm valves), 18Fr (26-mm valve) or 20Fr (29-mm valve) expandable sheaths (e-sheath, Edwards Lifesciences, Irvine, CA).



	Edwards-Sapien (26 mm)	Sapien XT (26 mm)	Sapien 3 (26 mm)
Prosthetic material	Stainless steel	Cobalt-Chromium	Cobalt-Chromium
Crimped profile	8.3 mm	8.0 mm	6.7 mm
Frame height (expanded)	16.1 mm	17.2 mm	20 mm
Frame height (crimped)	18.1 mm	20.6 mm	27 mm
Frame shortening (deployment)	2 mm	3.4 mm	7 mm

Figure 2-1: Photographs of the balloon-expandable SAPIEN valves and their respective characteristics. (A) Edwards-SAPIEN, (B) SAPIEN XT, and (C) and SAPIEN 3 valves[137]

The SAPIEN 3 THV (Edwards Lifesciences, Irvine, CA) is the latest generation of the balloon-expandable valves, and it also consists of a trileaflet pericardial bovine valve that is mounted in a cobalt chromium stent, which also incorporates an additional outer skirt to further fill paravalvular gaps and reduce paravalvular leak (Figure 2-1).[153,154] Also, the crimped frame is 27 mm high, shortening to 20 mm when deployed. This expanded length is slightly longer than the currently SAPIEN (16.1 mm) and SAPIEN XT (17.2 mm) THVs. Finally, the delivery system (Commander) has an even lower profile and incorporates some improvements (ex. increased flex properties) to facilitate valve alignment and proper position.[153,154]

2.2.2 Self-expanding valves

The first generation of the CoreValve system consisted of a self-expanding nitinol frame with a bovine pericardial heart valve, and was implanted using a 25Fr delivery catheter. The second generation of the CoreValve system consisted of 3 leaflets of porcine pericardium, the leaflets were seated higher in the nitinol frame to provide true supra-annular placement and the nitinol frame was redesigned to increase radial force in the inflow portion and expand the

outflow diameter for a more optimal anatomical fit. The valve was implanted using a 21Fr delivery catheter. Finally, the current third generation of the CoreValve aortic system (Figure 2-2) differs slightly from the previous version, as it incorporates minor changes in the sealing skirt (fabricated from three separate pieces instead of one) to facilitate uniform tissue thickness and improve the valve profile. The valve is available in 23-, 26-, 29- and 31-mm sizes, and is implanted using an 18Fr delivery system.

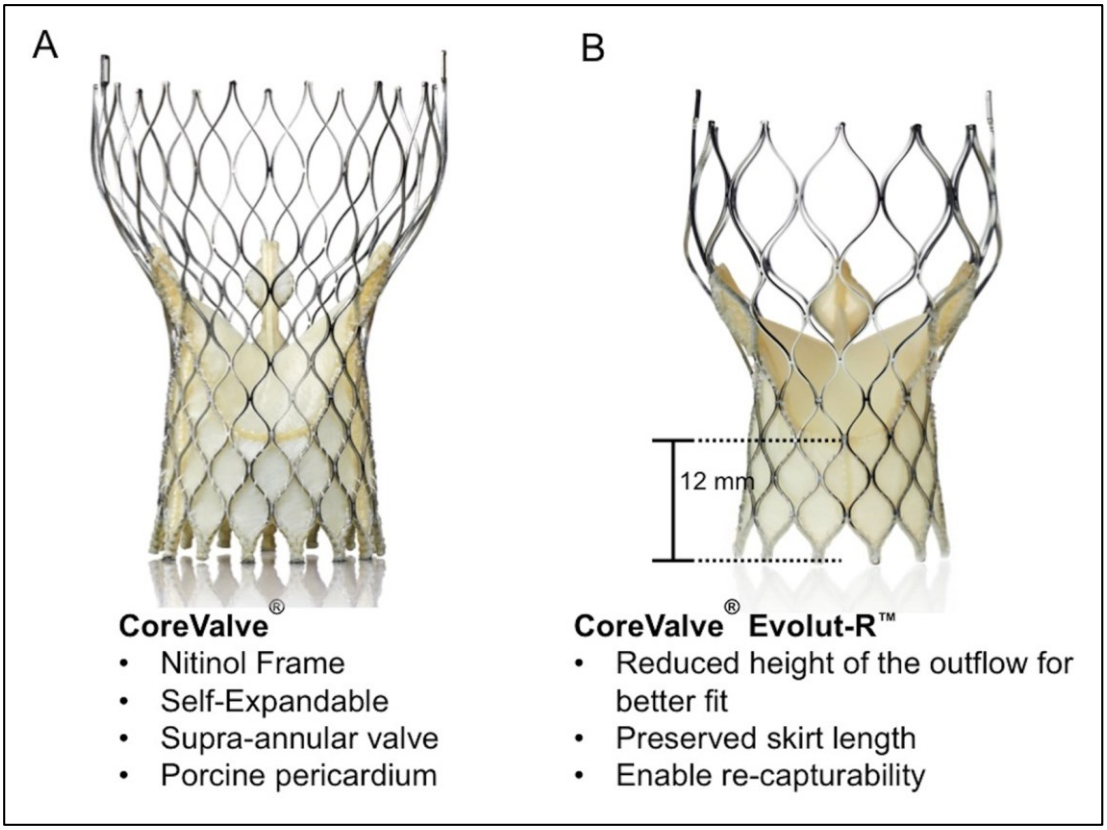


Figure 2-2: Photographs of self-expanding: (A) CoreValve; and (B) CoreValve Evolut-R, the new iteration[155]

A newer generation of the CoreValve system is the Evolut-R, which is currently being evaluated in larger studies and is already approved in some countries worldwide. The cell geometry and frame of the Evolut R have been redesigned to optimize frame interaction with the native anatomy, to improve conformability to the aortic annulus and reduce paravalvular leak (Figure 2-2).[155] The inflow has more consistent radial force across the sizing spectrum, and the outflow has been shortened and reshaped to provide improved alignment between valve housing and the native sinus, which is expected to reduce stress

on the left bundle branch. In addition, the new EnVeo R delivery catheter (Medtronic, Minneapolis, MN, USA) is 14 Fr-equivalent delivery system (true 18 Fr outer diameter) allowing the treatment of patients with femoral arteries of ~5 mm. Most importantly, the novel laser-cut nitinol-reinforced capsule provides the ability to resheath or recapture the partially deployed THV (up to 80% of maximal deployment) in order to reposition or retrieve the implant.

2.3 IMPLANTATION: APPROACHES AND TECHNIQUE

*2.3.1 **TAVR approaches***

The first TAVR with the balloon-expandable valve was performed antegradely through the femoral vein, followed by a transseptal puncture, crossing the mitral valve and finally positioning and implanting the THV in the aortic annulus.[149,150] This initial approach was complex and difficult to reproduce, and improvements in the prosthesis and delivery system caused it to be rapidly supplanted by the transfemoral and transapical approaches.[156-158] For the newer generation of the CoreValve system, with smaller profile sheath (18 Fr), the vast majority of patients have been treated by the transfemoral approach. Still the subclavian and transaxillary approaches have played an important role in those patients with unsuitable iliofemoral system.[159,160]

2.3.1.1 Transfemoral approach

The transfemoral approach has become the first access choice in the vast majority of the centers (Figure 2-3). Following an accurate evaluation of the iliofemoral anatomy using CT, the procedure can be performed under general anesthesia or profound sedation, either in a catheterization laboratory or in a surgical hybrid room. Femoral artery access for the procedure was initially obtained with surgical cutdown, nonetheless most centers are currently using a fully percutaneous approach, with various access site closure techniques.[161,162] The vascular access is obtained similarly for either SAPIEN valve and the CoreValve, and with the advent of lower profile sheath and the new iterations of the valves, almost 90% of the patients will be treated with TAVR by the transfemoral approach.

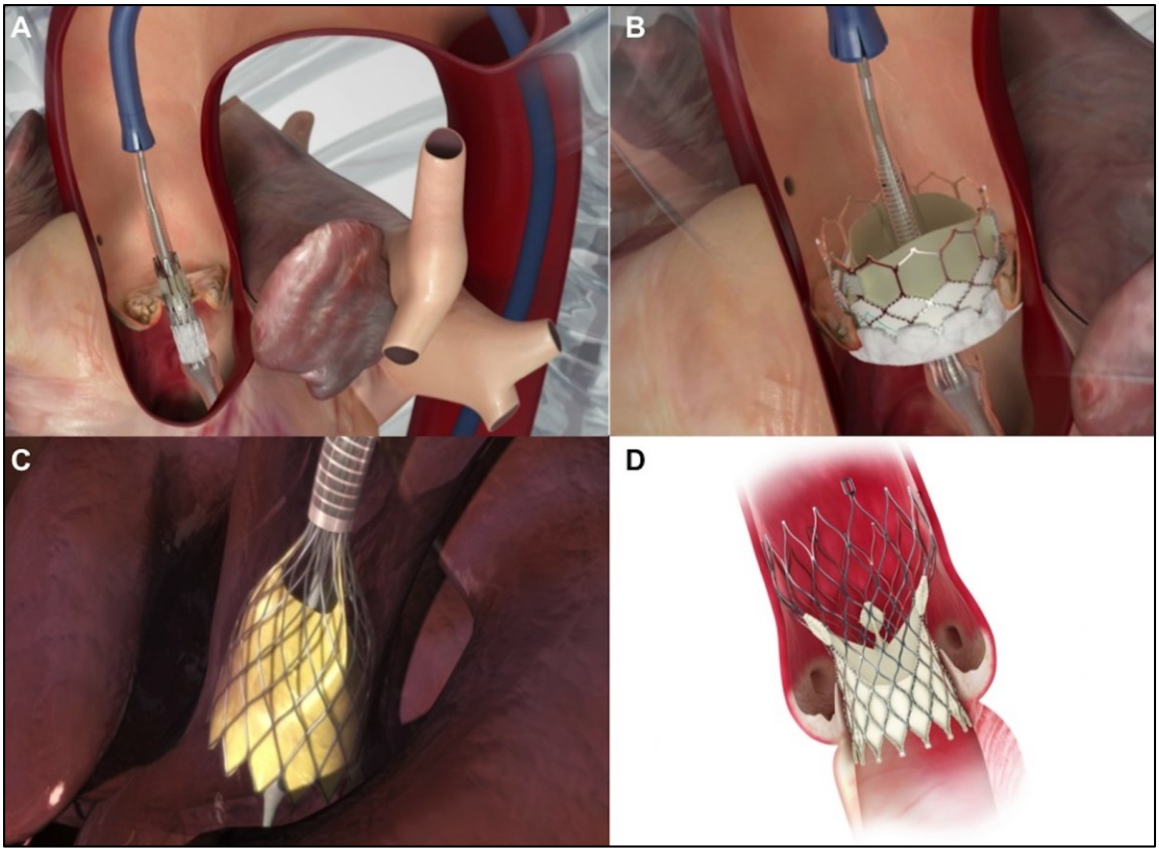


Figure 2-3: Image showing the positioning of a SAPIEN-3 valve by the transfemoral approach (A) and the final result (B). Image showing the positioning of a CoreValve by the transfemoral approach (C) and the final result (D)

2.3.1.2 Transapical approach

The transapical TAVR technique was first reported in 2006,[163] and it was developed for patients with non-optimal iliofemoral vessels that precluded the safe placement of the sheath.[136] A small left anterior minithoracotomy is required for the puncture of the apex and placement of the sheaths (Figure 2-4). For the current Edwards-SAPIEN and SAPIEN XT valves a 24Fr sheath is needed, and we recently described the new 18F Certitude delivery system for the transapical placement of the SAPIEN 3 valve.[154] This lower profile sheath might also reduce the occurrence of myocardial tears, myocardial injury and bleeding.

The transapical approach accounted for about half of the TAVR procedures performed with the Edwards-SAPIEN system.[143,164] Nowadays, with the use of lower profile devices for the transfemoral approach, about 20-30% of the procedures using balloon-expandable THVs are still performed by the transapical approach and further reduction is expected with the

SAPIEN 3 smaller profile sheath (Commander).[165] Apart from avoiding the passage of the catheter through both the iliofemoral system and the aorta, a possible advantage of this approach is the coaxiality of the valve prosthesis within the aortic annulus, which might help in the positioning of the valve, particularly in those patients with horizontal aorta.[166] The main disadvantages are the need for a thoracotomy, greater myocardial injury due to the apical perforation of the left ventricle[167] and the potentially life-threatening bleeding complications associated with myocardial tears during the surgical repair of the apex.[168] It has been shown that optimal analgesia is of major importance to reduce periprocedural pulmonary complications and improve survival in patients undergoing TAVR through the transapical approach.[169]

First-in-human CoreValve implantation by the transapical approach has been reported but this approach has not been further developed for this valve system.[170] Still, more recent transapical THVs have been developed with initial promising results: Engager valve (Medtronic, Inc., Minneapolis, MN, USA), JenaValve (JenaValve Technology, Munich, Germany) and Symetis Acurate (Symetis SA, Ecublens, Switzerland).[171,172]

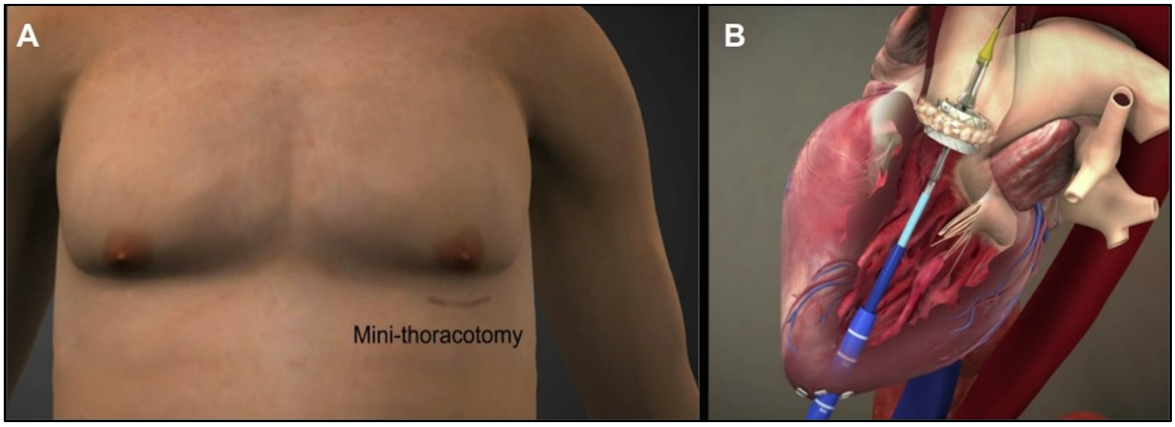


Figure 2-4: Image showing the location for mini-thoracotomy (A) in patients undergoing TAVR by the transapical approach, with the puncture of the apex (B)

2.3.1.3 Transaortic approach

The use of the transaortic approach through a small right sternotomy has been proposed more recently as a promising alternative approach with the Edwards and CoreValve systems (Figure 2-5).[173-176] This approach has the advantages of avoiding the use of large catheters through the iliofemoral system/aortic arch and a ventricular apex puncture. This approach has partially replaced the transapical approach in many centers and interestingly, a fully thoracoscopic approach has been recently described.[177]

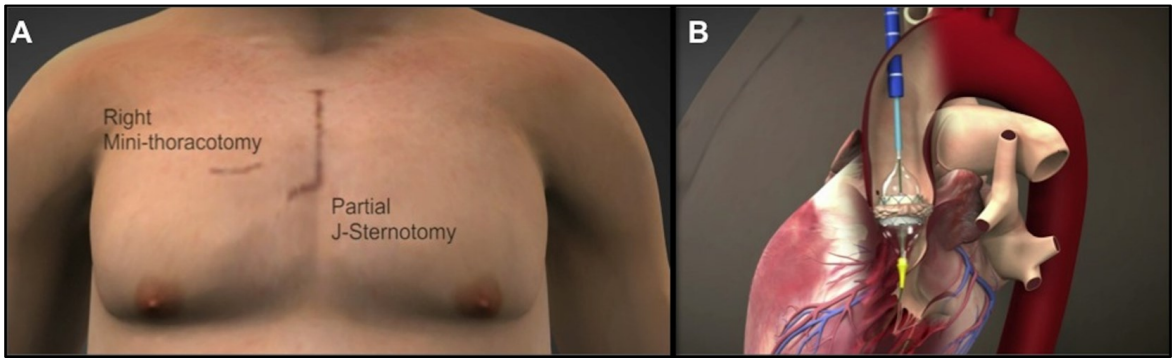


Figure 2-5: Image showing the location for mini-thoracotomy (A) in patients undergoing TAVR by the transaortic approach (B)

2.3.1.4 Subclavian and transaxilary approaches

Other alternatives to the transapical approach such as the subclavian and transaxillary approaches have also been developed for patients with non-appropiate iliofemoral arteries. Both the subclavian and transaxillary approaches have been used more frequently with the self-expanding valves with comparable short- and mid-term outcomes in relation to the transfemoral approach.[160,178] On the other hand the use of the subclavian/transaxilary approach in patients treated with a balloon-expandable THV has been limited to a few cases.[179,180]

2.3.2 Implantation technique

A balloon aortic valvuloplasty is usually performed prior to balloon-expandable THV implantation, although direct valve implantation without pre-dilatation has been successful described (Figure 2-6).[181] Subsequently, the valve is positioned using fluoroscopy, angiography and transesophageal echocardiography guidance, and valve expansion is obtained by balloon inflation under rapid pacing (160 to 200 bpm) in order to minimize cardiac output and avoid valve embolization during valve deployment (Figure 2-6). Whereas some studies have reported the usefulness of TEE guidance with no angiography for transapical THV implantation,[166,182] many centers are currently performing TAVR with local anesthesia and no TEE guidance with a high success rate.[183] Also, in the case of the balloon-expandable valves to allow proper positioning of the valve and minimize the risk of valve mal-positioning, a two-step or a slow balloon inflation technique may be used, in order to partially reposition the valve during its deployment.[184,185] CoreValve positioning is mostly performed by fluoroscopy and angiography, with little or no use of TEE, and the valve is deployed without rapid pacing (or minimal rapid pacing) by retracting the outer sheath of the delivery catheter (Figure 2-6).

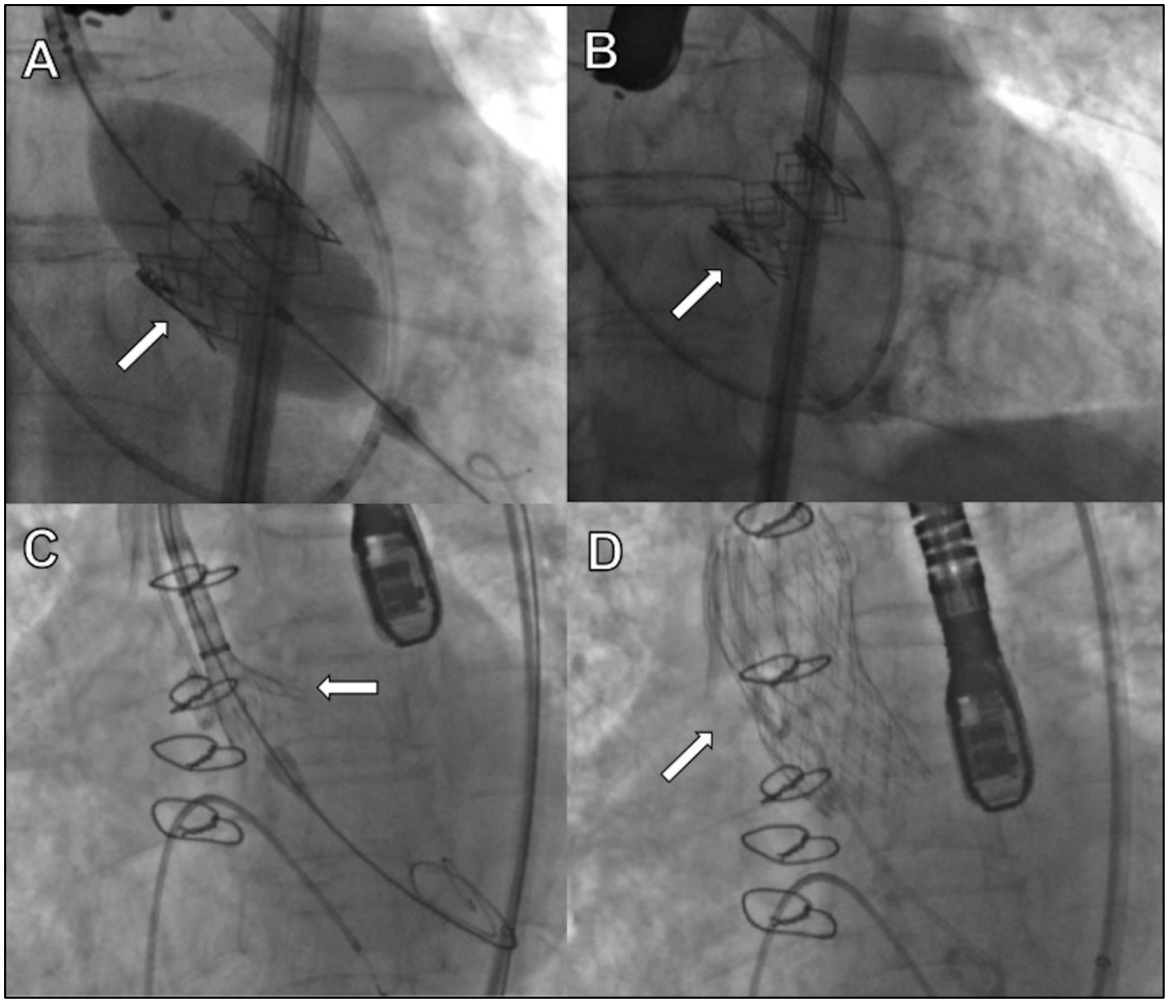


Figure 2-6: Case examples of the transfemoral TAVR implantation

Images of the balloon-expandable valve implantation technique. (A) Deployment of a balloon-expandable SAPIEN XT valve under rapid pacing. White arrows indicate the balloon during maximal expansion. (B) Fluoroscopic image of an Edwards SAPIEN XT valve following valve implantation (white arrow).[137] (C) The initial positioning of the CoreValve with angiography guidance (white arrow). (D) Final angiographic result of the CoreValve.

2.4 OUTCOMES OF THE TAVR PROCEDURES

Most patients treated with TAVR to date have been considered either inoperable or at a high risk for SAVR. Such patients tend to be octogenarians and exhibit a high rate of co-morbidities, such as coronary artery disease (~50%), chronic kidney disease (~50%), atrial fibrillation (~30%), chronic obstructive pulmonary disease (~25%) and/or peripheral vascular disease (~25%). This great burden of comorbidities led to high risk surgical scores in most TAVR studies, with mean logistic EuroSCORE and STS-PROM scores >20% and >8%, respectively.[138,139,143-146,164,165,186-189] There has been a great number of worldwide multicenter registries including patients with both balloon-expandable and self-expanding valves. Overall, the procedural success rate was >90% in all of the studies. Also, the *Placement of Aortic Transcatheter Valves* (PARTNER) trial is, to date, the most important prospective randomized trial on TAVR with a balloon-expandable SAPIEN valve. PARTNER included 2 distinct cohorts of patients. In the Cohort-B, 358 patients considered to be non-operable were randomized to medical treatment including BAV or TAVR (i.e. co-morbidities leading to a predicted risk of 50% or more of either death by 30 days after surgery or a serious irreversible condition; patients with co-morbidities leading to a life expectancy <1 year were excluded).[145] In the cohort-A, 699 patients considered to be at high surgical risk were randomly assigned to undergo either SAVR or TAVR (by both transfemoral or transapical approaches) or surgical replacement (i.e. predicted risk of operative mortality ≥15% as determined by site surgeon and cardiologist and/or a minimum STS score of 10).[146] Regarding the CoreValve, the most important study to date has been the US-CoreValve trial also with 2 cohorts, those considered inoperable that were compared with a pre-specified objective performance goal (based on previous data of the literature),[147] and the high-risk subset of patients that were randomly compared to SAVR.[148]

2.4.1 ***30-day mortality***

In evaluating the large multicenter registries,[138-144] the randomized PARTNER trials [145,146] and the US-CoreValve trials,[147,148] the overall 30-day mortality rate associated with TAVR ranged from 3.3 to 14.9% (Table 2-1). A recent meta-analysis including studies with at least 100 TAVR patients, showed that the 30-day mortality rate among 16,037 patients was

8.1% (8.1% for SAPIEN valve; 7.3% for CoreValve), which is somewhat lower than the mortality predicted by surgical risk scores.[190] With respect to the transarterial route, among 10,419 patients the 30-day mortality rate was 7.2% (6.3% for balloon-expandable valve; 7.5% for self-expanding valve).[190]

2.4.2 Long-term mortality

In the large multicenter registries,[138-144] the randomized PARTNER trials [145,146] and the US-CoreValve trials,[147,148] the overall 1-year mortality rate associated with TAVR ranged from 15-25% at 1-year follow-up (~20%) for the transfemoral approach and 22% to 37% (~30%) for the transapical approach.[190] A recent meta-analysis evaluating the adverse events associated with TAVR showed a 1-year mortality rate among 12,871 patients of 20.8% (22.4% for SAPIEN valve; 18.1% for CoreValve).[190] With respect to the transarterial route, among 7,350 patients the 1-year mortality rate was 18.3% (19.8% for the SAPIEN valve; 17.9% for CoreValve).[190]

There is still scant data on the long-term results associated with TAVR procedures. Gurvitch et al.[191] previously reported a survival rate of 51% at 3-year follow-up in 88 patients who had undergone TAVR with the balloon-expandable Edwards valve. Among the patients who survived the TAVR procedure, the survival rates were of 74% and 61% at 2- and 3-year follow-up, respectively. Buellesfeld et al.[192] reported a survival rate of 72% at 2-year follow-up following TAVR with the CoreValve system. The patients included in these studies represent the initial TAVR experience and the use of very early versions of the transcatheter valve and delivery catheter systems. More recently, the 5-years results from the PARTNER trial have been reported. In the Cohort-B of inoperable patients the risk of all-cause mortality at 5 years was 71.8% in the TAVR group versus 93.6% in the medical treatment group (hazard ratio 0.50, 95% CI 0.39-0.65; $p<0.0001$).[193] In the Cohort-A of high-risk patients, at 5 years, the risk of death was 67.8% in the TAVR group compared with 62.4% in the SAVR group (hazard ratio 1.04, 95% CI 0.86-1.24; $p=0.76$). Notably, no structural valve deterioration requiring SAVR in either group was detected.[194]

2.5 MAJOR COMPLICATIONS

The most frequent complications associated with TAVR and their respective rates in various studies are summarized in Table 2-1. The Valve Academic Research Consortium (VARC)[195] has proposed standardized consensus definitions for important clinical endpoints, including major complications in TAVR, and this has recently been reviewed as the VARC-2 criteria.[196] This initiative was of extreme importance in order to establish a more uniform and consistent evaluation of TAVR complications and to allow comparison between studies.

2.5.1 Major vascular complications

The use of large sheaths (18Fr to 24 Fr) was associated with a high rate (>10-15%) of vascular complications, [138-148] More recently the use of lower profile systems such as the SAPIEN XT and SAPIEN 3, as well as the CoreValve Evolut-R, translated into a significant reduction in vascular complications (<10%).[153,155,165] This has also been confirmed in the randomized PARTNER II trial, where the use of the SAPIEN XT valve was associated with a 9.6% rate of vascular complications versus 15.5% with the Edwards-SAPIEN valve (p=0.04).[189] Despite this decrease, vascular complications remain an issue due to the still relatively large size of the THV systems, in addition to the older age and high rate of adverse characteristics of the iliofemoral system (small vessel diameter, severe atherosclerotic disease and calcification) in the TAVR population. This highlights the importance of an accurate evaluation of the iliofemoral arteries prior to the procedure and the use of alternative approaches to the transfemoral (probably including borderline cases).[197,198] Finally, while surgical cut-down was the most frequent vascular access site technique used with >20F THV systems, percutaneous closure has become the standard with the use of smaller systems, and the optimization of the percutaneous closure technique is of major importance in reducing the occurrence of vascular complications associated with the transfemoral approach.[162,199]

Table 2-1: Thirty-day and 1-year outcomes from large multicenter TAVR registries, the PARTNER trial, US-CoreValve trial and meta-analysis

Study	Approach	Valve type	Logistic Euro SCORE (%) [mean±Std/ median (IQR)]	Procedural success (%)	30-day mortality (%)	1-year survival (%)	Major vascular complications (%)	Stroke (%)	Hemodialysis (%)	Permanent pacemaker (%)
Large Registries										
Belgian[138] (n=328)	TF/TA Edwards: 187 TF Corevalve: 141	Edwards: n=187 Corevalve: n=141	Overall: 28±16 Edwards: 30±16 Corevalve: 25±15	Overall: 97.0 Edwards: 97.0 Corevalve: 98.0	Overall: 11.0 Edwards: 12.0 Corevalve: 11.0	TF Edwards: 82 TA Edwards: 63 Corevalve: 79	Overall: 0.6 Edwards: 0.5 Corevalve: 0.7	Overall: 5.0 Edwards: 4.0 Corevalve: 5.0	Overall: 6 Edwards: 6 Corevalve: 7	Overall: 13 Edwards: 5 Corevalve: 22
Canadian[164] (n=339)	TF: 162 TA: 177	Edwards	Overall: 27.7±16.3 TF: 25.8±14.9 TA: 29.4±17.2	Overall: 93.3 TF: 90.5 TA: 96.1	Overall: 10.4 TF: 9.5 TA: 11.3	Overall: 76 TF: 75 TA: 78	Overall: 13 TF: 13.1 TA: 13.0	Overall: 2.3 TF: 3.0 TA: 1.7	Overall: 2.6 TF: 1.8 TA: 3.4	Overall: 4.9 TF: 3.6 TA: 6.2
European[19] n=646	TF: 646	Corevalve:	TF: 23.1±13.8	TF: 97.2	TF: 8.0	N/A	TF: 1.9	TF: 1.9	N/A	TF: 9.3
France[186] (n=244)	TF Edwards: 166 TA Edwards: 71 TF Corevalve: 66 SC Corevalve: 12	Edwards: n=166 Corevalve: n=78	Overall: 25.6±11.4 TF Edwards: 25.6±11.3 TA Edwards: 26.8±11.6 TF Corevalve: 24.7±11.2 SC Corevalve: 24.6±14.5	Overall: 98.3	Overall: 12.7 TF Edwards: 8.4 TA Edwards: 16.9 TF Corevalve: 15.1 SC Corevalve: 8.3	N/A	Overall: 7.3 TF Edwards : 6.3 TA Edwards: 5.6 TF Corevalve: 7.5 SC Corevalve: 8.3	Overall: 3.6 TF Edwards: 4.2 TA Edwards: 2.8 TF Corevalve: 4.5 SC Corevalve: 0	Overall: 1.6 TF Edwards: 1.0 TA Edwards: 2.8 TF Corevalve: 1.5 SC Corevalve: 0	Overall: 11.8 TF Edwards: 5.3 TA Edwards: 5.6 TF Corevalve: 25.7 SC Corevalve: 25.0
France-2[139] (n=3.195)	TF: 2.361 TA: 567	Edwards: n=2.107 Corevalve: N=1.043	Overall: 21.9±14.3 SAPIEN: 22.2±14.3 Corevalve: 21.3±14.3	Overall: 96.9 SAPIEN: 97.0 Corevalve: 97.6 TF: 97.1 TA: 95.9	Overall: 9.7 SAPIEN: 9.6 Corevalve: 9.4 TF: 8.5 TA: 13.9	Overall: 76 SAPIEN: 76 Corevalve: 76.3 TF: 78.3 TA: 67.7	Overall: 4.7 SAPIEN: 2.7 Corevalve: 4.5 TF: 5.5 TA: 1.9	Overall: 2.3 SAPIEN: 1.9 Corevalve: 2.6 TF: 2.2 TA: 2.1	N/A	Overall: 15.6 SAPIEN: 11.5 Corevalve: 24.2 TF: 15.2 TA: 13.6
German[22] n=697	TF: 644 SC: 22 TA: 26 Transaortic: 5	Edwards: n=109 Corevalve: n=588	Overall: 20.5±13.2	Overall: 98.4	Overall: 12.4	N/A	Overall: 19.5	Overall: 2.8	N/A	Overall: 39.9
Italian[20] n=663	TF: 599 SC: 64	Corevalve	23.0±13.7	98.0	0.9	85	2.0	1.2	N/A	6.6
SOURCE[143] (n=1,038)	TF: 463 TA: 575	Edwards	TF: 25.7±14.5 TA: 29.1±16.3	Overall: 93.8 TF: 95.2 TA: 92.7	Overall: 8.5 TF: 6.3 TA: 10.3	Overall: 76.1 TF: 81.1 TA: 72.1	Overall: 7.0 TF: 10.6 TA: 2.4	Overall: 2.5 TF: 2.4 TA: 2.6	Overall: 4.3 TF: 1.3 TA: 7.1	Overall: 7.0 TF: 6.7 TA: 7.3

Continued

Conclusion

Study	Approach	Valve type	Logistic Euro SCORE (%) [mean±Std/ median (IQR)]	Procedural success (%)	30-day mortality (%)	1-year survival (%)	Major vascular complications (%)	Stroke (%)	Hemodialysis (%)	Permanent pacemaker (%)
Large Registries										
United Kingdom[187] (n=870)	TF: 599 Other approaches: 271	Edwards: n=410 Corevalve: n=452	Overall: 18.5 (11.7, 27.9) TF: 17.1 (11, 25.5) Other routes: 21.4 (14.4, 33.6) Corevalve: 18.1 (11.1, 27.9) Edwards: 18.5 (12.4, 27.7)	Overall: 97.2 TF: 97.3 Other routes: 97.1 Corevalve: 98.2 Edwards: 98.1	Overall: 7.1 TF: 5.5 Other routes: 10.7 Corevalve: 5.8 Edwards: 8.5	Overall: 78.6 TF: 81.5 Other routes: 72.3 Corevalve: 78.3 Edwards: 79.4	Overall: 6.3 TF: 8.4 Other routes: 1.9 Corevalve: 6.2 Edwards: 6.3	Overall: 4.1 TF: 4.0 Other routes: 4.1 Corevalve: 4.0 Edwards: 4.2	N/A	Overall: 16.3 Corevalve: 24.4 Edwards: 7.4
Randomized trials										
PARTNER[26] High-risk cohort n=348	TF: 244 TA: 104	Edwards	Overall: 29.3±16.5	NA	Overall: 3.4 TF: 3.3 TA: 3.8	Overall: 75.8 TF: 77.8 TA: 71	Overall: 11.0	Overall: 4.7	Overall: 2.9	Overall: 3.8
PARTNER[25] Nonoperable cohort n=179	TF: 179	Edwards	26.4±17.2	98.8	5.0	30.7	TF: 16.2	TF: 6.7	TF: 1.1	TF: 3.4
PARTNER II[189] Non-operable Cohort-B	TF: 560	SAPIEN: n=276 SAPIENXT: n=284	-		SAPIEN: 5.1 SAPIEN XT: 3.5	SAPIEN: 76.3 SAPIEN XT: 77.5	SAPIEN: 15.5 SAPIEN XT: 9.6	SAPIEN: 4.1 SAPIEN XT: 4.3	-	SAPIEN: 5.9 SAPIEN XT: 6.4
US-Corevalve[147] Nonoperable cohort n=489	TF: 489	Corevalve	22.6 ± 17.1	99.4	8.4	75.7	8.2	2.3	N/A	21.6
US-Corevalve[148] High-risk cohort n=795	TF: 323 Non-TF: 67	Corevalve N=390	17.6±13.0	99.7	3.3	85.8	5.9	4.9	N/A	19.8
Meta-analysis*										
Khatri et al.[190] n=16.063	Transarterial: n=11.080 TA: n=4.893	SAPIEN: n=9.560 Corevalve: n=6.424	Overall: 24% SAPIEN: 24% Corevalve: 22%	-	All: 8.1 TF: 7.2 TA: 9.9	All: 79.2 TF: 81.7 TA: 74.6	All: 10.4 TF: 14.2 TA: 3.4	All: 2.9 TF: 3.5 TA: 3.0	All: 4.9 TF: 2.8 TA: 8.2	All: 13.1 TF: 15.6 TA: 5.8

*Meta-analysis including studies with > 100 patients.

Abbreviations: BEV: balloon-expandable valve; TF: transfemoral; TA: transapical; SC: subclavian; TAo: transaortic; N/A: data not available; EU: European Union; FRANCE: FRench Aortic National CoreValve and Edwards; EuroSCORE: European System for Cardiac Operative Risk Evaluation; PARTNER: Placement of Aortic Transcatheter Valves; SOURCE: SAPIEN Aortic Bioprosthesis European Outcome.

*2.5.2 **Stroke***

Cerebrovascular events are still among the most troublesome complications associated with TAVR. The mean 30-day major stroke rate in two recent meta-analyses including more than 10,000 patients undergoing TAVR was ~3.0%, ranging from 0% to 6.7%.[190,200] Of note, in the PARTNER trial (cohort A) the cerebrovascular event rate (including stroke and transient ischemic attack) was higher in the TAVR than the SAVR group at 30-day (5.5% vs. 2.4%, respectively; p=0.04) and at 1-year follow-up (8.3 vs. 4.3%, respectively; p=0.04).[146] Also in the non-operable cohort of the PARTNER trial, a higher rate of cerebrovascular events at 30-day (6.7% vs. 1.7%, respectively; p=0.03) and 1-year (10.6% vs. 4.5%, respectively; p=0.04) follow-up was found among TAVR patients than among those managed conservatively.[145] On the other hand, in the US-CoreValve study, TAVR was associated with similar stroke rates as compared to surgery at 30-days (3.9 vs. 3.1%, respectively; p=0.55) and at 1-year (5.8 vs. 7.0%, respectively; p=0.59).[148]

About half of cerebrovascular events following TAVR occur within the first 24 hours after the procedure, and mechanical factors such as valve embolization, multiple valve positioning attempts or balloon post-dilation have been identified as predictors of these acute events, whereas other factors such as atrial fibrillation have been associated with a higher rate of subacute (>24 hrs) events.[201] No study to date has identified any effect of valve type (balloon-expandable vs. self-expanding) on TAVR stroke rate. Also, the use of the transapical approach has not been associated with a lower rate of clinically apparent or silent stroke following TAVR, despite avoiding the passage of large catheters through the aortic arch and the retrograde crossing of the aortic valve.[143,164,202]

The use of embolic protection devices during the TAVR procedure and the optimization of antithrombotic therapy may play a major role in reducing the incidence of stroke associated with TAVR procedures.[203]

*2.5.3 **Acute kidney injury (AKI)***

The incidence of AKI and the need for hemodialysis following TAVR has ranged from 11.7% to 28%, and from 1.4% to 15.7%, respectively.[204-208] In the PARTNER trial (high-risk cohort)[146] the need for renal replacement therapy was similar in the TAVR and SAVR

patients, respectively, at 30 days (2.9% vs. 3.0%) and at 1-year follow-up (5.4% vs. 6.5%). Chronic kidney disease is one of the most frequent comorbidities among these fragile and old TAVR patients (prevalence of 30% to 50%),[136] and a higher degree of pre-procedural renal dysfunction was associated with a higher rate of post-procedural AKI.[208,209] Also, peri-procedural blood transfusion has been recognized as a significant predictive factor of AKI following TAVR,[204,206,207,209] highlighting the importance of avoiding unnecessary transfusions in those patients. Importantly, those patients presenting AKI have worse acute and midterm outcomes following TAVR.[204,206,207,209]

2.5.4 Intraventricular conduction abnormalities

The occurrence of new-onset intraventricular conduction disturbances is also a frequent complication related with TAVR.[210] While the use of balloon-expandable valves has been systematically associated with a lower rate of conduction disturbances compared to self-expanding valves, the rate of new-onset LBBB in patients without prior pacemaker or conduction disturbances remains as high as ~25% following balloon-expandable valve implantation.[210,211] Nonetheless, about half of these conduction disturbances resolve within a few days, and the other half persists at hospital discharge, resolving within the weeks-months after the procedure[211], which is not the case with self-expanding valves. A larger QRS at baseline and a lower (more ventricular) implantation of the balloon-expandable valves have been associated with a higher rate of conduction disturbances.[211] Of note, it has been shown recently that new-onset persistent left bundle-branch block and a QRS duration >160 ms were associated with a greater risk of sudden cardiac death (HR: 4.78, 95% CI: 1.56 to 14.63; p=0.006).[212]

The need for pacemaker implantation following balloon-expandable valve implantation has been nearly systematically <10%, much lower than the ~20% associated with the implantation of the CoreValve system.[136,190] Despite this lower pacemaker rate, Bagur et al.[213] found, in a case-matched study, a higher incidence of pacemaker implantation following TAVR with a balloon-expandable valve as compared to SAVR (7.3 versus 3.4%, respectively; p=0.014). However, no differences in the pacemaker rate were observed between TAVR (3.8%) and SAVR (3.6%) in the PARTNER I trial.[146]

2.5.5 Myocardial injury following TAVR

The studies to date evaluating the incidence of myocardial injury following TAVR are summarized in Tables 2-2 and 2-3. Overall, it has been shown that TAVR is systematically associated with some degree of myocardial injury, as determined by a rise in cardiac biomarkers (i.e. troponin and creatine kinase-MB - CKMB).[136,214-217] Additionally, Rodes-Cabau et al.[167] showed that a mild rise in cardiac biomarkers is frequently observed after a balloon-expandable TAVR, and the degree and extent of this elevation has been related with less improvement in LVEF and a higher cardiac mortality at 1-year follow-up.[167] Likewise, this systematic mild myocardial injury has also been verified in the setting of TAVR with the self-expanding CoreValve, where it was also related with increased short-term mortality.[214]

Additionally to this systematic mild rise in cardiac biomarkers denoting myocardial injury, the TAVR procedures are also associated with coronary obstruction, the extreme form of myocardial injury during TAVR procedures. This complication is generally due to the displacement of a calcified leaflet over the coronary ostia, and apart from some reports on its incidence (usually <1%) in some TAVR series,[144,146,164,165,186] specific clinical data on this important complication have been scarce and restricted to case reports and small case series, precluding any appropriate evaluation of the baseline characteristics of patients suffering this complication, as well as its management and clinical impact.

Table 2-2: Main characteristics of studies assessing the impact of myocardial injury following TAVR

Studies	Year	Subjects	Valve Type	Approach	Mean follow-up
Rodes-Cabau et al.[167]	2011	101	Balloon-expandable	TF: 38 / TA: 63	10 months
Yong et al.[214]	2012	119	Self-expanding	TF: 119	30 days
Dworakowski,et al.[215]	2012	42	Balloon-expandable	TF: 42	2.6 years
Barbash et al.[216]	2013	150	Balloon-expandable	TF: 103 / TA: 47	1 year
Carrabba et al.[217]	2013	68	Self-expanding	TF: 59 / TS: 3	1 year

Table 2-3: Incidence and predictors of myocardial injury following TAVR

Studies n	Incidence of Increased CKMB (mean/median peak value)	Incidence of Increased Troponin (mean/median peak value)	Multivariable Predictors of Injury	Multivariable Predictors 30-day/Long-term outcomes
Rodes-Cabau et al.[167]	77% / (18.6 µg/L)	99% / (0.48 µg/L)	Approach TA and baseline renal failure	Myocardial injury (predictor of long-term outcomes)
Yong et al.[214]	100% / (15.9 ng/ml)	100% / (0.28 ng/ml)	Absence of β-blocker use, peripheral arterial disease prosthesis depth, and procedural duration	Myocardial injury, preprocedural hospitalization, and left ventricular mass index
Dworakowski,et al.[215]	- / (6.82 µg/L)	- / (1.59 µg/L)	-	-
Barbash et al.[216]	76% / (180 ng/ml for TA; 27 ng/ml for TF)	98% / (6 ng/ml for TA; 1.4 ng/ml for TF; p<0.001)	Approach TA, absence of β -blocker on admission, and baseline renal failure	Peak in CKMB (both 30-day and 1 year) and troponin (30-day only)
Carrabba et al.[217]	100% / (11.5 µg/L)	100% / (cTnI: 3.8µg/L)	Acute kidney injury	

Legend: TF: transfemoral; TA: transapical; TS: transubclavian.

Compared to conventional open-heart surgery, TAVR is not associated with aortic cross-clamping and cardioplegia. Even so, the procedure involves some degree of myocardial injury due to tissue compression, caused by the balloon and valve prosthesis, as well as periprocedural conditions, resulting in myocardial oxygen supply-demand mismatch, such as balloon valvuloplasty, acute aortic regurgitation, and temporary hypotension during rapid ventricular pacing and gradual deployment of the bioprostheses (Figure 2-7).[167,214,215] Also, myocardial damage during TAVR could be triggered by direct myocardial injury either by the catheter, wire, and/or prosthesis manipulation. Finally, in the transapical approach, which is an alternative to the transfemoral approach,[164,218,219] the procedure involves the puncture of the ventricular apex for the introduction of large catheters, what has been related to more prominent elevation in cardiac biomarkers.[167] However, there is very few data on the incidence of myocardial injury according to the different mechanisms and approaches used, as well as related to other biomarkers such as natriuretic peptides. Also, no study to date has yet evaluated the relation of this biomarkers elevation with the presence, extent and patterns of irreversible myocardial injury following TAVR. Finally, the associated impact on short- and long-term outcomes is controversial.

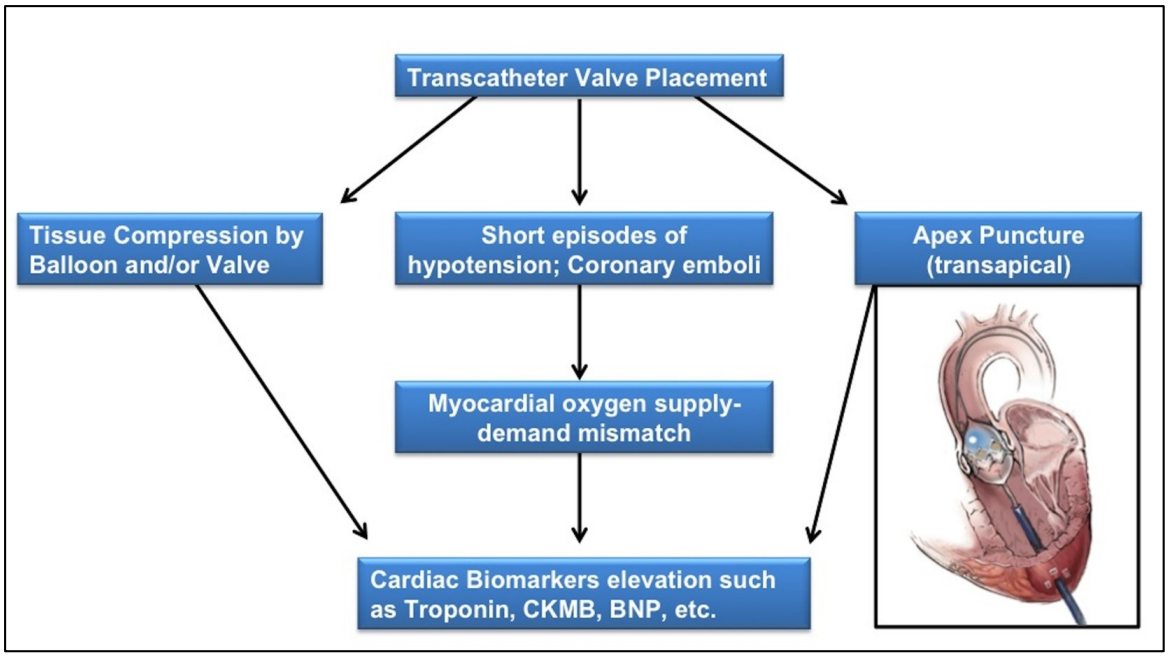


Figure 2-7: Potential mechanisms of myocardial injury in patients undergoing TAVR

CHAPTER 3:

HYPOTHESES AND OBJECTIVES

3.1 HYPOTHESES

3.1.1 General hypothesis

The general hypothesis of my PhD project is that the incidence, related factors and prognostic significance of cardiac biomarkers and natriuretic peptides elevation, as well as the presence, extent and patterns of irreversible myocardial injury following TAVR differ among the various TAVR approaches and that has a major impact on LV function recovery after TAVR, as well as on the early and late clinical outcomes.

3.1.2 Specific hypotheses

1) CK-MB levels after TAVR relate to the approach used and the type of transcatheter valve, an their serial measurements add a prognostic significance and may determine worse clinical prognostic, in the short- and long-term follow-up, and also impaired LV function.
2) NT-proBNP levels before TAVR add prognostic significance on the long-term follow-up, and their serial changes after the procedure are related to clinical factors and the approach utilized.
3) The transaortic approach that is used as an alternative to the transapical approach for patients that cannot undergo the transfemoral approach, is related to less myocardial injury as compared to the transapical approach, and this has a significant impact on LV function recovery following the procedure.
4) The presence, localization, and extent of irreversible myocardial injury following TAVR as determined by CMR correlate with the elevation of cardiac biomarkers and the type of approach used.
5) Coronary obstruction, one of the extreme forms of myocardial injury during TAVR procedures, is associated with identifiable clinical and anatomical risk factors that will help in recognizing those patients at increased risk, what will consequently aid to better prevent and/or treat this complication.

3.2 OBJECTIVES

3.2.1 General objectives

The general objective of my PhD project is to determine the incidence, related factors and prognostic significance of myocardial injury, as evaluated by cardiac biomarkers and natriuretic peptides elevation, following TAVR among the various approaches and transcatheter valves. Another objective is to determine the presence, extent and patterns of irreversible myocardial injury following TAVR, and their potential impact on LV function recovery after the procedure.

3.2.2 Specific objectives

1) The first objective is to determine the incidence, prognostic significance and factors associated with myocardial injury after TAVR as determined by the serial changes in CK-MB after the procedure.
2) The second objective is: i) to determine if NT-proBNP levels before TAVR add prognostic significance on the long-term follow-up; ii) to determine the NT-proBNP serial changes, related factors, and prognostic significance after TAVR, according to the different approaches used.
3) The third objective is to compare the degree of myocardial injury as determined by CK-MB and troponin elevation after TAVR using the transaortic vs. the transapical approaches, both alternatives to those patients that cannot undergo the transfemoral approach.
4) The fourth objective is to evaluate the presence, localization, and extent of myocardial injury measured by CMR following TAVR, and its correlation with cardiac biomarkers and the approach utilized.
5) The fifth objective is to provide further insights into the baseline characteristics, management, and clinical outcomes of patients with coronary obstruction as a complication of TAVR through a systematic review of all the studies on TAVR and coronary obstruction published thus far, and also by a multicenter worldwide registry with this complication.

CHAPTER 4: ARTICLE 1

Predictors and Clinical Impact of Myocardial Injury Following Transcatheter Aortic Valve Replacement: Insights from a Large Multicenter Registry

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4.1 RÉSUMÉ

PRÉDICTEURS ET IMPACT CLINIQUE DES LÉSIONS MYOCARDIQUES LORS DE L'IMPLANTATION PAR CATHÉTER DE LA VALVE AORTIQUE : RÉSULTATS D'UN GRAND REGISTRE MULTICENTRIQUE

Introduction : Les lésions myocardiques libérant des biomarqueurs cardiaques à la suite d'un remplacement de la valve aortique par cathéter (TAVR) sont très fréquentes, cependant l'impact clinique chez une large population de patients TAVR recevant différents types de prothèses par différentes approches demeure inconnu. Ceci limite la validation d'un seuil biochimique permettant de définir clairement un infarctus du myocarde post-TAVR.

Objectifs : Déterminer, dans une large cohorte de patients subissant un TAVR, l'incidence, l'impact clinique et les facteurs associés à l'élévation des biomarqueurs cardiaques post-TAVR.

Méthodes : Cette étude multicentrique incluait 1131 patients ayant eu un TAVR avec une valve expansible par ballonnet (58 %) ou auto-expansible (42 %). L'approche transfémorale ou transapicale (TA) a été choisie dans 73,1 % et 20,3 % des cas respectivement. La mesure de la créatine kinase-MB (CK-MB) a été obtenue initialement et à plusieurs moments au cours des 72 premières heures post-TAVR. Une échocardiographie a été réalisée initialement ainsi qu'au suivi de 6-12 mois.

Résultats : Dans l'ensemble, 66 % de la population ayant eu un TAVR a démontré un certain degré de lésion myocardique déterminée par une augmentation des concentrations de CK-MB [valeur maximale (IQR): 1,6-fois (0,9 to 2,8-fois)]. L'approche TA et des complications procédurales majeures tels que l'embolisation de la prothèse/la nécessité d'une seconde prothèse, les saignements majeurs mettant en danger la vie du patient et la conversion à une chirurgie à cœur ouvert étaient indépendamment associés à des concentrations maximale plus élevées de CK-MB ($p < 0,001$ pour tous). Cette augmentation de CK-MB était associée à une détérioration de la fonction ventriculaire gauche 6 à 12 mois post-TAVR ($p < 0,01$). Une plus grande augmentation des concentrations de CK-MB était indépendamment associée à une augmentation de la mortalité globale à 30 jours, à long-terme (médiane de 21 [8-36] mois) et de la mortalité cardiaque ($p < 0,001$ pour tous). Toute

augmentation des concentrations de CK-MB a été associée à des résultats cliniques défavorables, avec une augmentation progressive de mortalité tardive selon les différents dégrés d'augmentation de CK-MB (p <0,001).

Conclusion : Un certain degré de lésion myocardique a été détecté chez le 2/3 des patients post-TAVR, plus spécifiquement chez les patients TAVR-TA ou chez ceux présentant une complication procédurale majeure. Une augmentation plus grande des concentrations de CK-MB était associée à une augmentation de la mortalité aigue et tardive, et avait un impact négatif sur la fonction ventriculaire gauche.

Mots clés: Sténose aortique; Remplacement de valve aortique par cathéter; Biomarqueur cardiaque; Créatine kinase-MB; Transapical.

Ces travaux ont été présentés lors du congrès Transcatheter Cardiovascular Therapeutics (TCT) (San Francisco, EUA; octobre 2015).

4.2 ABSTRACT

Background: Cardiac biomarker release signifying myocardial injury post-transcatheter aortic valve replacement (TAVR) is common, yet its clinical impact within a large TAVR cohort receiving differing types of valve and procedural approaches is unknown. A validation of the most appropriate biochemical threshold for defining clinically relevant myocardial infarction post-TAVR has yet to be defined.

Objectives: To determine, in a large cohort of patients undergoing TAVR, the incidence, clinical impact and factors associated with cardiac biomarker elevation post-TAVR.

Methods: This multicenter study included 1,131 consecutive patients undergoing TAVR with balloon- (58%) or self-expandable (42%) valves. Transfemoral and transapical (TA) approaches were selected in 73.1% and 20.3% of patients, respectively. Creatine kinase-MB (CK-MB) measurements were obtained at baseline and at several time points within the initial 72 hours post-TAVR. Echocardiography was performed at baseline and at 6- to 12-month follow-up.

Results: Overall, 66% of the TAVR population demonstrated some degree of myocardial injury as determined by a rise in CK-MB levels [peak value (IQR): 1.6-fold (0.9 to 2.8-fold)]. A TA approach and major procedural complications such as valve embolization/need for a second valve, major/life threatening bleeding, conversion to open heart surgery and early experience were independently associated with higher peak of CK-MB levels ($p < 0.01$ for all), and this translated into impaired systolic left ventricular function at 6-12 months post-TAVR ($p < 0.01$). A greater rise in CK-MB levels independently associated with an increased 30-day, late (median of 21 [8-36] months) overall and cardiovascular mortality ($p < 0.001$ for all). Any increase in CK-MB levels was associated with poorer clinical outcomes, and there was a stepwise rise in late mortality according to the various degrees of CK-MB increase following TAVR ($p < 0.001$).

Conclusions: Some degree of myocardial injury was detected in two-thirds of patients post-TAVR, especially in those undergoing TA-TAVR or presenting with major procedural complications. A greater rise in CK-MB levels associated with greater acute and late mortality, imparting a negative impact on left ventricular function.

Key words: aortic stenosis, transcatheter aortic valve replacement, cardiac biomarkers, creatine kinase-MB, transapical

4.3 INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has emerged as a therapeutic alternative to surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis (AS) at very high or prohibitive peri-operative risk.[136] Compared with conventional open-heart surgery, TAVR procedures are less invasive due to the avoidance of aortic cross-clamping and cardioplegia. However, TAVR systematically associates with some degree of myocardial injury, defined biochemically by variable increases in cardiac biomarkers.[167,216,217] A negative clinical impact associated with a higher degree of myocardial injury post-TAVR has also been suggested,[167,220] and the recent Valve Academic Research Consortium (VARC-2) consensus on TAVR has established specific biomarkers cut-off values for defining clinically significant myocardial infarction post-TAVR.[167,196] However, a validation of these VARC definitions upon clinically relevant myocardial infarction post-TAVR is still lacking.

Prior studies evaluating myocardial injury post-TAVR included limited numbers of patients and duration of follow-up, with a paucity of cardiovascular outcomes data.[167,216,217] Also, a single transcatheter valve system (balloon- or self-expandable) and/or delivery approach were used in most prior studies.[167,216,217] Thus, a comprehensive understanding of the factors associated with myocardial injury post-TAVR in a real world all-comers population, incorporating the true clinical impact of varying degrees of myocardial injury detected biochemically, is currently lacking. Finally, most prior studies had focused on troponin levels as a biomarker of myocardial injury, yet there are limited data regarding the impact of creatinine kinase-MB (CK-MB) levels, which has undergone a more robust validation for defining peri-procedural myocardial infarction in the cardiac surgery and percutaneous coronary intervention fields.[221] The objectives of the present study were to evaluate the incidence, prognostic significance and factors associated with myocardial injury as determined by CK-MB elevation (including validation of the VARC-2 proposed cut-off for myocardial infarction) in a large multicenter cohort of patients undergoing TAVR with differing valve types and approaches.

4.4 METHODS

4.4.1 Study population

This was a multicenter study including 1,172 patients who underwent TAVR from March 2007 until December 2014, in different centers across North America, South America and Europe. A total of 41 patients were excluded due to procedural death (within the first 24 hrs following the procedure), precluding the collection of at least one blood sample for cardiac biomarker measurements post-procedure. Therefore, the final study population consisted of 1,131 patients, 486 patients (43.0%) from 3 centers in North America, 123 patients (10.9%) from 4 centers in South America and 522 patients (46.1%) from 6 centers in Europe. A balloon-expandable valve was used in 658 patients, being an Edwards-Sapien (Edwards Lifesciences Inc., Irvine, California) in 261 (23.1%), Sapien XT (Edwards Lifesciences Inc., Irvine, California) in 380 (33.6%), Sapien 3 (Edwards Lifesciences Inc., Irvine, California) in 14 (1.2%), and Inovare (Braile Biomedical, São Paulo, Brazil) in 2 patients (0.2%). Also, a self-expandable valve was used in 473 patients, being a CoreValve (Medtronic, Minneapolis, Minnesota) in 458 (40.5%), Portico (St. Jude Medical, Minneapolis, Minnesota) in 13 (1.1%), and Lotus (Boston Scientific SciMed Inc., Maple Grove, MN) in 1 (0.1%). Indications for TAVR, device type and approach were based on the assessment recommendation of the heart team at each center. Data were prospectively collected in a dedicated database at each center. The first half of patients treated at each center were considered as early TAVR experience. Clinical outcomes for the purpose of this study were defined according to the Valve Academic Research Consortium (VARC)-2 criteria.[196] Clinical follow-up was carried out by clinical visits and/or through phone contact at 1 month, 6- to 12-months post-TAVR, and yearly thereafter in all participating centers. Complete clinical follow-up was available in all but 6 patients, lost to follow-up (0.5%).

4.4.2 Measurements of serum markers signifying myocardial injury

Blood samples were collected at baseline, and at 6 to 12, 24, 48, and 72 hours post-TAVR, with CK-MB levels being measured at each time point. The upper normal limits for CK-MB were established at each participating institution based on the 99th percentile values in a healthy population. Myocardial injury was defined as a CK-MB increase above this upper

limit at any time point (up to 72 hours) post-TAVR. The degree of CK-MB elevation was calculated dividing the CK-MB level by the upper limit level and this was expressed as *x*-fold of increase. In those patients with elevated baseline CK-MB levels, myocardial injury was defined as any increase >20% post-procedure.[222]

4.4.3 Doppler-echocardiographic measurements

A Doppler echocardiographic examination was performed at baseline pre-TAVR, upon hospital discharge and at 6-months to 1-year post-TAVR. Echocardiographic data at follow-up was available in 532 patients (62.7% of the study population at risk). The following measurements were obtained in all patients: aortic annulus diameter, LV ejection fraction (LVEF) calculated by the biplane Simpson's method, mean trans-valvular gradient calculated with the Bernoulli formula, and the valve effective orifice area (AVA) calculated by the continuity equation. The presence and severity of aortic regurgitation (AR) was recorded in all patients. The severity of AR was classified according to the VARC-2 classification as follows: none/trace, mild, moderate, and severe.[196]

4.4.4 Statistical Analysis

Categorical variables are reported as n (%). Continuous variables are expressed as mean (SD) or median (25th to 75th interquartile range [IQR]) depending upon variable distribution. Group comparisons were performed using the Student t test or Wilcoxon rank sum test for continuous variables, and chi-square test for categorical variables. For the CK-MB analysis the values after the procedure were evaluated in relation to the upper-limit as determined at each center. Two experimental factors (subjects classified as random factor and time period as a fixed factor) were defined to analyse the changes in repeated CK-MB measurements over time (baseline, 6 to 12, 24, 48, and 72 h). Considering the presence of some missing CK-MB measurements in 11% of patients, the CK-MB levels over time were analyzed as a repeated-measures factor with the use of an unstructured covariance matrix to obtain unbiased estimates. Ulterior comparisons were performed using the Tukey's method. The normality assumption was verified with the Shapiro-Wilk tests on the error distribution from the Cholesky factorization of the statistical model. The Brown and Forsythe's

variation of Levene's test statistic was used to verify the homogeneity of variances. CK-MB elevation values were log-transformed to stabilize variances. Reported p-values were based on this transformation. The predictors of higher rise in CK-MB values were determined using a linear regression analyses normalized by baseline values. Uni- and multivariable logistic regression analyses were used to determine the predictors of 30-day mortality. Continuous variables were checked for the assumption of linearity using quartiles of the distribution and fractional polynomials before building the model in order to obtain the correct relationships. The graphic representations suggested linear relationships with the logit for all continuous variables. Uni- and multivariable Cox proportional hazard models were used to determine the predictors of cumulative late overall and cardiac mortality. The variables with a probability value <0.10 were candidates for the multivariable regression model building. Coronary artery disease was also added into the multivariable models. The final statistical model was built using 2 statistical approaches: a forward approach, Akaike's and Schwarz's Bayesian criteria. For the Cox models, the martingales residuals were used to examine the functional form of the continuous variables. Measurements of CK-MB elevation were log-transformed. After model building, the adequacy of the proportional hazards assumption was checked. To check the proportionality assumption, we first used the graphical representation of the logarithm cumulative hazard rates versus time to assess parallelism and the constant separation among the different values of nominal variables, whereas the continuous variables were stratified into 4 strata. Second, an artificially time-dependent covariate was added to the model to test the proportionality assumption. For all variables in the final models, the proportional hazards assumptions were not rejected as local tests linked to the time-dependent covariates were not significant and scatter plots were roughly constant over time. All analyses were performed using a hierarchical method in order to account for between-center variability. Mortality rates were presented using Kaplan-Meier estimates and comparisons between groups were performed using the log-rank test. The correlation between LVEF and CK-MB increase were evaluated with the Pearson's correlation. All results were considered significant with p values <0.05. Analyses were conducted using the statistical packages SAS, version 9.4 (SAS Institute Inc., Cary, NC) and Statistical Package for Social Sciences, version 20 (SPSS Inc, IBM, New York, USA).

4.5 RESULTS

The clinical, echocardiographic, procedural characteristics and 30-day outcomes of the study population are shown in **Table 4-1**. Also, the clinical, echocardiographic, and procedural characteristics and 30-day outcomes of the study population according to valve type are shown in **Table 4-2**.

Table 4-1: Clinical, echocardiographic, and procedural characteristics of the study population

Variable	All Patients (n = 1,131)
Clinical variables	
Age (years)	80 ± 7
Male sex	572/1,131 (50.6)
NYHA class	
I-II	266/1,123 (23.7)
III-IV	857/1,123 (76.3)
Coronary artery disease	608/1,131 (53.8)
Prior PCI	346/1,130 (30.6)
Prior CABG	253/1,131 (22.4)
History of atrial fibrillation	307/1,080 (28.4)
Cerebrovascular disease	142/880 (16.1)
Peripheral vascular disease	264/1,131 (23.3)
COPD	304/1,131 (26.9)
Porcelain aorta	153/1,131 (13.5)
eGFR (mL/min)	60.7 ± 25.5
CKD	608/1,130 (53.8)
STS-PROM (%)	8.2 ± 6.8
Echocardiographic variables	
LVEF (%)	56 ± 15
Mean aortic gradient (mmHg)	45.6 ± 16.8
Aortic valve area (cm^2)	0.64 ± 0.22
Moderate/severe mitral regurgitation	212/924 (22.9)
Procedural variables	
Success*	879/1,116 (78.8)
Approach	
Transfemoral	827/1,131 (73.1)
Transapical	230/1,131 (20.3)
Transaortic	48/1,131 (4.3)
Subclavian	26/1,131 (2.3)
Prosthesis type	
Balloon-expandable	658/1,131 (58.2)
Self-Expandable	473/1.131 (41.8)

Continued

Conclusion

Variable	All Patients (n = 1,131)
Prosthesis size (mm)	
≤ 26 mm	830/1,122 (74.0)
> 26 mm	292/1,122 (26.0)
Valve-in-valve	61/1,131 (5.4%)
Time of procedure "skin to skin" (min)	70 [60-88]
30-day outcomes	
Major vascular complications	136/1,130 (12.0)
Major or life-threatening bleeding	140/1,129 (12.4)
Valve embolization/need for a second valve	57/1,131 (5.0)
Pacemaker	173/1,130 (15.3)
Coronary obstruction	6/1,131 (0.5)
Stroke	40/1,131 (3.5)
Death	65/1,131 (5.7)
Hospitalization length (days)	7 [5-12]
Echocardiographic post-procedure	
LVEF (%)	57 ± 14
Mean aortic gradient (mmHg)	10.8 ± 6.0
Aortic valve area (cm^2)	1.56 ± 0.50
Moderate/severe mitral regurgitation	111/744 (14.9)
Moderate/severe aortic regurgitation	132/1,101 (12.0)

*Values are n (%), mean (±SD) or median [IQR]. * Following VARC-2 criteria[196]*
CKD = chronic kidney disease; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention;
STS-PROM = Society of Thoracic Surgeons predicted risk of mortality.

Table 4-2: Clinical, echocardiographic, and procedural characteristics according to valve type

Variable	Self-expandable (n = 473)	Balloon-Expandable (n = 658)	p value
Clinical variables			
Age (years)	81 ± 7	80 ± 8	0.161
Male sex	227/473 (48.0)	345/658 (52.4)	0.141
NYHA class			0.139
I-II	102/471 (21.7)	168/654 (25.7)	
III-IV	369/471 (78.3)	486/654 (74.3)	
Coronary artery disease	220/473 (46.5)	388/658 (59.0)	<0.001
Prior PCI	137/472 (29.0)	209/658 (31.8)	0.325
Prior CABG	58 (12.3)	195/658 (29.6)	<0.002
History of atrial fibrillation	103/435 (23.7)	204/645 (31.6)	0.005
Cerebrovascular disease	26/222 (11.7)	116/658 (17.6)	0.038
Peripheral vascular disease	83/473 (17.5)	181/658 (27.5)	<0.001
COPD	130/473 (27.5)	174/658 (26.4)	0.697
Porcelain aorta	33/473 (7.0)	120/658 (18.2)	<0.001
eGFR (mL/min)	60.1 ± 25.4	61.1 ± 25.6	0.500
CKD	258/472 (54.7)	350/658 (53.2)	0.625
STS-PROM (%)	9.2 ± 8.6	7.6 ± 5.6	0.003
Echocardiographic variables			
LVEF (%)	60 ± 14	54 ± 15	<0.001
Mean aortic gradient (mmHg)	48.9 ±16.3	43.2 ±16.8	<0.001
Aortic valve area (cm^2)	0.63 ± 0.23	0.65 ± 0.21	0.163
Procedural variables			
Success*	352/463 (76.0)	527/653 (80.7)	0.060
Prosthesis size (mm)			<0.001
≤ 26 mm	256/464 (55.2)	574/658 (87.2)	
> 26 mm	208/464 (44.8)	84/658 (12.8)	
Valve-in-valve	23/473 (4.9)	38/658 (5.8)	0.503
Time of procedure “skin to skin” (min)	90 [70-95)	70 [60-86]	0.009
Contrast Volume	133 [90-206]	50 [30-80]	0.001
30-day outcomes			
Major vascular complications	48/472 (10.2)	88/658 (13.4)	0.103
Major or life-threatening bleeding	49/472 (10.4)	91/657 (13.9)	0.081
Need of second valve	34 (7.2)	21/658 (3.2)	0.002
Coronary obstruction	0	6/652 (0.9)	0.044
Pacemaker	110/472 (23.3)	63/658 (9.6)	<0.001
Stroke	20/473 (4.2)	20/658 (3.0)	0.286
Death	28/473 (5.9)	43/658 (6.5)	0.711
Hospitalization length (days)	8 [5-15]	7 [5-10]	<0.001

*Values are n (%), mean (±SD) or median [IQR]. * Following VARC-2 criteria [196]*
Abbreviations as shown in Table 4-1.

4.5.1 ***Serum markers of myocardial injury post-TAVR***

The median peak values of CK-MB at each time point within the initial 72 hours post-TAVR, overall and stratified according to the approach (TA vs. non-TA) are shown in **Figure 4-1**. CK-MB levels were within normal limits in 92.0% of the patients at baseline and rose above the upper normal limit in 65.6% of patients, with a median increase of 1.6-fold (IQR: 0.9 to 2.8-fold) at 12-24 h post-TAVR, and returned to baseline values at 72 h post-TAVR. In the TA cohort, CK-MB levels rose above the upper normal values in 97.3% of patients compared with 54.4% of patients in the non-TA (TF, transaortic and trans-subclavian) cohort ($p<0.001$), with median peak values of 2.2-fold [IQR: 1.6 to 3.3-fold] and 1.2-fold [IQR: 0.7 to 2.4-fold], respectively ($p<0.001$). The percent of patients with increased CK-MB levels grouped according to the degree of rise in CK-MB post-TAVR in the entire study population and to the approach are shown in **Figure 4-2**.

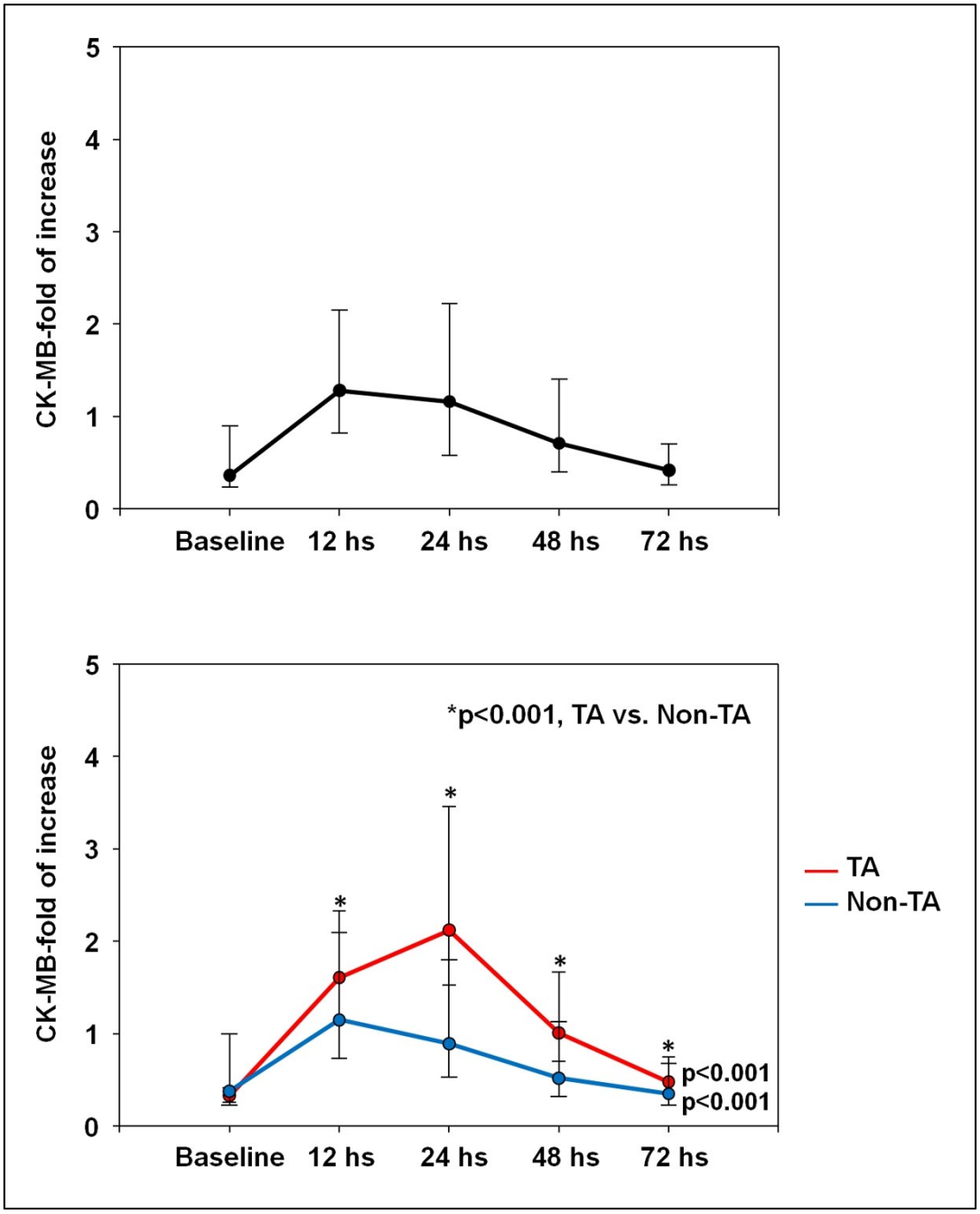

Figure 4-1: Changes in serum markers of myocardial injury following TAVR

Changes in creatine kinase-myocardial band (CK-MB) levels within the 72 h following transcatheter aortic valve replacement (TAVR) in the entire study population (A) and grouped according to the approach (transapical [TA] vs. non-TA) (B). Values are expressed as median (25th to 75th interquartile range).

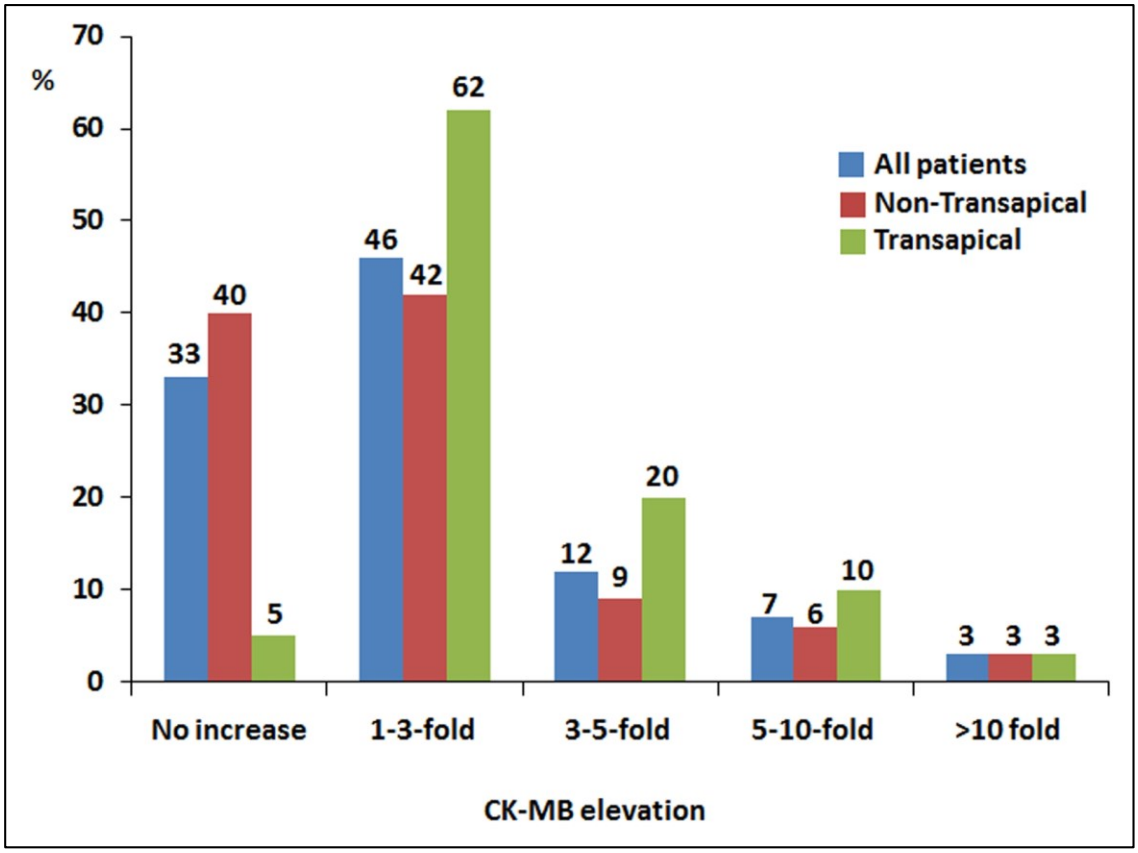

Figure 4-2: Degree of increase in CK-MB levels following TAVR

Percent of patients with increased CK-MB values according to the degree of CK-MB elevation in all patients and according to the approach (TA vs. non-TA). Abbreviations as in Figure 4-1.

4.5.2 Predictors of myocardial injury post-TAVR

The degree of myocardial injury according to baseline and procedural characteristics of the entire study population is shown in **Table 4-3**. Factors associated with a greater degree of myocardial injury in the multivariable analysis were a TA approach (R^2: 0.070, p<0.001), early TAVR experience (R^2: 0.013, p<0.001) and procedural complications such as valve embolization/need for a second valve (R^2: 0.019, p<0.001), major/life threatening bleeding (R^2: 0.007, p=0.001), and conversion to open heart surgery (R^2: 0.013, p<0.001). The degree of myocardial injury according to baseline and procedural characteristics for the non-TA cohort is shown in **Table 4-4**. Factors associated with a greater degree of myocardial injury in the multivariable analysis (non-TA cohort) were the use of a self-expandable valve (R^2: 0.039, p<0.001), valve embolization/need for a second valve (R^2: 0.009, p=0.008), major/life threatening bleeding (R^2: 0.009, p=0.003), conversion to open

heart surgery (R^2: 0.022, p<0.001) and early TAVR experience (R^2: 0.011, p=0.001). The results were similar when only the CoreValve system was evaluated in the self-expandable valve group (**Table 4-5**).

In an additional analysis, the factors associated with an increase in CK-MB levels >5 fold were also evaluated. The baseline and procedural characteristics of patients according to a CK-MB increase >5 fold are shown in **Table 4-6**. The results of the uni- and multivariable analyses for determining the predictors of a CK-MB rise >5 fold in the entire study population and the non-TA cohort are shown in **Table 4-7**. The TA approach, valve embolization/need for a second valve and conversion to open heart surgery were the independent predictors of a rise in CK-MB >5 fold post-TAVI (p<0.05 for all).

Table 4-3: Overall degree of CKMB increase following TAVR according to baseline and procedural variables (n=1,131)

Variables	CK-MB Fold	p value
Baseline variables		
Age, y		
≥ Median (82 yrs)	1.58 (0.85-2.71)	0.242
< Median (82 yrs)	1.44 (0.81-2.60)	
Sex		
Male	1.51 (0.85-2.64)	0.783
Female	1.50 (0.80-2.73)	
History of atrial fibrillation/flutter		
Yes	1.36 (0.72-2.36)	0.371
No	1.50 (0.85-2.65)	
Coronary artery disease		
Yes	1.52 (0.86-2.69)	0.549
No	1.47 (0.80-2.66)	
Prior CABG		
Yes	1.58 (0.89-2.47)	0.599
No	1.47 (0.82-2.69)	
Prior PCI		
Yes	1.52 (0.87-2.68)	0.583
No	1.50 (0.82-2.66)	
Cerebrovascular disease		
Yes	1.60 (0.85-2.95)	0.246
No	1.53 (0.83-2.70)	

Continued

Conclusion

Variables	CK-MB Fold	p value
Peripheral vascular disease		
Yes	1.75 (1.11-2.78)	<0.001
No	1.39 (0.79-2.67)	
COPD		
Yes	1.50 (0.88-2.61)	0.701
No	1.50 (0.82-2.69)	
eGFR (ml/min)		
≥ Median (60 ml/min)	1.49 (0.82-2.67)	0.471
< Median (60ml/min)	1.51 (0.84-2.67)	
STS-PROM		
≥ Median (6%)	1.53 (0.88-2.51)	0.105
< Median (6%)	1.47 (0.82-2.78)	
Porcelain aorta		
Yes	1.74 (1.08-2.82)	0.027
No	1.44 (0.80-2.64)	
Procedural variables		
Prosthesis type		
Balloon-expandable	1.53 (0.80-2.65)	0.015
Self-expandable	1.44 (0.87-2.69)	
Approach		
Transfemoral/ Transaortic/Trans-subclavian	1.20 (0.73-2.35)	<0.001
Transapical	2.20 (1.63-3.34)	
Device success		
Yes	1.50 (0.83-2.63)	0.029
No	1.52 (0.89-2.85)	
Life-threatening/major bleeding		
Yes	2.27 (1.16-3.83)	<0.001
No	1.41 (0.79-2.44)	
Major vascular complications		
Yes	1.82 (0.95-3.24)	0.001
No	1.46 (0.81-2.60)	
Valve embolization/ need for a second valve		
Yes	2.39 (1.19-6.44)	<0.001
No	1.48 (0.82-2.60)	
Conversion to surgery		
Yes	4.65 (1.64-7.76)	<0.001
No	1.48 (0.82-2.64)	
Coronary obstruction		
Yes	7.46 (3.27-9.02)	<0.001
No	1.50 (0.83-2.64)	
Experience		
Early	1.81 (0.98-3.19)	<0.001
Late	1.19 (0.72-2.16)	

Abbreviations as shown in Table 4-1.

Table 4-4: Overall degree of CKMB increase following TAVR in the non-transapical cohort (transfemoral, transaortic and trans-subclavian) according to the baseline and procedural variables

Variables	CK-MB Fold	p value
Baseline variables		
Age, y		
≥ Median (82 yrs)	1.21 (0.73-2.36)	0.713
< Median (82 yrs)	1.19 (0.73-2.35)	
Sex		
Male	1.19 (0.73-2.40)	0.607
Female	1.22 (0.73-2.27)	
History of atrial fibrillation/flutter		
Yes	1.04 (0.64-1.94)	0.113
No	1.25 (0.75-2.29)	
Coronary artery disease		
Yes	1.17 (0.72-2.37)	0.978
No	1.27 (0.75-2.34)	
Prior CABG		
Yes	1.11 (0.67-2.29)	0.923
No	1.25 (0.75-2.36)	
Prior PCI		
Yes	1.19 (0.72-2.27)	0.540
No	1.22 (0.73-2.37)	
Cerebrovascular disease		
Yes	1.19 (0.70-2.29)	0.819
No	1.13 (0.70-2.36)	
Peripheral vascular disease		
Yes	1.28 (0.73-2.27)	0.215
No	1.19 (0.73-2.36)	
COPD		
Yes	1.16 (0.72-2.09)	0.265
No	1.24 (0.73-2.39)	
eGFR (ml/min)		
≥ Median (60 ml/min)	1.17 (0.75-2.37)	0.635
< Median (60ml/min)	1.25 (0.69-2.34)	
STS-PROM		
≥ Median (6%)	1.15 (0.69-2.11)	0.051
< Median (6%)	1.25 (0.75-2.45)	
Porcelain aorta		
Yes	1.19 (0.75-1.94)	0.363
No	1.20 (0.73-2.37)	

Continued

Conclusion

Variables	CK-MB Fold	p value
Procedural variables		
Prosthesis type		
Balloon-expandable	0.99 (0.65-1.97)	<0.001
Self-expandable	1.42 (0.86-2.69)	
Device success		
Yes	1.19 (0.73-2.29)	0.039
No	1.33 (0.74-2.66)	
Life-threatening/major bleeding		
Yes	2.00 (0.94-3.60)	<0.001
No	1.17 (0.70-2.20)	
Major vascular complications		
Yes	1.68 (0.90-2.98)	<0.001
No	1.17 (0.70-2.25)	
Valve embolization/ need for a second valve		
Yes	1.62 (1.04-6.45)	<0.001
No	1.19 (0.72-2.28)	
Conversion to surgery		
Yes	4.41 (1.53-7.28)	<0.001
No	1.19 (0.73-2.29)	
Coronary obstruction		
Yes	5.37 (3.09-28.6)	<0.001
No	1.19 (0.73-2.32)	
Experience		
Early	1.39 (0.81-2.86)	<0.001
Late	1.10 (0.68-1.98)	

Abbreviations as shown in Table 4-1.

Table 4-5: Uni- and multivariate analyses for the prediction of CK-MB rise in patients treated with the CoreValve or Edwards SAPIEN valve systems

	Univariate R^2	p value	Multivariate Model R^2	p value
Overall population*				
Transapical	0.068	<0.001	0.070	<0.001
Early experience	0.027	<0.001	0.013	<0.001
Conversion to surgery	0.018	<0.001	0.013	<0.001
Valve embolization/second valve	0.025	<0.001	0.019	<0.001
Major or Life threatening bleeding	0.026	<0.001	0.007	0.001
Non-transapical cohort*				
CoreValve	0.036	<0.001	0.039	<0.001
Early experience	0.015	<0.001	0.011	0.001
Conversion to surgery	0.018	<0.001	0.022	<0.001
Major or Life threatening bleeding	0.016	<0.001	0.009	0.003
Valve embolization/second valve	0.023	<0.001	0.007	0.009
Transfemoral only cohort*				
CoreValve	0.038	<0.001	0.041	<0.001
Early experience	0.015	<0.001	0.009	0.004
Conversion to surgery	0.019	<0.001	0.023	<0.001
Major or Life threatening bleeding	0.019	<0.001	0.012	0.001
Diabetes	0.008	0.009	0.008	0.009
Valve embolization/second valve	0.023	<0.001	0.007	0.012

**Adjusting for the baseline value in CKMB*
Abbreviations as shown in Table 4-1.

Table 4-6: Clinical, echocardiographic, and procedural characteristics according to the increase in CK-MB

Variable	≤ 5-Fold (n=1.022)	> 5-Fold (n=107)	p value
Clinical variables			
Age (years)	80 ± 7	81 ± 7	0.564
Male sex	522 (51.1)	50 (45.9)	0.302
NYHA class			0.595
I-II	247 (24.3)	24 (22.0)	
III-IV	769 (75.7)	85 (78.0)	
Coronary artery disease	547 (53.5)	61 (56.0)	0.627
Prior PCI	317 (31.0)	29 (26.6)	0.339
Prior CABG	231 (22.6)	22 (20.2)	0.565
History of atrial fibrillation	275 (28.0)	32 (32.3)	0.367
Cerebrovascular disease	121 (15.3)	21 (23.3)	0.050
Peripheral vascular disease	237 (23.2)	27 (24.8)	0.711
COPD	282 (27.6)	22 (20.2)	0.097
Porcelain aorta	141 (13.8)	12 (11.0)	0.419
eGFR (mL/min)	60.7 ± 25.4	60.6 ± 26.8	0.987
CKD	548 (53.6)	69 (56.6)	0.4701
STS-PROM (%)	8.1 ± 6.6	8.9 ± 8.5	0.327
Echocardiographic variables			
LVEF (%)	56 ± 15	60 ± 13	0.022
Mean aortic gradient (mmHg)	45.2 ± 16.8	49.1 ± 16.7	0.022
Aortic valve area (cm^2)	0.64 ± 0.22	0.66 ± 0.22	0.402
Procedural variables			
Success*	804 (79.8)	75 (69.4)	0.013
Prosthesis type			0.367
Balloon-expandable	599 (58.6)	59 (54.1)	
Self-Expandable	423 (41.4)	50 (45.9)	
Prosthesis size (mm)			0.733
≤ 26 mm	746 (73.6)	84 (77.8)	
> 26 mm	267 (26.4)	27 (22.1)	
Early experience	500 (48.9)	60 (55.6)	0.190
Valve-in-valve	57 (5.6)	4 (3.7)	0.402
Time of procedure “skin to skin” (min)	70 [60-85]	92 [75-125]	<0.001
30-day outcomes			
Major vascular complications	117 (11.5)	19 (17.4)	0.069
Major or life-threatening bleeding	116 (11.4)	24 (22.2)	0.001
Need of second valve	40 (3.9)	15 (12.2)	<0.001
Pacemaker	149 (14.6)	24 (22.0)	0.041
Coronary obstruction	3 (0.3)	3 (2.8)	0.014
Stroke	29 (2.8)	11 (10.1)	<0.001
Death	43 (4.2)	22 (20.2)	<0.001
Hospitalization length (days)	7 [5-11]	8 [6-14]	0.033

*Values are n (%), mean (±SD) or median [IQR]. * Following VARC-2 criteria [196]*
Abbreviations as shown in Table 4-1.

Table 4-7: Univariate and multivariate analyses of CK-MB increase >5-Fold following TAVR

	Univariate	p value	Multivariate Model	p value
	OR (95% CI)		OR (95% CI)	
Overall population*				
TA approach	4.86 (2.35-10.0)	<0.001	5.70 (2.55-12.70)	<0.001
Device success	0.49 (0.31-0.77)	0.002	-	-
Life-threatening/major bleeding	2.69 (1.59-4.53)	<0.001	-	-
Major vascular complications	1.85 (1.01-3.38)	0.047	-	-
Valve embolization/Need second valve	5.05 (2.70-9.45)	<0.001	2.83 (1.21-6.61)	0.016
Stroke	4.25 (1.97-9.18)	<0.001	-	-
Conversion to surgery	13.06 (5.04-33.80)	<0.001	7.85 (2.53-24.32)	<0.001
Coronary obstruction	14.72 (2.91-74.33)	0.001	-	-
Non-transapical cohort*				
Device success	0.51 (0.29-0.88)	0.015	-	-
Life-threatening/major bleeding	2.31 (1.19-4.48)	0.013	-	-
Valve embolization/Need second valve	4.57 (2.17-9.61)	<0.001	3.09 (1.13-8.40)	0.028
Conversion to surgery	12.32 (3.90-38.89)	<0.001	6.90 (1.90-24.97)	0.003
Coronary obstruction	24.87 (2.58-239.84)	0.006	-	-

**Adjusting for the baseline value in CKMB*
Abbreviations as shown in Table 4-1.

4.5.3 Clinical impact of myocardial injury

A total of 65 patients (5.7%) had died at 30 days post-TAVR, and a further 328 patients died (29.0%) at a median follow-up of 21 [8-36] months post-TAVR. A total of 191 patients died from cardiac causes (16.9%, 58.2% of the deaths). The variables associated with a higher risk of 30-day mortality, cumulative late overall and cardiac mortality are shown in **Table 4-8**. A greater increase in CK-MB levels was associated with increased 30-day mortality (OR: 2.26 for each increase of 1-fold above upper limit values, 95% CI: 1.76-2.90, p<0.001), and remained independently associated with greater 30-day mortality in the multivariate analysis (OR: 1.78, 95% CI: 1.30-2.44, p<0.001). Greater increments in CK-MB levels post-TAVR were also independently associated with late cumulative mortality (HR: 1.32 for each increase of 1-fold increase above the upper limit values, 95% CI: 1.12-1.54, p<0.001) and late cardiac mortality (HR: 1.39, 95% CI: 1.12-1.74, p=0.003). In a

subanalysis of the TF and TA cohorts, a greater increase in CK-MB levels remained as an independent predictor of 30-day and late mortality in the TF cohort ($p<0.001$ for both; **Table 4-9**), but not in the TA cohort (**Table 4-10**).

Kaplan-Meier overall and cardiac survival curves according to differing degrees of CK-MB increments (<1, 1-3, 3-5 and >5 fold) are shown in **Figures 4-3** and **4-4**, for the overall and non-TA cohorts, respectively. Any increase in CK-MB levels (<1-fold vs. >1-fold) was associated with a higher mortality ($p<0.001$), and there was a stepwise increase in late mortality according to the various degrees of CK-MB elevation following TAVR ($p <0.001$). In those patients with increased CK-MB levels, a >5-fold increase was associated with a higher overall (33.6% vs. 22.9% at 2 years, $p<0.001$), and cardiac mortality (25.8% vs. 14.1%, $p<0.001$). In the non-TA cohort, a >5-fold increase in CK-MB levels was also associated with increased overall (30.6% vs. 20.1%, $p<0.001$) and cardiac mortality (24.6% vs. 12.1%, $p<0.001$).

The correlation between the increase in CK-MB levels and the changes in LVEF between baseline and follow-up (Δ) for the entire population are shown in **Figure 4-5**. The increase in CK-MB levels following the procedure demonstrated a weak, but significant negative impact in changes of LVEF between baseline and follow-up ($r = -0.17$, $p <0.001$). Also, the patients presenting with either unchanged or reduced LVEF 6-12 months post-TAVR compared to baseline exhibited greater CK-MB levels as compared with those patients whose LVEF significantly improved following TAVR ($p=0.004$; **Figure 4-6**).

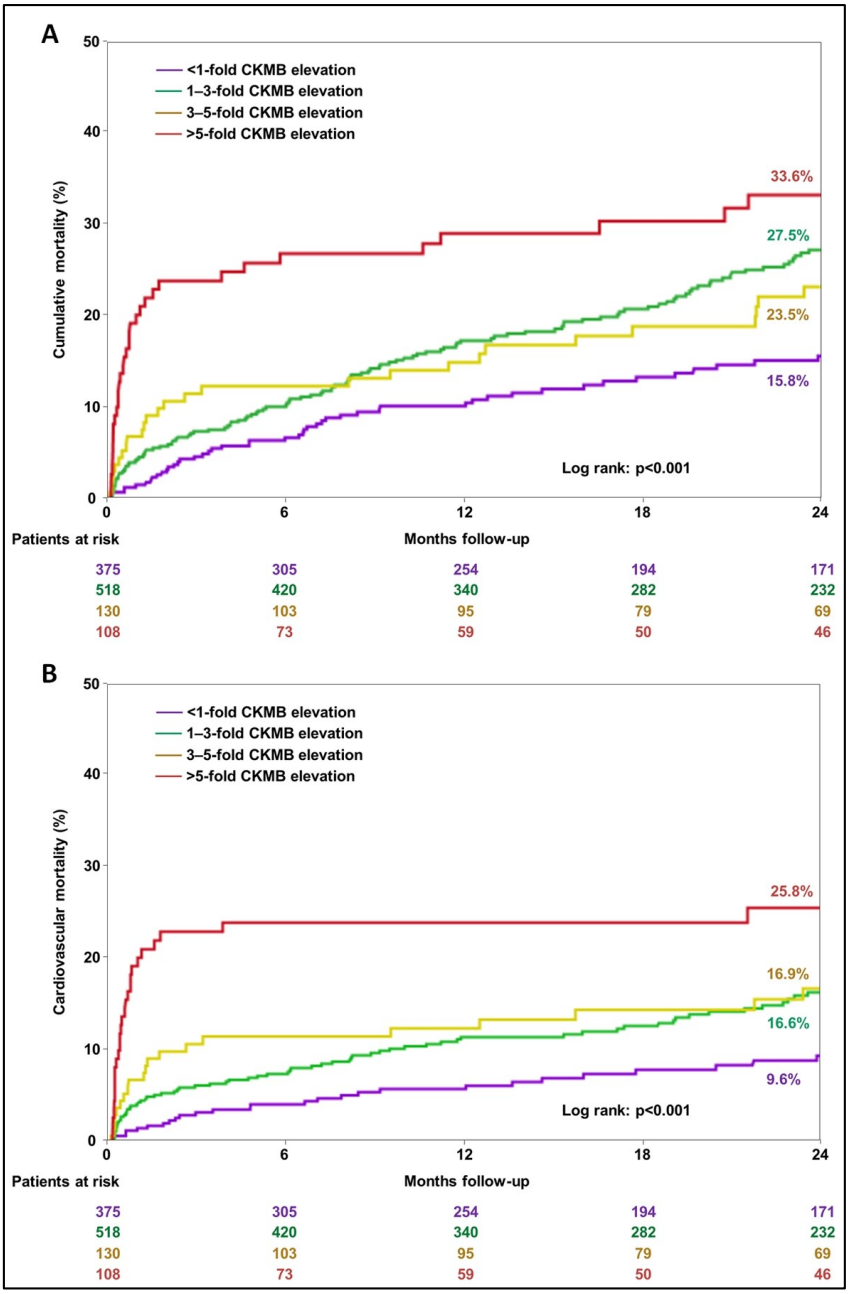

Figure 4-3: Kaplan-Meier mortality curves in all patients

Kaplan-Meier mortality curves for cumulative overall death (A), and for cardiovascular death (B), according to the percentiles of CK-MB peak of increase following TAVR. Abbreviations as in Figure 1. For group comparisons in (A) group<1 vs. groups 1-3, 3-5 and >5, p<0.05; in (B) group 1 vs. groups 1-3, 3-5 and >5, p<0.01

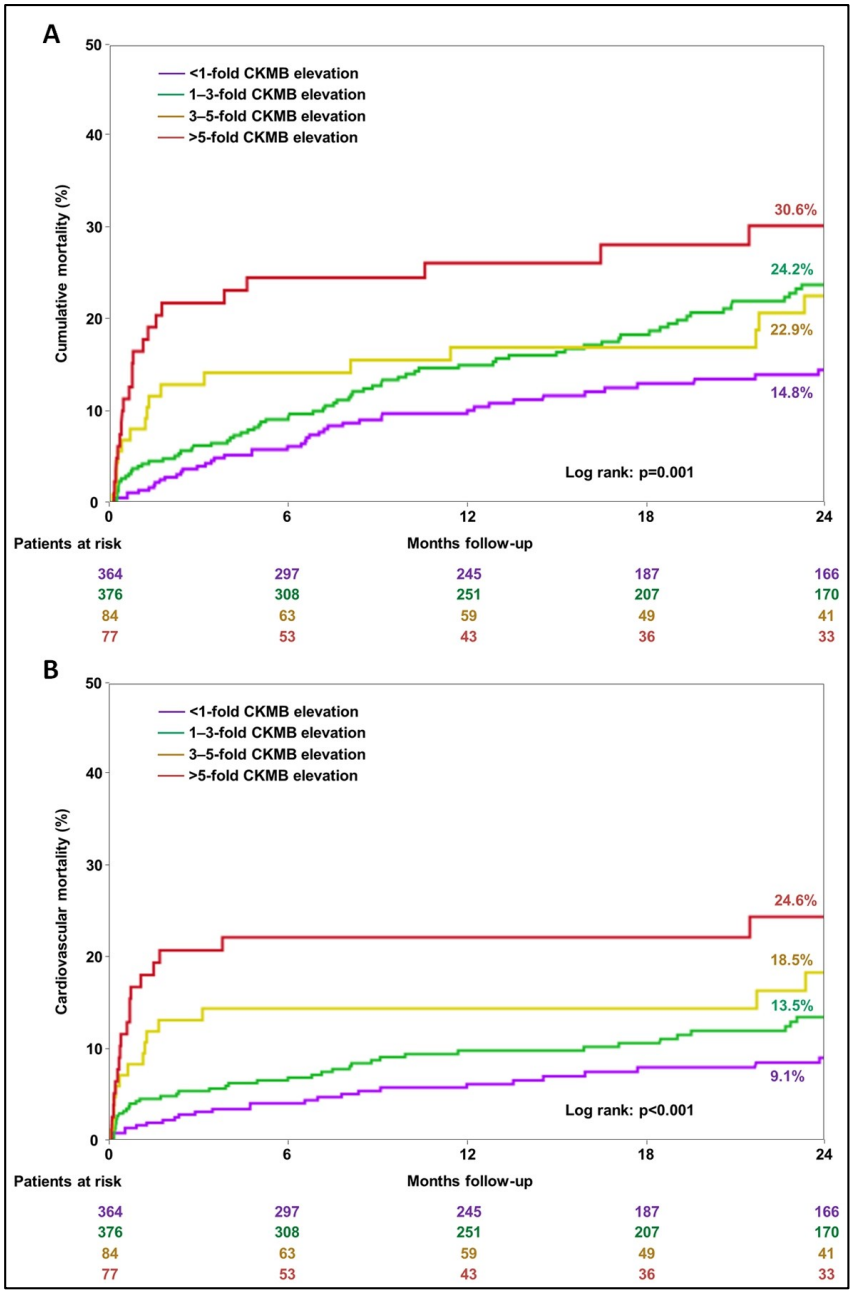

Figure 4-4: Kaplan Meier survival curves in non-TA patients

Kaplan-Meier mortality curves for cumulative overall death (A), and for cardiovascular death (B), according to the percentiles of CK-MB peak of increase following TAVR. Abbreviations as in Figure 1. For group comparisons in (A) group<1 vs. groups 1-3, 3-5 and >5, p<0.05; in (B) group 1 vs. groups 3-5 and >5, p<0.01

Table 4-8: Univariate and multivariate analyses of clinical outcomes post-TAVR

	Univariate	p value	Multivariate Model	p value
	OR/HR (95% CI)		OR/HR (95% CI)	
30-day mortality (n=65)				
Coronary artery disease	0.75 (0.45-1.25)	0.275	-	-
Peripheral vascular disease	1.84 (1.04-3.26)	0.035	-	-
LVEF	0.98 (0.97-0.99)	0.041	0.98 (0.96-0.99)	0.026
Early experience	1.99 (1.17-3.38)	0.011	-	-
Major or life-threatening bleeding	5.83 (3.38-10.04)	<0.001	3.07 (1.57-5.99)	0.001
Stroke	3.97 (1.64-9.60)	0.002	-	-
Acute kidney injury	10.01 (5.66-17.7)	<0.001	6.11 (3.32-11.22)	<0.001
CK-MB elevation*	2.26 (1.76-2.90)	<0.001	1.71 (1.25-2.35)	<0.001
Cumulative mortality (n=328)				
Male sex	1.27 (1.02-1.60)	0.036	-	-
NYHA class III-IV	1.92 (1.40-2.64)	<0.001	1.85 (1.29-2.66)	<0.001
History of atrial fibrillation	1.82 (1.44-2.30)	<0.001	1.69 (1.30-2.20)	<0.001
Coronary artery disease	1.18 (0.94-1.48)	0.157	-	-
Cerebrovascular disease	1.36 (1.02-1.82)	0.035	-	-
Peripheral vascular disease	1.46 (1.13-1.90)	0.004	-	-
COPD	1.52 (1.20-1.93)	<0.001	1.42 (1.08-1.87)	0.01
TA approach	1.57 (1.15-2.15)	0.005	-	-
Early experience	1.29 (0.98-1.69)	0.060	-	-
Life-threatening/major bleeding	2.01 (1.54-2.64)	<0.001	-	-
Stroke	2.05 (1.30-3.23)	0.002	-	-
Acute kidney injury	2.67 (2.09-3.42)	<0.001	2.12 (1.60-2.80)	<0.001
CK-MB elevation*	1.42 (1.26-1.62)	<0.001	1.32 (1.12-1.54)	<0.001
Cumulative cardiac mortality (n=191)				
Male sex	1.36 (1.01-1.83)	0.042	-	-
NYHA class III-IV	1.73 (1.16-2.60)	0.008	-	-
History of atrial fibrillation	1.62 (1.18-2.21)	0.003	-	-
Coronary artery disease	0.99 (0.74-1.33)	0.959	-	-
Peripheral vascular disease	1.55 (1.11-2.15)	0.009	-	-
COPD	1.54 (1.13-2.09)	0.006	1.68 (1.15-2.45)	0.007
LVEF	0.99 (0.98-0.99)	0.022	0.99 (0.98-0.99)	0.039
Moderate/Severe mitral regurgitation	1.56 (1.07-2.27)	0.022	-	-
TA approach	1.81 (1.20-2.71)	0.004	-	-
Early experience	1.48 (1.05-2.08)	0.024		
Life-threatening/Major bleeding	2.29 (1.62-3.22)	<0.001	1.75 (1.14-2.69)	0.010
Stroke	2.79 (1.64-4.75)	<0.001	-	-
Acute kidney injury	3.73 (2.74-5.07)	<0.001	3.06 (2.07 - 4.52)	<0.001
CK-MB elevation*	1.60 (1.37-1.87)	<0.001	1.39 (1.12-1.74)	0.003

Abbreviations as shown in Table 4-1.
**For every 1-fold of increase of CK-MB levels in relation to the upper limit.*

Table 4-9: Univariable and multivariable analyses of the predictors of poorer outcomes post-TAVR in the transfemoral cohort

	Univariate	p value	Multivariate Model	p value
	OR/HR (95% CI)		OR/HR (95% CI)	
30-day mortality (n=40)				
LVEF	0.98 (0.96-0.99)	0.031	0.97 (0.94-0.99)	0.031
Early experience	2.08 (1.08-4.00)	0.028	2.65 (1.17-5.98)	0.019
Life-threatening/major bleeding	5.10 (2.47-10.55)	<0.001	4.14 (1.75-9.76)	0.001
Acute kidney injury	8.72 (4.27-17.8)	<0.001	5.00 (2.27-10.9)	<0.001
CK-MB elevation*	1.13 (1.07-1.19)	<0.001	1.71 (1.17-2.51)	0.006
Cumulative mortality (n=199)				
NYHA class III-IV	1.86 (1.25-2.77)	0.002	1.82 (1.19-2.80)	0.006
History of atrial fibrillation	2.01 (1.47-2.73)	<0.001	1.93 (1.40-2.67)	<0.001
Coronary artery disease	0.99 (0.75-1.34)	0.989	-	-
COPD	1.42 (1.02-1.98)	0.037	1.44 (1.01-2.04)	0.044
Life-threatening/major bleeding	1.55 (1.01-2.38)	0.046	-	-
Stroke	2.92 (1.66-5.12)	<0.001	2.33 (1.16-4.67)	0.017
Acute kidney injury	2.56 (1.84-3.56)	<0.001	2.42 (1.72-3.42)	<0.001
CK-MB elevation*	1.33 (1.13-1.56)	<0.001	1.22 (1.03-1.45)	0.025
Cumulative cardiac mortality (n=113)				
NYHA class III-IV	1.62 (0.98-2.66)	0.058	-	-
History of atrial fibrillation	1.73 (1.14-2.62)	0.009	1.65 (1.06-2.56)	0.025
Coronary artery disease	0.97 (0.66-1.42)	0.861	-	-
COPD	1.65 (1.09-2.52)	0.019	1.91 (1.21-3.00)	0.006
Life-threatening/major bleeding	1.80 (1.05-3.08)	0.032	-	-
Stroke	3.52 (1.75-7.10)	<0.001	2.50 (1.02-6.13)	0.046
Acute kidney injury	3.28 (2.16-4.99)	<0.001	2.73 (1.62 - 4.59)	<0.001
CK-MB elevation*	1.50 (1.23-1.84)	<0.001	1.34 (1.08-1.68)	0.009

Abbreviations as shown in Table 4-1.
*For every 1-fold of *increase* of CK-MB levels in relation to the upper limit.

Table 4-10: Univariable and multivariable analyses of the predictors of poorer outcomes post-TAVR in the transapical cohort

	Univariate		Multivariate Model	
	OR/HR (95% CI)	**p value**	**OR/HR (95% CI)**	**p value**
30-day mortality (n=19)				
Major or life-threatening bleeding	7.25 (2.68-19.62)	<0.001	3.54 (1.15-10.9)	0.027
Acute kidney injury	10.64 (3.78-29.97)	<0.001	7.05 (2.31-21.55)	<0.001
CK-MB elevation*	2.39 (1.35-4.21)	0.003	-	-
Cumulative mortality (n=112)				
Male sex	1.62 (1.10-2.40)	0.015	-	-
NYHA class III-IV	1.88 (0.98-3.62)	0.059	-	-
History of atrial fibrillation	1.61 (1.07-2.41)	0.023	-	-
Coronary artery disease	1.31 (0.85-2.01)	0.215	-	-
Cerebrovascular disease	1.46 (0.97-2.22)	0.071	-	-
COPD	1.42 (0.97-2.08)	0.076	-	-
Life-threatening/major bleeding	2.21 (1.49-3.29)	<0.001	1.70 (1.09-2.64)	0.017
Acute kidney injury	2.43 (1.62-3.65)	<0.001	1.73 (1.09-2.74)	0.019
CK-MB elevation*	1.28 (0.95-1.73)	0.110	-	-
Cumulative cardiac mortality (n=68)				
Early experience	2.88 (1.02-8.14)	0.045	-	-
Life-threatening/Major bleeding	2.38 *1.45-3.93)	<0.001	1.85 (1.10-3.10)	0.021
Acute kidney injury	3.22 (1.95-5.32)	<0.001	2.73 (1.62 - 4.59)	<0.001
CK-MB elevation*	1.31 (0.91-1.90)	0.137	-	-

Abbreviations as shown in Table 4-1.
**For every 1-fold of increase of CK-MB levels in relation to the upper limit.*

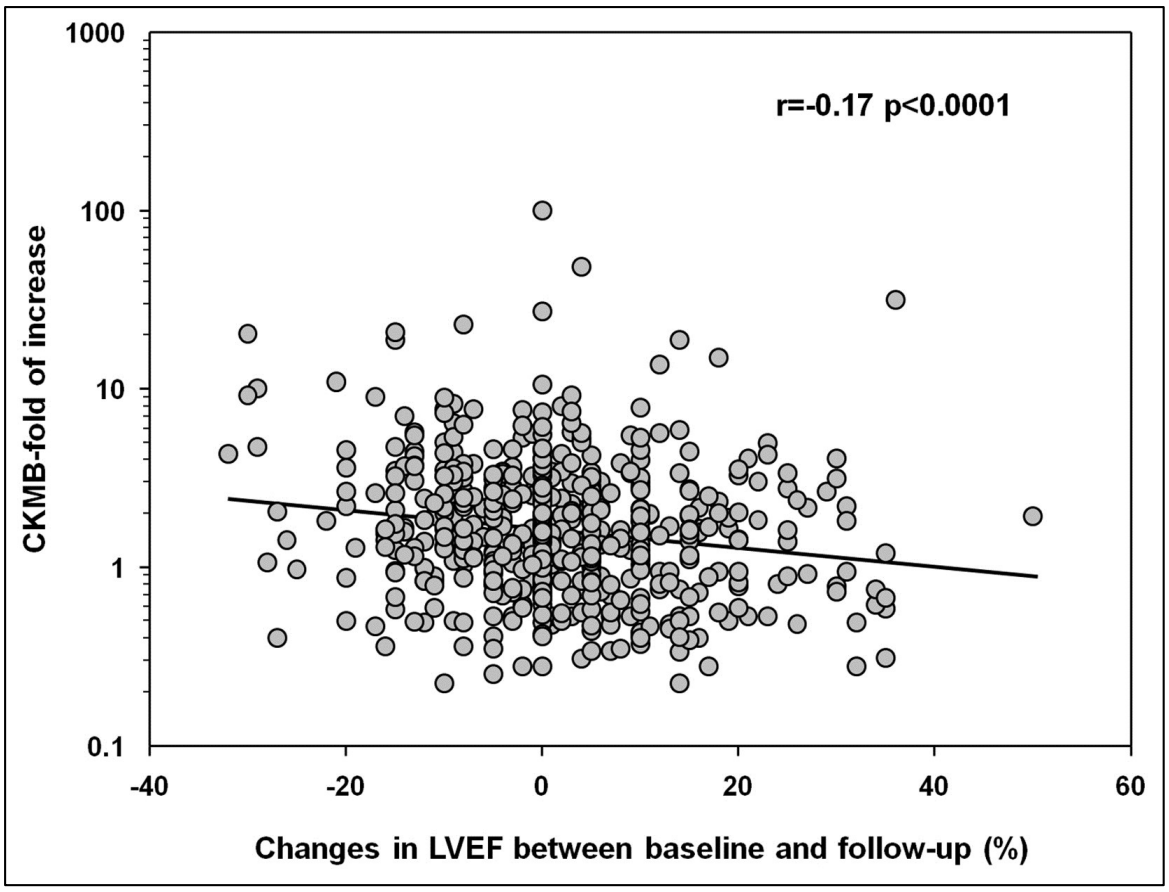

Figure 4-5: Myocardial injury and LVEF changes following TAVR

Relationship between the maximal increase in CK-MB levels and the changes in left ventricular ejection fraction (LVEF) following TAVR. Abbreviations as in Figure 4-1.

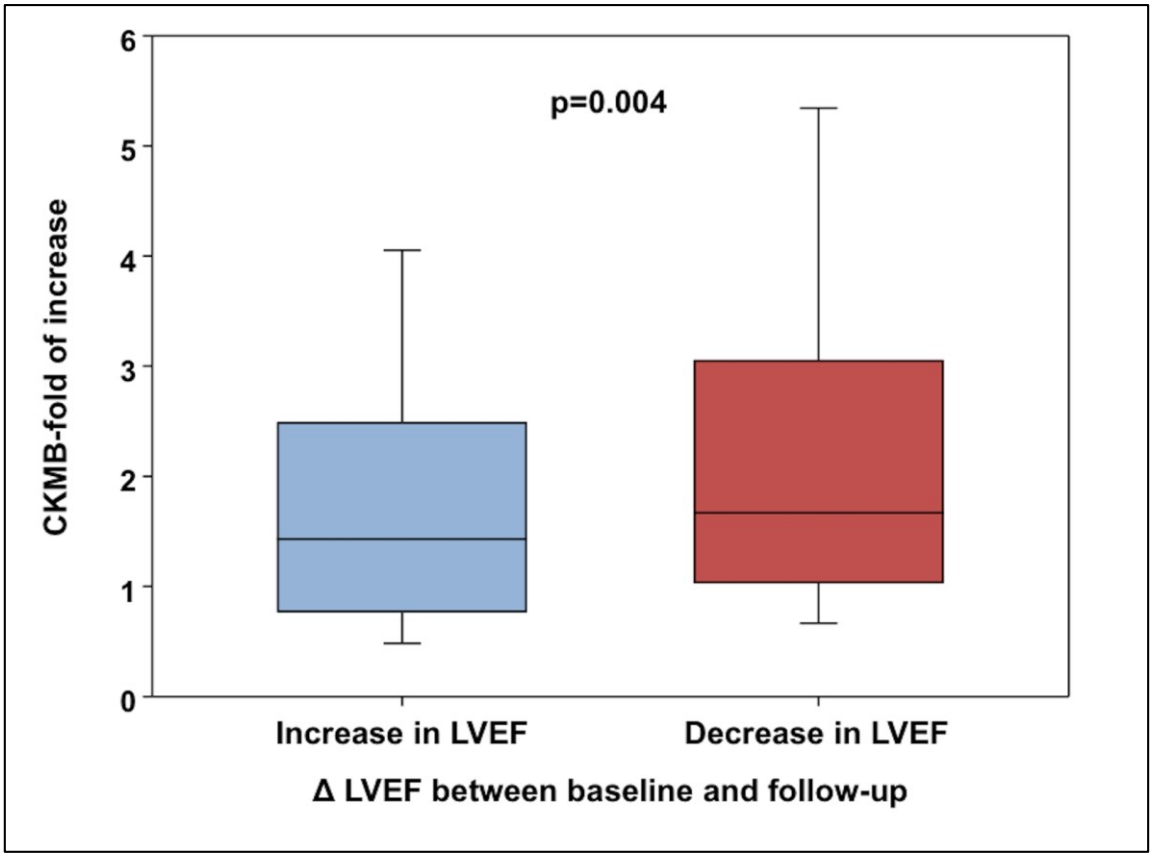

Figure 4-6: Absolute change (Δ) in LVEF according to the CK-MB peak after TAVR

Median levels of peak in CK-MB after TAVR according to the increase or decrease in left ventricular ejection fraction (LVEF) between the baseline and 6- to 12 –month echocardiography. Values are expressed as median (25th to 75th interquartile range). Abbreviations as in Figure 4-1 and 4-5.

4.6 DISCUSSION

The present large-scale real-world study demonstrates that some degree of myocardial injury, as determined by a post-procedural rise in CK-MB levels, is common following TAVR. The use of the TA approach and major procedural complications such as valve embolization/need for a second valve, major/life threatening bleeding and conversion to open surgery were the most important factors associated with a larger increase in CK-MB levels. Greater degree of myocardial injury was independently associated with poorer outcomes as determined by an increase in 30-day and late mortality, as well as impaired LVEF at 6- to 12-month follow-up. Any increase in CK-MB levels following TAVR was associated with poorer clinical outcomes, with a stepwise increase in mortality according to the various degrees of CK-MB elevation (**Figure 4-7; Central Illustration**).

4.6.1 Incidence and degree of myocardial injury post-TAVR

The vast majority of patients undergoing SAVR experience some degree of myocardial injury reflected by rise in CK-MB levels, and an increase >5-fold the upper normal limits occurs in nearly 20% of these patients.[223,224] While avoiding the need for cardiopulmonary bypass translates into a lesser degree of myocardial injury during TAVR, up to two-thirds of patients undergoing TAVR had significant elevation in CK-MB levels post-procedure, and the frequency of CK-MB increase > 3-fold and ≥ 5-fold the upper normal limits occurred in 21.0% and 9.6% of cases respectively. These findings appear similar to those observed during percutaneous coronary intervention.[225]

In accordance with prior smaller studies, a TA approach was found to be one of the most important factors determining a higher degree of myocardial injury post-TAVR in the present study.[167,216] TA-TAVR involves puncturing and introducing a large bore catheter through the LV apex, and this has been postulated as the primary reason for biomarker elevations in such instances.[167,226] Additionally, this has been related to new myocardial necrosis as evaluated by CMR, involving ~5% of the myocardium at the apex,[226] leading to apical wall abnormalities.[220,226,227] Several studies have found the TA approach to be independently associated with mortality,[139,228] and a recent study identified that this approach correlates with late mortality secondary to advanced heart failure.[212] The results of this study highlight the importance of myocardial injury as the potential pathophysiological link between TA approach and increased mortality, outlining the importance of minimizing myocardial damage in such cases (i.e. reducing sheath size, avoiding myocardial tears, etc.).

Major peri-procedural complications such as major/life threatening bleeding, valve embolization/need for a second valve and conversion to open heart surgery were also associated with a greater increase in CK-MB levels. Prior studies have shown the negative clinical impact of these complications following TAVR.[203,229] The present study suggests that an association with a higher degree of myocardial injury may further contribute to poorer outcomes in such patients. While the link between open heart surgery and myocardial injury is obvious, one may hypothesize that periods of severe hypotension, longer procedures with increased ischemic times and increased device manipulation may have contributed to the increased levels of CK-MB levels in patients suffering from major bleeding or device

malpositioning/embolization. An early stage in the TAVR experience was also associated with a greater CK-MB increase, suggesting a role of both the learning curve and the advancements in the TAVR technology on the degree of myocardial injury post-TAVR.

Apart from major periprocedural complications, the use of a self-expandable valve was also associated with a mild but significant higher rise in CK-MB levels in the non-TA cohort. Similar to the results reported in the CHOICE (Comparison of Balloon-Expandable vs Self-expandable Valves in Patients Undergoing Transcatheter Aortic Valve Replacement) trial,[230] patients receiving a self-expandable valve exhibited longer procedural times, received a higher volume of contrast agent and had an increased incidence of valve embolization/need for a second valve compared to the balloon-expandable group. This may partially explain the differences in myocardial injury between valve types, but given the non-randomized nature of the study, future studies are warranted to confirm and better understand the mechanisms associated with these results. Importantly, no differences between valve types were observed in those patients with the highest increase (>5-fold) in CK-MB levels.

4.6.2 Clinical impact of peri-procedural TAVR-related myocardial injury

The occurrence and degree of myocardial injury following cardiac surgery and percutaneous coronary intervention have been associated with poorer short and mid-term clinical outcomes.[221,231] Importantly, the degree of CK-MB increase and the associated worse outcomes formed the basis for defining the occurrence of clinically relevant myocardial infarction following such procedures.[221] This is of major clinical relevance considering the changes in the acute and late management of such patients, as compared with those without peri-procedural myocardial infarction.

Following a similar theme, prior studies in the TAVR field have demonstrated increased short- and mid-term mortality to be associated with greater rise in biomarkers of myocardial injury following the procedure.[167,196,214,216,232] However the limited number of patients/events in most studies precluded a formal validation of a threshold of biomarker elevation representing a “clinically relevant” myocardial infarction following TAVR. Our study confirms the major impact of myocardial injury as determined by CK-MB rise post-TAVR on 30-day and 1-year overall mortality, and extends prior observations by showing an increased risk of late (>1-year) overall and cardiac mortality in relation with higher

degrees of myocardial injury. In accordance with prior studies,[233] any increase in CK-MB values associated with poorer outcomes, with an apparent stepwise increase in late mortality according to the various degrees of CK-MB elevation following TAVR. Interestingly, according to the VARC-2 criteria for defining clinically relevant myocardial infarction,[196] a >5-fold CK-MB increase threshold was associated with a higher mortality rate. This suggests that patients with greater degrees of myocardial injury could potentially benefit from both a closer clinical follow-up as well as medications for preventing adverse LV remodeling in such cases (i.e. ACE inhibitors, angiotensin-receptor blockers, beta-blockers, spironolactone). However, this needs further prospective evaluation in future studies. Interestingly, the correlation between a greater increase in CK-MB levels and mortality post-TAVR was apparent in the TF but not in the TA approach cohort, though the relatively low number of patients in the TA group might partially explain such results.

Greater elevations in CK-MB levels were also correlated with impaired LV function at mid-term follow-up, which is consistent with previous studies.[167,226,227] Therefore, it is important to keep in mind that strategies for reducing the ensuing myocardial injury in TAVR patients, especially in those patients with impaired baseline LVEF pre-TAVR, are of utmost importance.[227,233] Accordingly, it has been suggested that in those patients with low LVEF deemed unsuitable for TF-TAVR, other alternative approaches such as transaortic, subclavian or transcarotid would be preferable over the TA approach. Improvements in the design of the TA delivery systems for minimizing apical trauma should also be encouraged.[227,228] Additionally, future enhancements to the TF delivery system with easier to use transcatheter valves, may facilitate deployment with shorter rapid-pacing runs and lower ischemic times.[234]

*4.6.3 **Study Limitations***

Although the present analysis comprises a large cohort of TAVR-patients with systematic cardiac biomarker evaluation, the patients were however not randomized according to approach and valve type. Consequently, the multivariable analysis may not have accounted for the unmeasured between-group confounders unduly influencing study conclusions. The participating centers used different assays for measuring CK-MB levels and this inter-center variability may have influenced the results. This was partially compensated by the

use of a relative increase in CK-MB levels with respect to the upper normal limits (fold or increase) as recommended by VARC-2.[196] Also, a hierarchical analysis was performed to account for between-center/country variance. Echocardiographic data was based on each site report, and no central echocardiographic core laboratory analysis was available. All centers were encouraged to calculate the LVEF via the Simpson's method in order to improve accuracy and reduce variability.[235] While data on prior coronary artery disease and need for revascularization was complete, no data was available on the completeness of coronary revascularization prior to TAVR. The influence of this factor on myocardial injury post-TAVR will need to be determined in future studies. Additionally, one might argue that cardiac troponins should be the preferred biomarkers for the diagnosis of myocardial injury because of their higher sensitivity and specificity as compared to CK-MB.[222,236,237] Nonetheless, acute and chronic comorbidities frequently lead to small elevations in troponin levels at baseline, that together with the recently developed ultra and highly-sensitive assays, along with its diverse analytical sensitivity,[238] will likely lead to a myriad of challenges to define a precise cutoff of myocardial injury in such patients according to troponin.[236] Finally, the early mortality rate observed in our study was relatively high compared to more recent TAVR series. Future studies in the context of TAVR, with the systematic measurement of CK-MB and troponin, are necessary to further evaluate its prognostic significance and confirm the most appropriate cut-off to predict worse clinical outcomes, also with valve types other than Sapien and CoreValve systems, including the latest generation of transcatheter valves.

4.7 CONCLUSION

In conclusion, myocardial injury as determined by CK-MB rise is frequent among TAVR patients, especially with TA-TAVR and in those patients suffering from major procedural complications. These results support the use of alternative approaches to TA, particularly in some patients at risk like those with impaired LVEF. Also, reducing the size of transfemoral sheaths, increasing heart team experience and the retrievability/repositionability properties of most of the more recent generation transcatheter valves should be associated with a significant reduction in bleeding and malpositioning/embolization complications, and this may translate into a reduction in the degree of myocardial injury post-TAVR. This however will need to be determined in future studies. A higher degree of myocardial injury was associated with poorer acute and late outcomes. Although any increase in CK-MB levels associates with poorer clinical outcomes, there is a stepwise increase in late mortality according to the various degrees of CK-MB elevation. In line with the VARC-2 definition for clinically relevant myocardial infarction post-TAVR, a CK-MB rise >5-fold the upper normal limits related with incremental mortality rates, although the best cutoff for predicting mortality should be confirmed in future studies.

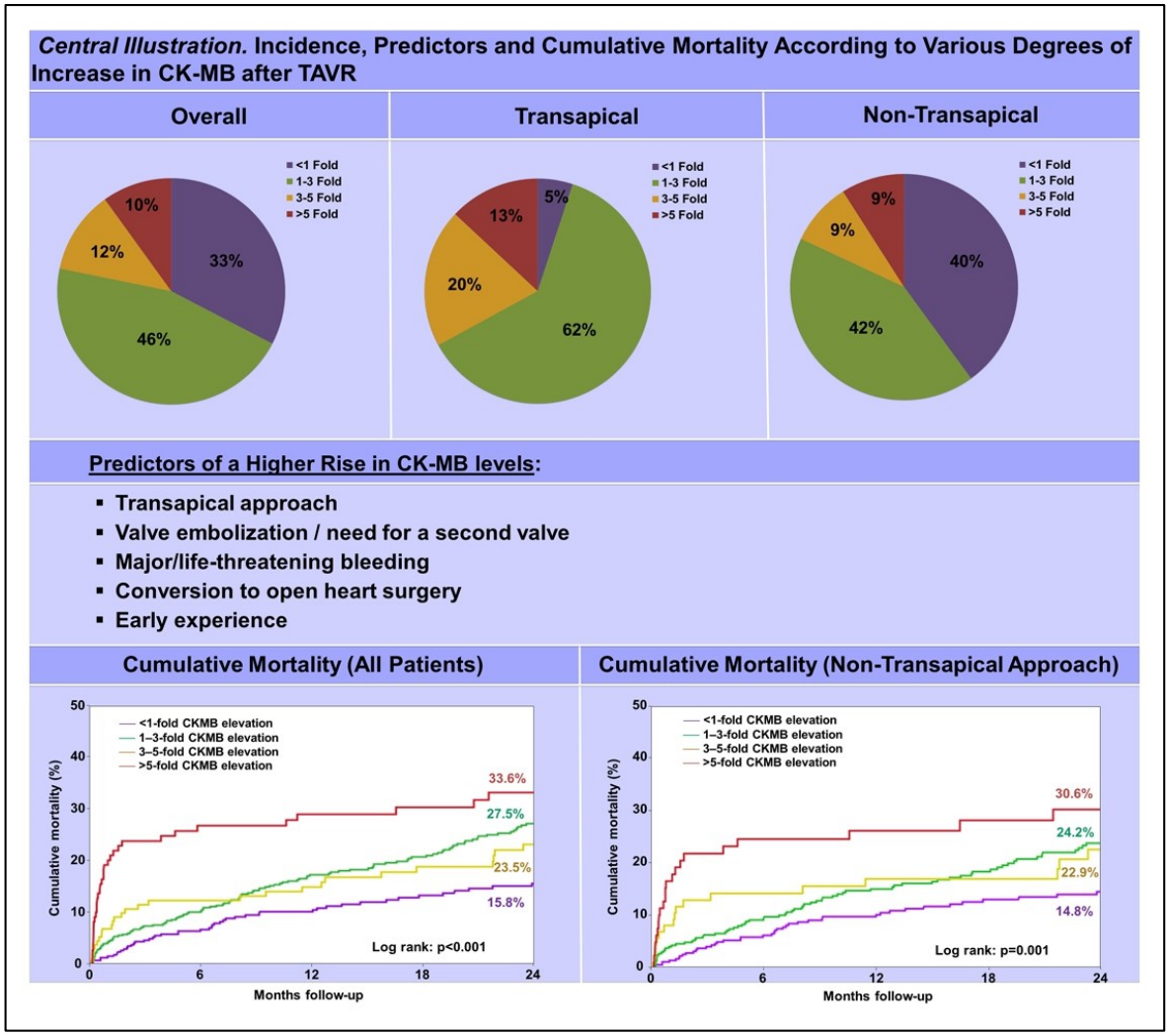

Figure 4-7: Central Illustration - Incidence, predictors and cumulative mortality according to various degrees of increase in CK-MB levels following TAVR

Median levels of peak in CK-MB after TAVR according to the increase or decrease in left ventricular ejection fraction (LVEF) between the baseline and 6- to 12 –month echocardiography. Values are expressed as median (25th to 75th interquartile range). Abbreviations as in Figure 1.

4.8 SOURCES OF FUNDINGS

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4.9 DISCLOSURE

Drs. Lemos, Sarmento-Leite, Alonso-Briales and Perin have served as a proctor for Medtronic CoreValve implantation. Dr. Amat-Santos is supported by the Insituto de Salud Carlos III through a Rio Hortega contract. Dr. de Brito and Siqueira has served as a proctor for Edwards Lifesciences and Medtronic. Dr. Ruel has served as a proctor for Medtronic and has received a research grant from Edwards Lifesciences. Dr. Nietlispach has served as a consultant for Edwards Lifesciences, Medtronic, St Jude Medical and Direct Flow Medical. Dr. Moris has served as a proctor and advisor for Medtronic. Dr. Urena is supported by a research PhD grant from Laval University-Quebec. Dr. Dumont is consultant for Edwards Lifesciences. Dr. Pibarot has Core Lab contracts with Edwards Lifesciences for which he receives no direct compensation. Dr. Rodés-Cabau is a consultant for Edwards Lifesciences and St. Jude Medical; and has received a research grant from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

CHAPTER 5: ARTICLE 2

Long-Term Prognostic Value And Serial Changes Of Plasma N-terminal Pro B-type Natriuretic Peptide In Patients Undergoing Transcatheter Aortic Valve Implantation

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5.1 RÉSUMÉ

VALEUR PRONOSTIQUE ET VARIATIONS À LONG TERME DES NIVEAUX SÉRIQUES DU PEPTIDE NATRIURÉTIQUE DE TYPE B CHEZ LES PATIENTS SUBISSANT UN REMPLACEMENT VALVULAIRE AORTIQUE TRANSCATHÉTER

Introduction : Il y a très peu de données sur l'utilité d'évaluer les neuro-hormones cardiaques chez les patients subissant une implantation de valve aortique par cathéter (TAVI).

Objectif : Les objectifs de cette étude étaient d'évaluer les valeurs de base et les changements sériés de la fraction N-terminale du peptide natriurétique de type B (NT-proBNP) suite à des TAVI, les facteurs reliés à ces changements et la valeur pronostique du NT-proBNP.

Méthodes : Un total de 333 patients consécutifs ont été inclus, et les caractéristiques de base, de la procédure et de le suivi (médiane: 20 [9 à 36] mois) ont été recueillies de façon prospective. Les concentrations de NT-proBNP ont été mesurées initialement et à la suite de la procédure TAVI, à 1-, 6-, 12 mois, puis annuellement.

Résultats : Les valeurs de base de NT-proBNP étaient élevées chez 86 % des patients (médiane: 1 692 pg/mL); les patients avec un NT-proBNP élevé avaient une fraction d'éjection du ventricule gauche et un volume d'éjection du ventricule gauche plus bas, une masse du ventriculaire gauche plus élevée et plus d'insuffisance rénale ($p < 0,01$ pour tous). Des niveaux plus élevés de NT-proBNP étaient indépendamment associés à la mortalité globale à long terme, ainsi que à la mortalité cardiaque ($p < 0,001$ pour les deux). Une valeur de base de NT-proBNP de ~2000 pg/mL semblait être le seuil optimal associé à des résultats cliniques significativement défavorables ($p < 0,001$). Les niveaux de NT-proBNP étaient diminués de 23 % ($p < 0,001$) à 6-12 mois, et restaient stables jusqu'à 4 ans de suivi. Chez 39 % des patients, cependant, il y avait un manque d'amélioration du NT-proBNP, principalement en raison de facteurs pré-procéduraux comme la fibrillation auriculaire chronique, le gradient transaortique plus faible et la régurgitation mitrale modérée / sévère ($p < 0,01$ pour tous).

Conclusion : La plupart des candidats de TAVI présentaient des niveaux élevés de NT-proBNP, et un manque d'amélioration a été observé chez un tiers des patients après le TAVI. Aussi, des niveaux plus élevés de NT-proBNP prédisaient une mortalité globale et cardiaque plus élevées à un suivi médian de 2 ans. Ces résultats soutiennent l'utilisation du NT-proBNP pour le processus de prise en charge et de suivi des patients TAVI.

Mots clés : Sténose aortique; Implantation de valve aortique par cathéter; Remplacement de valve aortique par cathéter; Peptides natriurétiques de type B; NT-ProBNP.

Ces travaux ont été présentés lors du congrès de l'American Heart Association Scientific Sessions 2013 (Dallas, États-Unis; novembre 2013).

5.2 ABSTRACT

Background: Little is known about the usefulness of evaluating cardiac neurohormones in patients undergoing transcatheter aortic valve implantation (TAVI).

Objectives: The objectives of this study were to evaluate the baseline values and serial changes of N-terminal pro-brain natriuretic peptide (NT-proBNP) following TAVI, its related factors and prognostic value.

Methods: A total of 333 consecutive patients were included, and baseline, procedural and follow-up (median: 20 [9 to 36] months) data were prospectively collected. Systematic NT-proBNP measurements were performed at baseline, hospital discharge, 1-, 6-, 12-months, and yearly thereafter.

Results: Baseline NT-proBNP values were elevated in 86% of the patients (median: 1692 pg/mL); lower left ventricular ejection fraction and stroke volume index, higher left ventricular mass, and renal dysfunction were associated with greater baseline values ($p < 0.01$ for all). Higher NT-proBNP levels were independently associated with increased long-term overall and cardiovascular mortality ($p < 0.001$ for both), with a baseline cut-off level of ~2,000 pg/mL best predicting worse outcomes ($p < 0.001$). At 6- to 12-month follow-up, NT-proBNP levels had decreased ($p < 0.001$) by 23%, and remained stable up to 4-year follow-up. In 39% of the patients, however, there was a lack of NT-proBNP improvement, mainly due to pre-procedural chronic atrial fibrillation, lower mean transaortic gradient and moderate/severe MR ($p < 0.01$ for all).

Conclusion: In conclusion, most TAVI candidates presented high NT-proBNP levels, and a lack of improvement was observed in more than one third of the patients after TAVI. Also, higher NT-proBNP levels predicted a greater overall and cardiac mortality at a median follow-up of 2 years. These findings support to the implementation of NT-proBNP measurements for the clinical decision-making process and follow-up of TAVI patients.

Key words: aortic stenosis, transcatheter aortic valve implantation, transcatheter aortic valve replacement, natriuretic peptides markers, NT-ProBNP.

5.3 INTRODUCTION

Natriuretic peptides (NP) are elevated in a number of cardiovascular diseases such as cardiac hypertrophy, acute coronary syndromes and heart failure.[91,39,240] In the context of aortic stenosis (AS) both B-type natriuretic peptide (BNP) and its prohormone - N-Terminal-proBNP (NT-proBNP) levels are also elevated, and the degree of their increase has been correlated with the severity of AS, symptoms status, and clinical outcomes following surgical aortic valve replacement (SAVR).[91,241] In the context of transcatheter aortic valve implantation (TAVI) some studies have suggested an association between NP levels and early and 1-year outcomes following TAVI. However, most of these studies included a limited number of patients, relatively short follow-up periods (≤1 year), and very few data on cardiovascular outcomes (i.e. cardiac death, heart failure).[242-247] More importantly, while a significant decrease in NP levels has been shown after TAVI, the degree of these changes and the factors associated with the lack of cardiac neurohormonal improvement have not yet been evaluated. The aims of this study were therefore to evaluate the serial changes, related factors, and the prognostic significance of NT-proBNP on the long-term follow-up of a large cohort of TAVI patients.

5.4 METHODS

5.4.1 Patient Population

A total of 333 consecutive patients with symptomatic AS considered as not suitable or at very high risk for SAVR underwent a TAVI procedure and were included in the study. Details about the TAVI procedure have been provided elsewhere.[136] All baseline and procedural characteristics were prospectively collected on pre-set data collection forms. Baseline co-morbidities were defined according to the Society of Thoracic Surgeons (STS) criteria, and periprocedural events according to the VARC-2 criteria.[196] Coronary artery disease was defined as the presence of coronary lesion with a diameter stenosis ≥50% in vessels ≥2.0mm, or prior coronary revascularization. The procedures were performed under a compassionate Clinical Program approved by Health Canada, and all patients provided signed informed consent for the procedures.

5.4.2 Clinical data

Clinical follow-up was carried out at 30 days, 6-, 12- months, and yearly thereafter. The median follow-up was 20 [9-36] months, and no patient was lost to follow-up. All clinical events during the follow-up period were defined according to the VARC-2 criteria.[196] All patients underwent a Doppler echocardiographic examination at baseline before the intervention and at hospital discharge. The New York Heart Association (NYHA) class was evaluated before the procedure and at each point time during the follow-up period.

5.4.3 Laboratory data

Plasma NT-proBNP peptide levels were measured within 48 hours before the TAVI procedure, and thereafter daily during hospitalization, at 30 days, 6 months, 1 year, and yearly thereafter. The blood samples were collected in EDTA-containing tubes, and were immediately centrifugated. NT-proBNP was measured using a chemoluminescent immunoassay kit (Elecsys® proBNP II, Roche, Minneapolis, Minnesota; normal value for the general population < 450 pg/ml). The increase in NT-proBNP levels was also evaluated using the suggested cut-off levels for elderly (normal values <1800 pg/ml and < 900 pg/ml for ages > 75 y and between 50-75 y, respectively) and renal dysfunction (<1200 pg/ml).[248] At 6- to 12-month follow-up, the patients were considered as non-responders (failure to improve their NT-proBNP levels) if their NT-proBNP value was equal or greater as compared to the baseline value.

5.4.4 Doppler Echocardiographic Data

The following measurements were obtained in all patients: aortic annulus diameter, left ventricular ejection fraction (LVEF) calculated with the Simpson method, mean transvalvular gradient calculated with the Bernoulli formula, and the valve EOA measured by the continuity equation. The EOA was indexed for body surface area (EOAi), and the occurrence of prosthesis-patient mismatch was defined as severe if the EOAi was < 0.65 cm^2/m^2. In patients with a body mass index ≥ 30 kg/cm^2, the PPM was classified as severe if the EOAi was < 0.60 cm^2/m^2.[249] The presence and degree of aortic regurgitation (AR) was recorded in all patients. The degree of AR was classified as follows: trivial, mild,

moderate, and severe[249]. The left ventricular mass (LVM) as follows: LVM (g) = 1.04 [(LV end-diastolic diameter + LV diastolic posterior wall thickness + LV diastolic posterior wall thickness)^3 - (LV end - diastolic diameter)3] x 13.6. Stroke volume was obtained by multiplying the left ventricular outflow tract (LVOT) area by the velocity-time integral measured by pulsed wave Doppler in the LVOT. Both the LVM index (LVMi) and stroke volume index (SVi) were calculated in relation to the body surface area.

5.4.5 Study End-Points

The end-points for this study included the determination of the prognostic significance of NT-proBNP before TAVI procedures, and evaluate its serial changes and related factors on long-term follow-up.

5.4.6 Statistical Analysis

Continuous variables were expressed as mean (standard deviation) or median (25-75% interquartile range) according to variable distribution. Group comparisons were analyzed using the Student t test or Wilcoxon rank sum test for continuous variables, and chi-square or Fisher's exact tests for categorical variables. A repeated measures model with interaction was used to analyze the changes of NT-ProBNP over time. Model including log transformed NT-proBNP satisfied assumption of normality of residuals. Posterior comparisons were performed using the Tukey's technique. The predictors of increased NT-proBNP values at baseline were determined using a linear regression analyses and the lack of NT-proBNP improvement at 1-year follow-up was determined using a logistic regression analysis. Univariate logistic regression analysis was used to determine the predictors of 30-day mortality. Univariate and multivariate Cox Proportional Hazard models were used to determine the predictors of cumulative late mortality, cardiac mortality, and the composite of cardiac mortality and rehospitalization due to heart failure. All of the variables exhibiting a p value <0.05 at the univariate analysis were included in the multivariate model. A receiver-operating characteristic (ROC) curve analysis was used to determine the best baseline NT-proBNP cutoff levels predicting increased overall late mortality, cardiac mortality, and the composite of cardiac mortality and re-hospitalizations due to heart failure at follow-up. Survival curves were constructed using Kaplan-Meier estimates and the log-

rank test was used for comparison between groups. The results were considered significant with p values < 0.05. All analyses were conducted using the statistical package SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

5.5 RESULTS

5.5.1 Population Characteristics and predictors of a greater NT-proBNP at baseline

The main baseline and procedural characteristics of the study population are shown in **Table 5-1**. Baseline NT-proBNP levels were elevated in 86% of the patients using the standard criteria (450 pg/ml), with a median baseline NT-proBNP value was of 1692 [667-3910] pg/mL. Also, 75.8% and 53.2% of the patients had increased NT-proBNP levels according to the criteria of Kim et al.[248] for renal failure and age, respectively. The distribution of the study population according to baseline NT-proBNP levels is shown in **Figure 5-1**. The factors associated with greater baseline NT-proBNP levels are shown in **Table 5-2**. In the multivariate analysis, the variables associated with greater NT-proBNP levels were renal dysfunction (R^2= 0.097, p<0.001), lower LVEF (R^2= 0.127, p<0.001), lower SVi (R^2= 0.015, p=0.027), and greater LVMi (R^2= 0.033, p<0.001).

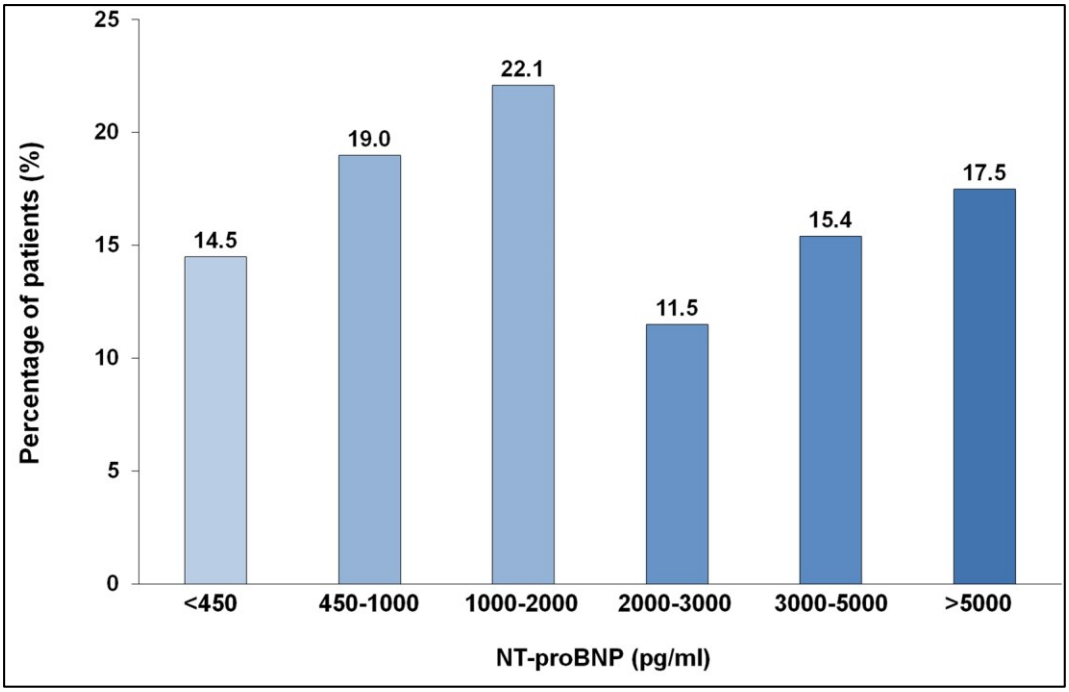

Figure 5-1: Distribution of TAVI candidates according to baseline NT-proBNP levels

Table 5-1: Clinical, echocardiography, and procedural characteristics of the study population

Variable	All Patients (n = 1,131)
Clinical variables	
Age (years)	79.6 ± 7.8
Men	177 (53.2%)
New York Heart Association functional class	
I-II	69 (20.8%)
III-IV	262 (78.9%)
Diabetes mellitus	113 (33.9%)
Hypertension	293 (88.0%)
Coronary artery disease	210 (63.1%)
Prior coronary artery bypass graft	126 (37.8%)
Atrial fibrillation (history)	101 (30.3%)
Cerebrovascular disease	65 (19.5%)
Peripheral vascular disease	116 (34.9%)
Chronic obstructive pulmonary disease	99 (29.7%)
Estimated glomerular filtration (mL/min)	57.4 ± 23.0
Society of Thoracic Surgeons predicted risk of mortality (%)	7.3 ± 4.9
N-terminal B-type natriuretic peptide (pg/ml)	1692 (667-3910)
Echocardiographic variable pre-procedure	
Left ventricular ejection fraction (%)	53.8 ± 13.8
Mean aortic gradient (mmHg)	41.0 ± 16.1

Continued

Conclusion

Variable	All Patients (n = 1,131)
Aortic valve area (cm^2)	0.65 ± 0.21
Pulmonary systolic arterial pressure (mmHg)	43.2 ± 14.0
Moderate/severe mitral regurgitation	86 (25.8%)
Stroke volume index (ml/m^2)	35.1 ± 10.2
Left ventricular mass index (g/m^2)	117.8 ± 36.0
Procedural variable	
Procedural success*	285 (85.6%)
Approach	
Transapical	177 (53.2%)
Transfemoral	131 (39.3%)
Transaortic	25 (7.5%)
Prosthesis type	
Sapien	188 (56.5%)
Sapien XT	131 (39.3%)
Sapien 3	7 (2.1%)
Portico	7 (2.1%)
Prosthesis size (mm)	
20 mm	2 (0.6%)
23 mm	174 (52.7%)
26 mm	128 (38.8%)
29 mm	26 (7.9%)
Echocardiographic variable post-procedure	
Left ventricular ejection fraction (%)	53.4 ± 13.0
Mean aortic gradient (mmHg)	12.0 ± 6.7
Aortic valve area (cm^2)	1.46 ± 0.35
Moderate/severe aortic regurgitation	40 (13.7%)
Severe prosthesis/patient mismatch	37 (14.4%)

Data are presented as mean ± SD, median (interquartile range) or n (%).
**Following VARC-2 criteria*

Table 5-2: Predictors of elevated N-terminal B-type natriuretic peptide values at baseline

Variable	Univariate			Multivariate model		
	Standardized coefficient (beta)	R^2	p value	Standardized coefficient (beta)	R^2	p value
Clinical variable						
Age (years)	-0.019	0.0004	0.719			
Men	0.107	0.0114	0.058			
New York Heart Association functional class III-IV	0.089	0.0081	0.103			
Diabetes mellitus	0.074	0.0055	0.177			
Hypertension	0.002	0.00001	0.971			
Coronary artery disease	0.104	0.0109	0.058			
Prior coronary artery bypass graft	-0.007	0.00001	0.901			
Chronic atrial fibrillation	0.043	0.0019	0.434			
Cerebrovascular Disease	0.094	0.0089	0.086			
Peripheral vascular disease	0.048	0.0023	0.381			
Chronic obstructive pulmonary disease	-0.059	0.0035	0.282			
Estimated glomerular filtration (mL/min)	-0.333	0.111	<0.001	-0.282	0.097	<0.001
Society of Thoracic Surgeons predicted risk of mortality (%)	0.242	0.058	<0.001			
Echocardiographic variable						
Left ventricular ejection fraction (%)	-0.328	0.108	<0.001	-0.213	0.127	<0.001
Mean aortic gradient (mmHg)	-0.036	0.001	0.514			
Aortic valve area (cm^2)	-0.093	0.009	0.096			
Pulmonary systolic arterial pressure (mmHg)	0.140	0.019	0.015	0.089	0.008	0.108
Moderate/severe mitral regurgitation	0.069	0.005	0.211			
Stroke volume index (ml/m^2)	-0.166	0.027	0.005	-0.136	0.015	0.027
Left ventricular mass index (g/m^2)	0.316	0.100	<0.001	0.226	0.033	0.001

5.5.2 Clinical follow-up and prognostic value of baseline NT-proBNP levels

A total of 116 patients (34.8%) had died after a median follow-up of 20 [9-36] months, 61 of them (18.3%) of cardiac causes. The variables associated with a higher risk of cumulative late mortality are shown in **Table 5-3**. Baseline NT-proBNP level independently predicted an increased late mortality (HR: 1.03 for each increase of 1000 pg/mL, 95% CI: 1.01-1.08), and it was the only independent predictor of both cardiac mortality (HR: 1.04 for each increase of 1000 pg/mL, 95% CI: 1.01-1.08) and the combined endpoint of cardiac mortality and re-hospitalization due to heart failure following TAVI (HR: 1.03 for each increase of 1000 pg/mL, 95% CI: 1.01-1.09). A baseline NT-proBNP cut-off value of 1900 pg/mL best identified the patients at higher risk for late cumulative mortality (AUC 0.65 [0.59-0.71]; sensitivity = 60.9%, specificity = 59.7%; p <0.001). A baseline NT-proBNP cut-off value of 2200 pg/mL best identified the patients at higher risk of cardiac death or cardiac death/rehospitalization due to heart failure (AUC 0.64 [0.58-0.71]; sensitivity = 58.3%, specificity = 64.6%; p <0.001). The Kaplan-Meier survival curves according to baseline NT-proBNP values (< or ≥ 2000 pg/mL) are shown in **Figure 5-2**.

Table 5-3: Univariate and multivariate analyses of clinical outcomes after TAVI

Variable	Univariate		Multivariate Model	
	OR/HR (95% CI)	p value	HR (95% CI)	p value
Thirty-day mortality (n=29)				
Men	2.24 (1.01-5.04)	0.049	-	-
Baseline N-terminal B-type natriuretic peptide †	1.04 (1.01-1.08)	0.043	-	-
Cumulative mortality (n=116)				
Men	1.64 (1.14-2.38)	0.008	-	-
Chronic atrial fibrillation/flutter	1.57 (1.03-2.38)	0.034	-	-
Chronic obstructive pulmonary disease	1.65 (1.14-2.39)	0.009	1.72 (1.11-2.66)	0.015
Estimated glomerular filtration*	1.20 (1.08-1.33)	0.001	1.18 (1.03-1.36)	0.026
Baseline N-terminal B-type natriuretic peptide†	1.07 (1.02-1.12)	<0.001	1.03 (1.01-1.08)	0.045
Mean aortic gradient††	1.15 (1.01-1.33)	0.033	-	-
Stroke volume index‡	1.35 (1.04-1.75)	0.003	1.27 (1.01-1.68)	0.034
Cumulative cardiac mortality (n=61)				
Baseline N-terminal B-type natriuretic peptide†	1.06 (1.02-1.10)	<0.001	1.04 (1.01-1.08)	0.035
Left ventricular ejection fraction§	1.12 (1.02-1.23)	0.019	-	-
Moderate to severe mitral regurgitation	1.72 91.01-2.93)	0.046	-	-
Stroke volume index ‡	1.39 (1.01-1.92)	0.013	-	-
Cumulative non cardiac mortality (n=55)				
Men	1.77 (1.03-3.02)	0.038	-	-
Chronic atrial fibrillation/flutter	1.86 (1.04-3.33)	0.037	-	-
Chronic obstructive pulmonary disease	1.82 (1.07-3.12)	0.029	2.11 (1.20-3.73)	0.009
Estimated glomerular filtration*	1.18 (1.03-1.35)	0.047	1.20 (1.04-1.39)	0.008
Cumulative cardiac mortality and/or rehospitalization for heart failure (n=96)				
Men	1.52 (1.01-2.27)	0.044	-	-
Chronic atrial fibrillation/flutter	1.91 (1.24-2.95)	0.004	-	-
Estimated glomerular filtration*	1.16 (1.04-1.30)	0.020	-	-
Baseline N-terminal B-type natriuretic peptide†	1.05 (1.01-1.09)	0.002	1.03 (1.01-1.09)	0.026
Left ventricular ejection fraction§	1.15 (1.06-1.25)	0.002	-	-
Mean aortic gradient††	1.27 (1.08-1.50)	0.002	0.98 (0.97-0.99)	0.034
Severe to moderate mitral regurgitation	1.59 (1.04-2.45)	0.034	-	-
Stroke volume index ‡	1.35 (1.03-1.77)	0.007	-	-
Left ventricular mass index¶	1.01 (1.01-1.01)	0.037	-	-

***** Per 10 mL/min decrease in eGFR.
† Per 1000 pg/mL increase in NTproBNP.
†† Per 10 mmHg decrease in Mean aortic gradient.
‡ Per 10 mL decrease in Stroke Volume index.
§ Per 5% decrease in LVEF.
¶ Per 10 g/m^2 decrease in Left ventricular mass index.

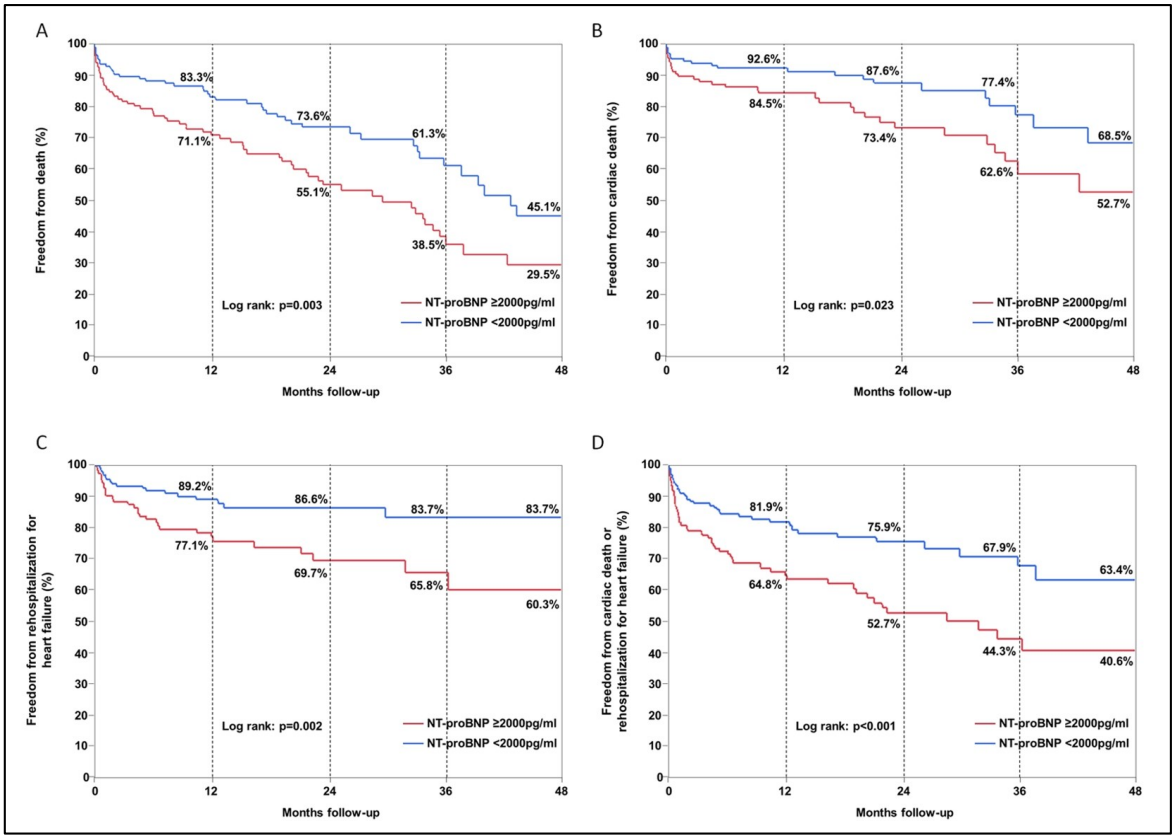

Figure 5-2: Kaplan-Meier survival curves at 4-year follow-up according to baseline NT-proBNP values for (A) overall mortality, (B) cardiac mortality, and (C) rehospitalization due to heart failure, and (D) cardiac mortality and rehospitalization due to heart failure

5.5.3 Changes in NT-proBNP levels after TAVI

The early and late changes in NT-proBNP levels following TAVI are shown in **Figure 5-3**. The NT-proBNP levels decreased by -23% [-62;+31] at 1-year follow-up and remained stable up to 4-year follow-up (p <0.001). The early changes in NT-proBNP levels differed according to the approach used during the TAVI procedure. Whereas in patients treated by transfemoral approach, the NT-proBNP levels did not change immediately after the procedure (hospital discharge, p =0.799) and decreased up to 6- to 12-month follow-up (-25% [-69;+37) (p <0.001), in patients treated by transapical or transaortic approach the NT-proBNP levels increased at hospital discharge (+23% [-20;+127] in the transapical group, p <0.001; +32% [+23;+146] in the transaortic group, p =0.007), decreased afterwards until 6- to 12-month follow-up, and then remained stable up to 4 years (p <0.001 and p =0.003, for transapical group and the transaortic group, respectively).

At 6- to 12-month follow-up, a total of 69 patients failed to improve their NT-proBNP levels as compared to baseline (out of 179 patients at risk, 39%). The changes in NT-proBNP levels between baseline and 1-year follow-up in these patients (non-responders) compared to those who had improved their NT-proBNP levels (responders) are shown in **Figure 5-4** and the main baseline and echocardiographic characteristics of these 2 groups are compared in **Table 5-4**. Patients in the non-responder group increased the NT-proBNP values by +71% [+22;+164] at 1-year follow-up ($p < 0.001$) compared to a decrease of -51% [-75;-31] in the responder group ($p < 0.001$), $p<0.001$ for comparison between groups. The factors associated with the lack of NT-proBNP improvement after TAVI are shown in **Table 5-5**. In the multivariate analysis, the predictors of the lack of NT-proBNP improvement were chronic atrial fibrillation (AF; OR 2.40 [1.06-5.44], $p = 0.036$), a lower mean gradient (OR 0.98 [0.95-0.99] per 10 mmHg, $p = 0.025$), and moderate to severe mitral regurgitation (MR; OR 2.11 [1.03-4.34], $p = 0.042$).

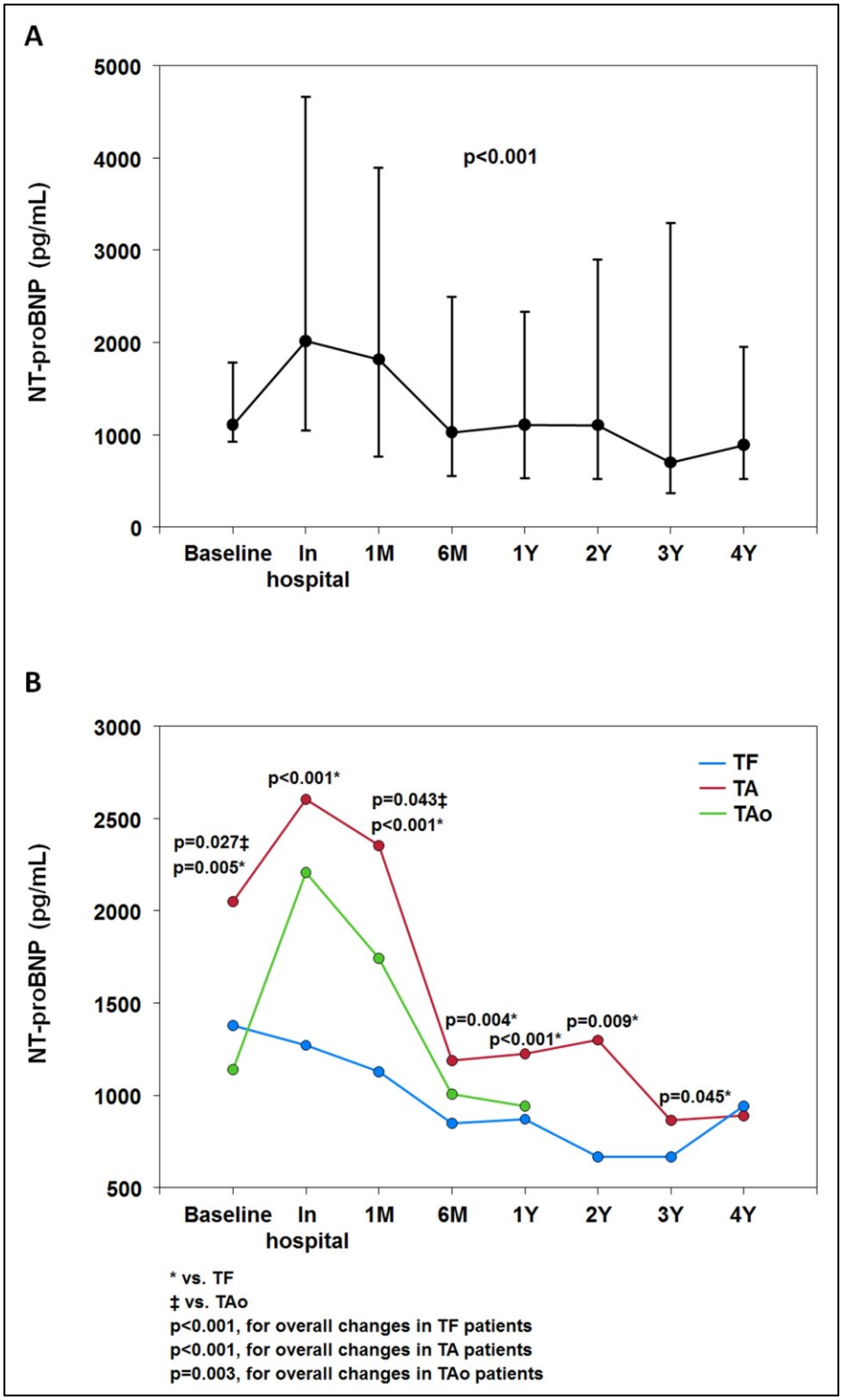

Figure 5-3: Changes in serum markers of NT-ProBNP following TAVI

Changes in serum markers of NT-ProBNP following TAVI for (A) the entire study population and (B) according to the approach used during the TAVI procedure
TF: transfemoral; TA: transapical; TAo: transaortic

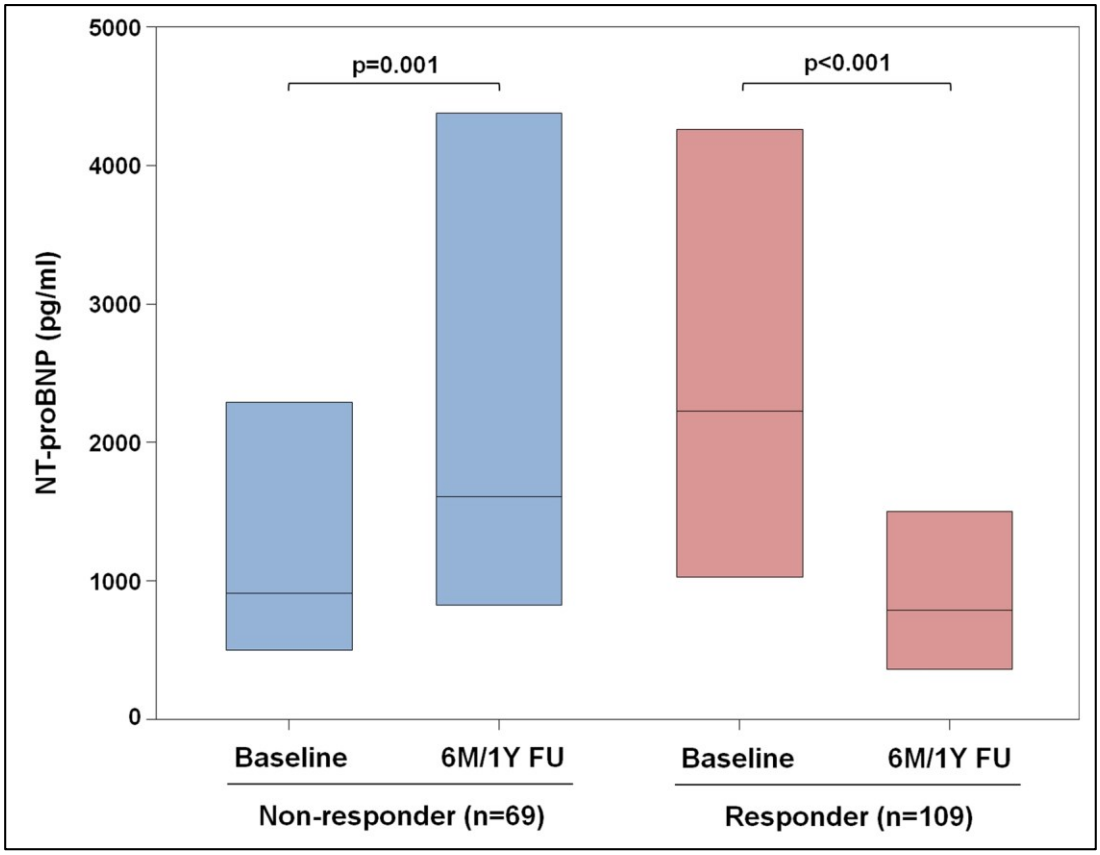

Figure 5-4: NT-proBNP levels values according to the presence (responders) or lack (non-responders) of improvement in NT-proBNP levels at follow-up.

6M/1Y: 6- to 12-month follow-up

Table 5-4: Baseline and procedural characteristics, according to the changes in NT-proBNP levels (responders vs. non- responders) over time

Variable	Non-responder (n=69)	Responder (n=109)	p value
Clinical Variable			
Age (years)	78.8 ± 7.3	80.5 ± 7.3	0.123
Men	40 (58.0)	68 (62.4)	0.637
NYHA class			
I-II	17 (24.6)	17 (15.6)	0.171
III-IV	52 (75.4)	92 (84.4)	
Diabetes mellitus	24 (34.8)	37 (33.9)	1.00
Hypertension	60 (87.0)	98 (89.9)	0.628
Coronary artery disease	38 (55.1)	69 (63.3)	0.346
Prior coronary artery bypass graft	28 (40.6)	36 (33.0)	0.338
Atrial fibrillation (by history)	20 (29.0)	15 (13.8)	0.019
Cerebrovascular disease	12 (17.4)	23 (21.1)	0.568
Peripheral vascular disease	29 (42.0)	34 (31.2)	0.151
Chronic obstructive pulmonary disease	19 (27.5)	25 (22.9)	0.593
Estimated glomerular filtration (ml/min/1.73m^2)	56.5 ± 22.4	56.8 ± 22.9	0.932
Society of Thoracic Surgeons predicted risk of mortality (%)	6.8 ± 4.1	7.2 ± 4.1	0.522
Procedural success*	57 (82.6)	98 (89.9)	0.174
Approach			
Transfemoral	22 (31.9)	45 (41.3)	0.472
Transapical	44 (63.8)	59 (54.1)	
Transaortic	3 (4.3)	5 (4.6)	
Echocardiographic variable pre-procedure			
Left ventricular ejection fraction (%)	55.1 ± 12.6	53.3 ± 14.6	0.417
Mean Gradient (mmHg)	36.6 ± 11.7	43.3 ±18.7	0.009
Aortic valve area (cm^2)	0.68 ± 0.16	0.63 ± 0.24	0.185
Pulmonary systolic arterial pressure (mmHg)	43.6 ± 14.6	43.0 ± 13.2	0.799
Moderate/severe mitral regurgitation	23 (33.3)	22 (20.2)	0.049
Stroke volume index (ml/m^2)	37.0 ± 7.8	35.9 ± 11.0	0.481
Left ventricular mass index (g/m^2)	118.3 ± 36.0	119.4 ± 32.7	0.836
Echocardiographic variable post-procedure			
Left ventricular ejection fraction (%)	55.3 ± 12.5	54.1 ± 12.8	0.559
Mean Gradient (mmHg)	11.4 ± 6.6	12.5 ± 6.13	0.262
Aortic valve area (cm^2)	1.48 ± 0.38	1.42 ± 0.32	0.303
Aortic regurgitation ≥ 2	16 (23.2)	20 (18.5)	0.449
Severe prosthesis mismatch	8 (11.6)	12 (11.0)	1.00

Data are presented as n (%) or mean (±SD).
** Following VARC-2 criteria*

Table 5-5: Predictors of the lack of improvement in N-terminal B-type natriuretic peptide levels at 6- to 12-month follow-up (n=69 out of 179 patients)

Variable	Univariate		Multivariate Model	
	OR (95% CI)	p value	OR (95% CI)	p value
Clinical variable				
Age (years)	0.98 (0.92-1.01)	0.124		
Men	1.20 (0.65-2.22)	0.557		
Diabetes	1.04 (0.55-1.96)	0.909		
Hypertension	0.75 (0.29-1.91)	0.545		
New York Heart Association functional class III-IV	0.57 (0.27-1.20)	0.139		
Chronic atrial fibrillation/flutter	2.56 (1.20-5.43)	0.015	2.40 (1.06-5.44)	0.036
Coronary artery disease	0.71 (0.39-1.31)	0.275		
Prior coronary artery bypass graft	1.39 (0.74-2.59)	0.307		
Cerebrovascular disease	0.78 (0.36-1.71)	0.545		
Peripheral vascular disease	1.60 (0.86-2.99)	0.142		
Chronic obstructive pulmonary disease	1.28 (0.64-2.55)	0.489		
Estimated glomerular filtration*	1.02 (0.89-1.16)	0.815		
Transfemoral approach	1.50 (0.79-2.83)	0.208		
Procedural success**	0.55 (0.22-1.29)	0.162		
Echocardiographic variable pre-procedure				
Left ventricular ejection fraction (%)	1.01 (0.99-1.03)	0.415		
Mean Gradient (mmHg)	0.97 (0.95-0.99)	0.011	0.98 (0.95-0.99)	0.025
Aortic valve area (cm^2)	2.59 (0.63-10.7)	0.189		
Pulmonary systolic arterial pressure (mmHg)	1.00 (0.98-1.03)	0.797		
Mitral regurgitation III-IV	1.99 (1.01-3.99)	0.049	2.11 (1.03-4.34)	0.042
Stroke Volume index (ml/m^2)	1.02 (0.98-1.05)	0.480		
Left ventricular mass index (g/m^2)	0.99 (0.99-1.01)	0.835		
Echocardiographic variable post-procedure				
Left ventricular ejection fraction (%)	1.01 (0.98-1.03)	0.556		
Mean Gradient (mmHg)	0.97 (0.92-1.02)	0.265		
Aortic valve area (cm^2)	1.67 (0.63-4.38)	0.301		
Moderate/severe aortic regurgitation	1.21 (0.58-2.54)	0.603		
Severe Prosthesis Mismatch	0.97 (0.37-2.55)	0.958		

**Per 10 mL/min decrease in eGFR.*
*** Following VARC-2 criteria.*

In order to further evaluate the low gradient factor, the patients were divided in 3 groups according to baseline mean transaortic gradient and LVEF: low LVEF/low-gradient AS (LVEF < 50%, mean gradient < 40%), preserved LVEF/low-gradient AS (LVEF ≥ 50%, mean gradient <40 mmHg), and high-gradient AS (mean gradient ≥ 40 mmHg). The results regarding NT-proBNP changes in these groups are shown in **Figure 5-5**. The NT-proBNP levels improved at 1-year follow-up in the high-gradient AS group (median decrease of -46% [-71;+15], p =0.010), and remained similar to baseline in the preserved LVEF/ low-gradient group (p =0.353), and in the low-LVEF/low-gradient group (p =0.552). In order to further evaluate the moderate/severe MR factor, the changes in the degree of MR at 6- to 12-month follow-up were evaluated. Of the 42 patients with baseline moderate/severe MR who survived at 6- to 12-month follow-up, 22 patients (52%) had improved by at least one degree the severity of MR. The changes in NT-proBNP values according to the changes in MR overtime are shown in **Figure 5-5**.

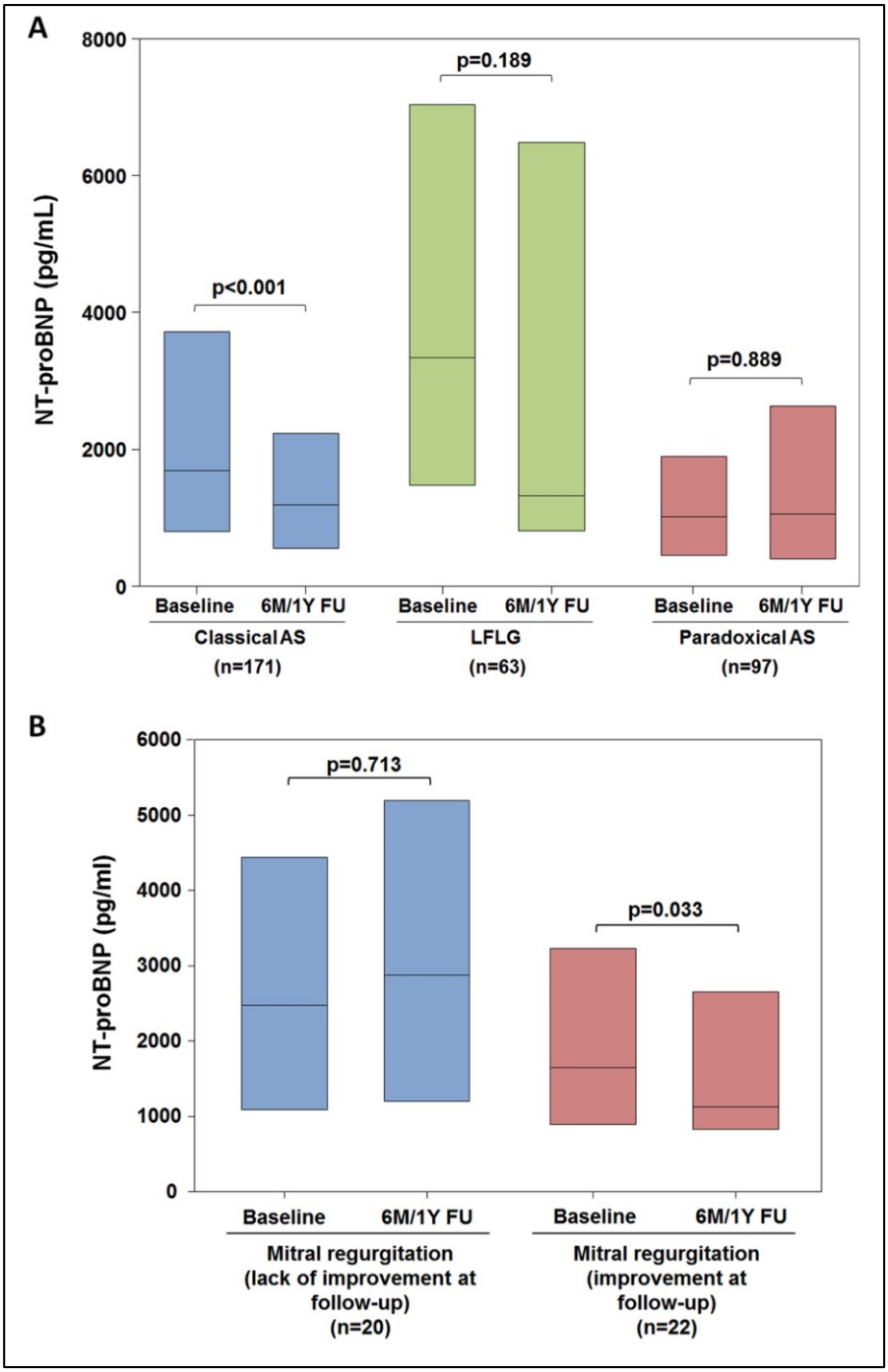

Figure 5-5: NT-proBNP changes over time according to transvalvular aortic gradient and left ventricular ejection fraction, as well as according to mitral regurgitation status

(A) NT-proBNP changes over time according to transvalvular aortic gradient and left ventricular ejection fraction. Classical AS: high-gradient aortic stenosis (mean gradient ≥ 40%); LFLG: low flow (LVEF<50%) and low gradient AS (<40 mmHg); paradoxical AS: preserved LVEF (≥50%) and low gradient AS (<40 mmHg). (B) NT-proBNP changes over time according to changes in mitral regurgitation severity in those patients with moderate/severe mitral regurgitation at baseline.
FU: follow-up, AS: aortic stenosis, LVEF: left ventricular ejection fraction, 6M/1Y: 6- to 12-month follow-up.

5.5.4 Functional status and NT-proBNP values

A total of 262 patients (79%) were in NYHA class III-IV before the TAVI procedure, and exhibited higher NT-proBNP levels as compared to those patients in NYHA class I-II (2037 [950-4536] pg/mL vs. 742 [381-1851] pg/mL, p <0.001). At 1-year follow-up, 89.6% of the patients were in NYHA class I-II and exhibited lower NT-proBNP levels compared to those in NYHA class >II (924 [506-1999] pg/mL vs. 2112 [1186-5288] pg/mL, p <0.001). Improvements of ≥2 functional class over time were associated with a significant decrease of NT-proBNP levels (p <0.001, **Figure 5-6**).

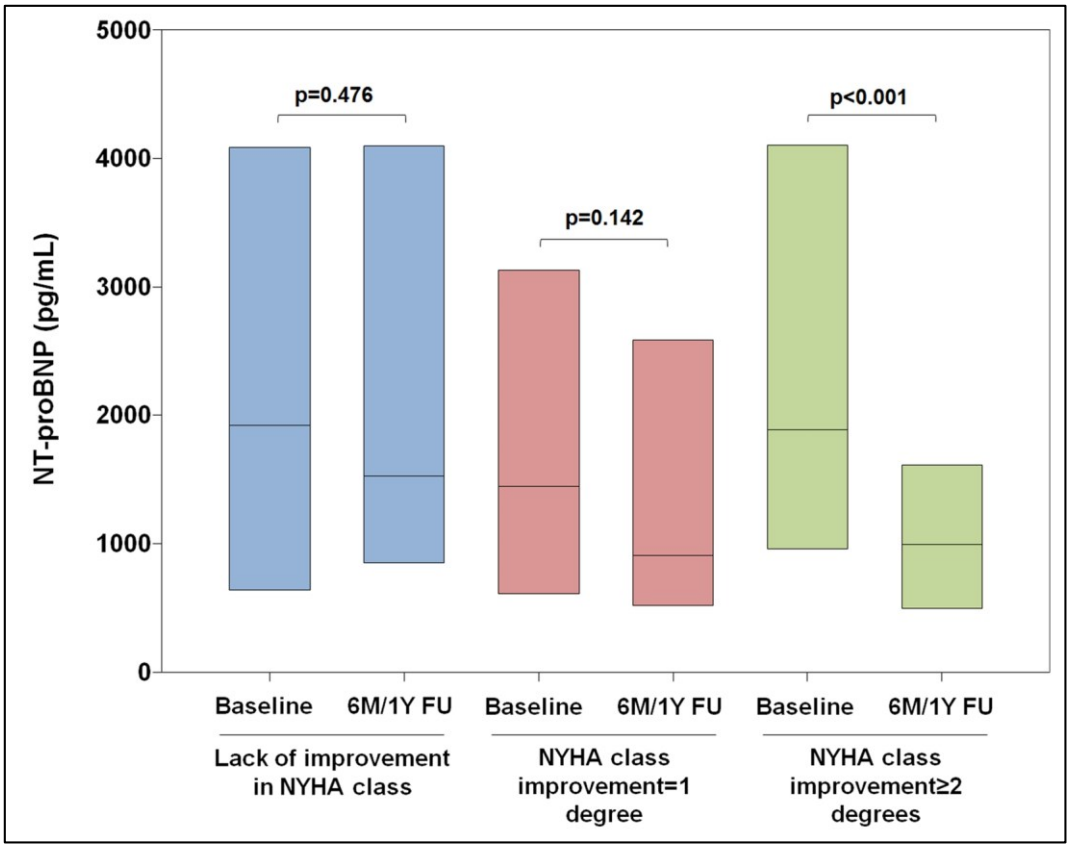

Figure 5-6: Correlation between changes in NT-proBNP and NYHA class over time.

6M/1Y: 6- to 12-month follow-up; FU: follow-up; NYHA: New York Heart Association functional class.

5.6 DISCUSSION

5.6.1 Preoperative NT-proBNP levels

Prior studies in the field of SAVR have shown that most patients with severe symptomatic AS exhibit elevated levels of NP, and this has been related mainly to changes in LV remodeling and function.[95,250,251] In the context of TAVI, prior studies have also shown elevated levels of NP in patients undergoing the procedure.[242,244-247] Consistent with these studies, NT-proBNP levels were elevated in 86% of TAVI candidates in the present study, with a median increase as high as 4 times the upper normal limit. These levels of NT-proBNP are much higher than those reported in studies including various patients with heart failure and AS undergoing SAVR.[91,239] This probably reflects the more advanced process of the disease in TAVI candidates, which leads to a higher degree of ventricular remodeling and lower LV function, both involved in a greater rise in NP values.[242,244-247] Also, TAVI candidates are usually older than those undergoing SAVR, and have a higher prevalence of renal insufficiency (about half of our patients), both well known factors related to increased NP levels.[252,253]

5.6.2 Prognostic value of NT-proBNP levels

In patients with AS undergoing SAVR, preoperative NP levels have been associated with a higher early and late mortality rates, especially in those diagnosed with low-LVEF, low-flow, low-gradient AS.[91,95,241] Several studies have shown an association between higher NP levels and early and 1-year mortality following TAVI.[244-247] However, the vast majority of studies to date have had a limited sample size and/or follow-up, precluding the possibility of drawing definite conclusions about their predictive value in TAVI candidates.[242-247] The present study confirmed the incremental prognostic value of measuring the NP levels before the TAVI procedure up to 2 years, with higher NT-proBNP levels (cut-off level of about 2,000 pg/mL) independently determining a higher global and cardiovascular mortality risk, as well as the combined endpoint of cardiac mortality and rehospitalization due to heart failure. These results suggest that TAVI candidates with NT-proBNP levels of >2,000 pg/mL need to be carefully evaluated, and this factor should probably be incorporated into the clinical decision making process. If the TAVI procedure

is finally performed in such patients, a closer follow-up, probably in a heart failure clinic should be implemented in order to improve cardiovascular outcomes of these high-risk group of patients.[254]

5.6.3 Changes in NT-proBNP following TAVI

Most of the patients (61%) showed improved NT-proBNP levels within 12 months after TAVI, with a median percent decrease of about 50%. This decrease in NP values was faster with the transfemoral in relation to the transapical approach, consistent with previous studies in the literature. [242,244,247] The introduction of large catheters through the ventricular apex has been associated with a greater degree of myocardial injury following TAVI and this might explain this early increase in NP levels following transapical TAVI.[167] The relief of the left ventricular afterload following SAVR has been associated with a progressive regression of left ventricular hypertrophy and cardiac reverse remodeling, and this may translate into a significant decrease in NP levels over time.[255,256] Nonetheless, NT-proBNP levels failed to decrease within the year following TAVI in up to 39% of the patients, and this suggests that factors other than afterload release are also involved in cardiac neurohormonal changes in this population. This study showed that baseline pre-procedural variables such as chronic AF, a lower transvalvular aortic gradient and moderate-to-severe MR determined an increase in NT-proBNP levels despite successful TAVI.

Chronic AF is present in about one third of TAVI candidates,[257] and it has been shown to be a predictor of late mortality following TAVI.[141] Chronic AF has been associated with an increase in NP levels in patients with and without AS,[258] and it may partially explain the poorer outcomes observed in these patients after the TAVI procedure. MR has also been associated with increased NP values in patients managed clinically and in those undergoing surgery, these increased values reflect both ventricular remodeling and atrial enlargement and may also correlate with the severity of the disease.[259] Consistent with prior studies,[260] about half of our patients with moderate or severe MR failed to show an improvement in MR after TAVI.

Patients with low-gradient AS (with or without low LVEF) failed to show improved NT-proBNP values at 1-year follow-up at the same level as those with high-gradient AS. A

reduction in BNP after SAVR has been shown in patients with low LVEF, low-flow, low-gradient AS,[91,261] and a tendency towards NT-proBNP improvement was also observed in our cohort. However, patients with preserved LVEF low-gradient AS tended to have increased NT-proBNP values after the TAVI procedure. The persistence of myocardial fibrosis and associated diastolic dysfunction may partially explain these results.[256] These findings also highlight the importance of careful confirmation of stenosis severity with the use of dobutamine stress echocardiography and/or aortic valve calcium scoring by computed tomography.[261,262]

5.6.4 Limitations

The lack of data on diastolic function was one of the main limitations of this study. Nonetheless, as much as ~30% of the population had AF that precluded an accurate measurement of diastolic function. The NT-proBNP cut-off value of 450 pg/mL was used to determine the patients with increased NT-proBNP levels at baseline, even though other cut-off values have been used in the literature according to different risk factors (i.e., age, renal function, etc.).[248] However, no study to date has validated the use of these different cut-off values in the TAVI population. The low number of early events precluded the possibility of evaluating the prognostic value of baseline NT-proBNP on 30-day outcomes in a multivariate model. The number of patients with either residual moderate-severe AR or severe prosthesis-patient mismatch after TAVI was relatively low; future studies with a larger number of patients will have to evaluate the impact of these features on cardiac neurohormones.

5.6.5 Conclusions

In conclusion, NT-proBNP levels were highly elevated in the vast majority of patients with severe AS and high or prohibitive surgical risk. Higher baseline NT-proBNP levels, especially >2,000 pg/mL, determined a higher cardiovascular mortality leading to a higher overall mortality following TAVI, irrespective of surgical risk scores or traditional co-morbidities. This suggests that this biomarker should probably be incorporated into the risk evaluation of TAVI candidates. While TAVI was associated with a significant decrease in NT-proBNP levels within the year following the procedure, more than one third of the

patients failed to show improved NT-proBNP levels despite AS release due to baseline conditions such as chronic AF, low transvalvular aortic gradient and moderate-severe MR. A closer follow-up of these patients, with serial NT-proBNP measurements over time may help to improve cardiovascular outcomes, and the potential role of heart failure clinics in the evaluation and follow-up of TAVI candidates should be evaluated in future studies.

5.7 SOURCES OF FUNDINGS

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5.8 DISCLOSURE

Dr Robert DeLarochellière is consultant for St. Jude Medical. Dr Eric Dumont is consultant for Edwards Lifesciences. Dr Josep Rodés-Cabau is consultant for Edwards Lifesciences and St. Jude Medical.

CHAPTER 6: ARTICLE 3

Myocardial Injury After Transaortic Versus Transapical Transcatheter Aortic Valve Replacement

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6.1 RÉSUMÉ

LÉSIONS MYOCARDIQUES APRÈS L'IMPLANTATION DE VALVE AORTIQUE PAR CATHÉTER PAR VOIE TRANSAORTIQUE VS TRANSAPICALE

Introduction : La libération de biomarqueurs en lien avec des lésions myocardiques après un remplacement de la valve aortique par cathéter (TAVR) est commune, mais peu de données existent concernant les patients TAVR traités par l'approche transaortique. Notre objectif était d'évaluer l'incidence et la signification pronostique de l'augmentation des biomarqueurs cardiaques chez les candidats TAVR par approche non-transfémorale, en comparant l'approche transaortique et transapicale.

Méthodes : Après l'exclusion des patients considérés aptes au TAVR par l'approche transfémorale, 251 patients (transaortique=45; transapicale=206) ont été prospectivement évalués. Les concentrations de créatine kinase-MB (CK-MB) et les troponines cardiaques T (cTnT) ont été mesurées initialement et à 6-12, 24,48 et 72 heures suivant le TAVR. Une échocardiographie et des suivis cliniques ont été effectués initialement et à 6-12 mois.

Résultats : À la suite du TAVR, les concentrations de cTnT ont augmenté au-dessus des valeurs normales chez tous les patients (valeur maximale: 0,64 μg/l [IQR: 0,39-1,03 μg/l]), alors que les concentrations de CK-MB ont augmenté de 88 % chez les patients (transaortique: 51 %, transapicale: 96 %, p<0,001; valeur maximale: 20,1 μg/l [IQR: 14,3-31,6 μg/l]). En comparaison à l'approche transaortique, l'approche transapicale était associée à une plus grande augmentation de ces deux marqueurs cardiaques (p<0,001 pour les deux), et à une moins grande amélioration de la fraction d'éjection du ventricule gauche (VG) (p=0,058) et de la déformation longitudinal du VG (p=0,039) au suivi de 6-12 mois. Une plus grande augmentation des concentrations de cTnT était indépendamment associée à la mortalité à 30 jours, ainsi qu'à la mortalité cardiovasculaire et globale à 1 an (p<0,001 pour tous). Une augmentation de 15 fois les concentrations de cTnT était le seuil optimal permettant de déterminer des résultats moins favorables (p<0,001).

Conclusion : Les lésions myocardiques péri-procédurales lors du TAVR chez les candidats où l'approche transfémorale n'est pas envisageable ont été démontrées chez tous les patients, cependant l'approche transapicale était associée à des lésions myocardiques significativement plus importantes en comparaison à l'approche transaortique. Un degré

plus important de lésions myocardiques s'est traduit par une amélioration moins importante de la fraction d'éjection ventriculaire gauche et par un plus faible taux de survie à court et moyen terme.

Mots clés : Sténose aortique; Remplacement de valve aortique par cathéter; Lésion myocardique; Transaortique; Transapical.

Ces travaux ont été présentés lors du congrès Transcatheter Cardiovascular Therapeutics (TCT) (San Francisco, EUA; octobre 2015) et au congrès de la Société Brésilienne de Cardiologie Interventionnelle (Brasilia, 2015), où il y a gagné le prix des meilleurs abstracts au Congrès.

6.2 ABSTRACT

Background: The release of cardiac biomarkers of myocardial injury after transcatheter aortic valve replacement (TAVR) is common, but no data exist on those patients undergoing TAVR through transaortic approach. We aimed to evaluate the incidence and prognostic significance of the increase in cardiac biomarkers in non-transfemoral TAVR candidates, comparing transaortic and transapical approaches.

Methods: After excluding patients deemed suitable for transfemoral TAVR, 251 consecutive patients (transaortic=45; transapical=206) were prospectively evaluated. Creatine kinase-MB (CK-MB) and cardiac troponin T (cTnT) levels were measured at baseline and at 6-12,24,48, and 72 hours following TAVR. Baseline and 6-12 month echocardiographic and clinical follow-up were performed.

Results: Following TAVR, cTnT increased above the upper normal values in all patients (peak value: 0.64μg/l[IQR: 0.39-1.03μg/l]), whereas CK-MB levels increased in 88% of patients (transaortic:51%, transapical:96%,$p<0.001$; peak value: 20.1μg/l[IQR: 14.3-31.6μg/l]). Compared with the transaortic approach, transapical approach was associated with a greater rise in both cardiac biomarkers ($p<0.001$ for both), and a lesser improvement in left ventricular ejection ($p=0.058$) and global longitudinal strain ($p=0.039$) at 6-12-month follow-up. Greater increases of cTnT levels independently associated with 30-day and 1-year overall and cardiovascular mortality ($p<0.001$ for all). A 15-fold rise in cTnT levels was the optimal threshold for determining poorer outcomes ($p<0.001$).

Conclusions: Peri-procedural TAVR-related myocardial injury in non-transfemoral candidates was demonstrated in all patients, but transapical approach was associated with significantly greater myocardial injury compared with transaortic approach. A higher degree of myocardial injury translated into reduced left ventricular function improvement and lower early- and mid-term survival rates.

Key word: Aortic stenosis; Transcatheter aortic valve replacement; Myocardial injury; Transaortic; Transapical.

6.3 INTRODUCTION

Transcatheter aortic valve replacement (TAVR) invariably results in peri-procedural myocardial protein release consistent with myocardial injury,[167,214-217] and greater degrees of myocardial injury post-TAVR associate with reduced early and midterm survival.[167,196,214,216,226] The transapical (TA) approach for performing TAVR, a common alternative in patients deemed unsuitable for transfemoral (TF)-TAVR, correlates with greater elevations of myocardial proteins, likely related to the puncture and insertion of large-bore catheters through the ventricular apex.[167,216,217]

Transaortic (TAo)-TAVR, performed via a mini right (or mid) sternotomy, has recently emerged as a promising alternative to TA-TAVR.[173-175] Potential advantages of TAo-TAVR are the possibility of rapid conversion to full sternotomy in the advent of severe complications, and the avoidance of left ventricular apical perforation. However, no data currently exist comparing the extent and clinical impact of myocardial injury following TAo versus TA-TAVR. The objectives of the present study were therefore to evaluate, in TAVR candidates not suitable for TF approach, the incidence and prognostic significance of myocardial injury following TAVR globally and comparing the TAo and TA approaches.

6.4 METHODS

6.4.1 ***Study population***

Following exclusion of patients undergoing TF-TAVR, between May 2007 and January 2014, 251 consecutive patients undergoing TAVR for severe symptomatic aortic stenosis were prospectively evaluated. The study was performed in accordance to the Ethics Committee and the need for individual patient informed consent was waived due to the retrospective and anonymous nature of the study. TAo-TAVR was introduced as an alternative novel procedural approach in late 2011. Hence, the specific TAVR approach of the studied population was left to the discretion of the Heart Team. Details of TAVR procedures have been previously described in detail.[136] A total of 206 patients underwent TA-TAVR and 45 patients underwent TAo-TAVR. Baseline co-morbidities were defined according to the Society of Thoracic Surgeons (STS) criteria, and all clinical events according to the VARC-2 criteria.[196]

6.4.2 Laboratory biochemical measurements

Blood samples were collected at baseline, and at 6 to 12, 24, 48, and 72 hours post-TAVR. Creatine kinase-MB mass (CK-MB) and cardiac troponin T (cTnT) levels were measured at each time point via electrochemiluminescence immunoassay (Roche, Minneapolis, Minnesota). Based on the 99th percentile in a healthy population and the requirement of a ≤ 10% coefficient variation, the upper normal limits for CK-MB and cTnT levels at our institution were 10 and 0.05 µg/l, respectively. Significant myocardial injury was defined as a CK-MB level >10 µg/l or a cTnT level > 0.05 µg/l.

6.4.3 Echocardiography measurements

Doppler echocardiography examination was performed at baseline, at hospital discharge post-TAVR, and at 6- to 12-month follow-up. All images were analyzed in a central echocardiography core laboratory at the Quebec Heart and Lung Institute. LV ejection fraction (LVEF) was calculated with the biplane Simpson method or visual estimation. The degree of aortic regurgitation was classified as either none/trivial, mild, moderate, and severe.[263] LV longitudinal strain was determined offline by 2D speckle-tracking method, using commercially available software (TomTec Imaging Systems, Munich, Germany). Global longitudinal strain (GLS) was calculated as the average of longitudinal strain of the 2-chamber, 3-chamber, and 4-chamber apical views. GLS data were expressed in absolute value (|%|).

Echocardiographic exams were available in 223 patients at hospital discharge (98.7% of patients at risk), and in 179 patients at follow-up (95.2% of the patients at risk). Evaluation of the LVEF was performed in all patients, yet GLS evaluation was not possible in 29% and 39% of patients at hospital discharge and at follow-up respectively, due to the suboptimal image quality (poor echogenicity and inadequate frame rate: i.e. < 50 fps).[264] Delta LEVF and GLS were calculated as the difference between baseline (|%|) and follow-up values (|%|) at 6- to 12 months.

6.4.4 Statistical analysis

The propensity score matching analysis, using a one-to-two matching process, was performed to adjust for the intergroup (TAo vs. TA) differences in baseline characteristics caused by the selection bias inherent to the non-randomized nature of the study. Selected variables were age, gender, NYHA class, previous coronary artery disease, prosthesis size, and valve type, using a logistic regression analysis. The maximum difference of propensity score for a match was established at 10%. An analysis of variance for repeated measures was performed to test for equal means at different times (baseline, 6 to 12, 24, 48, and 72 hours post TAVR) for the cardiac enzyme values, and a 2-way analysis of variance for repeated measures with interactions was used to compare the changes in cardiac enzyme levels at different time points between groups. In the multivariate analysis all variables with p value <0.05 were entered in the model. A linear regression was used to determine the variables associated with a higher rise in cTnT levels, and a logistic regression analysis was used to determine the predictors of 30-day mortality. Univariate and multivariate Cox proportional hazard models were used to determine the predictors of cumulative late mortality, cardiac mortality, and the composite of cardiac mortality and re-hospitalization due to heart failure. A receiver-operating characteristic (ROC) curve analysis was used to determine the best cTnT peak value cutoff predicting increased 30-day and late (1-year) mortality. All analyses were conducted using the statistical package SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

6.5 RESULTS

6.5.1 Baseline characteristics of the study population

Table 6-1 describes clinical, echocardiographic and procedural characteristics of the study population overall and according to the anatomical procedural approach. **Table 6-2** describes baseline and procedural characteristics of the propensity-matched population (TAo and TA).

Table 6-1: Clinical, echocardiographic, and procedural characteristics of the study population

Variable	All Patients (n=251)	TAO (n=45)	TA (n=206)	p value
Clinical variables				
Age (years)	79±8	81±7	78±8	0.051
Male sex	116 (46.2)	16 (35.6)	100 (48.5)	0.113
NYHA class				0.003
I-II	54 (21.5)	17 (37.8)	37 (18.0)	
III-IV	197 (78.5)	28 (62.2)	169 (82.0)	
Diabetes mellitus	90 (35.9)	17 (37.8)	73 (35.4)	0.767
Dyslipidemia	20 7(82.5)	33 (73.3)	174 (84.5)	0.075
Hypertension	229 (91.2)	39 (86.7)	190 (92.2)	0.232
Coronary artery disease	168 (66.9)	20 (44.4)	148 (71.8)	<0.001
Complete revascularization	51 (34.7)	4 (25.0)	47 (35.9)	0.388
Incomplete revascularization	96 (65.3)	12 (75.0)	84 (64.1)	0.388
Previous myocardial infarction	92 (36.7)	12 (26.7)	81 (39.3)	0.111
History of Atrial fibrillation	72 (28.7)	13 (28.9)	59 (28.6)	0.973
Cerebrovascular disease	58 (23.1)	9 (20.0)	49 (23.8)	0.585
Peripheral vascular disease	129 (51.4)	19 (42.2)	110 (53.4)	0.174
COPD	88 (35.1)	15 (33.3)	73 (35.4)	0.789
eGFR (mL/min)	57.2±22.6	59.3±21.4	56.7±22.9	0.477
STS-PROM (%)	7.3±4.4	7.0±4.3	7.4±4.5	0.617
Echocardiographic variables				
LVEF (%)	53±14	56±13	52±14	0.106
Mean aortic gradient (mmHg)	39.6±16.1	42.1±14.7	39.0±16.4	0.241
Aortic valve area (cm^2)	0.65±0.23	0.63±0.20	0.65±0.24	0.547
PSAP (mmHg)	42.7±13.6	39.3±13.5	43.3±13.6	0.115
Moderate/severe mitral regurgitation	74 (29.5)	11 (24.4)	63 (30.6)	0.413
Procedural variables				
Success*	214 (85.3%)	38 (84.4)	176 (85.4)	0.865
Prosthesis type				<0.001
Edwards Sapien	160 (64.0)	12 (26.7)	148 (72.2)	
Sapien XT	82 (32.8)	30 (66.7)	52 (25.4)	
Sapien 3	4 (1.6)	2(4.4)	2 (1.0)	
Self-Expandable	4 (1.6)	1 (2.2)	3 (1.5)	
Prosthesis size (mm)				0.014
23 mm	129 (51.6)	24 (53.3)	105 (51.2)	
26 mm	89 (35.6)	10 (22.2)	79 (38.5)	
29 mm	32 (12.8)	11 (24.5)	21 (10.2)	
Valve-in-Valve	20 (8.0)	1 (2.2)	19 (9.2)	0.116
Balloon Post-Dilatation	56 (22.3)	9 (20.0)	47 (22.8)	0.681
Time of procedure "skin to skin" (min)	78±35	93±62	75±25	0.002
Contrast amount (ml)	20 [12-40]	47 [27-73]	20 [10-30]	<0.001
Number of pace runs	5±2	4±1	6±2	0.001

*Values are n (%), mean (±SD) or median [IQR]. * Following VARC-2 criteria [196]*
NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; LVEF: left ventricular ejection fraction; PSAP: pulmonary systolic arterial pressure.

Table 6-2: Clinical and echocardiographic characteristics of the propensity-matched population, stratified according to TAVR approach

Variable	TAO (n=37)	TA (n=65)	p value
Clinical variables			
Age (years)	80.0±7.6	79.6±7.6	0.791
Male sex	14 (37.8)	24 (36.9)	1.00
NYHA class			
I-II	10 (27.0)	18 (27.7)	0.311
III-IV	27 (72.9)	47 (72.3)	
Diabetes mellitus	14 (37.8)	18 (27.7)	0.375
Dyslipidemia	27 (72.9)	48 (73.9)	1.00
Hypertension	33 (89.2)	58 (89.2)	1.00
Coronary artery disease	20 (54.1)	31 (47.7)	0.681
Complete revascularization	4 (25.0)	7 (25.9)	1.00
Incomplete revascularization	12 (75.0)	20 (74.1)	
Previous myocardial infarction	12 (32.4)	12 (18.5)	0.146
History of Atrial fibrillation	12 (32.4)	14 (21.5)	0.245
Cerebrovascular disease	7 (18.9)	12 (18.5)	1.00
Peripheral vascular disease	16 (43.2)	25 (38.5)	0.678
COPD	13 (35.1)	22 (33.9)	1.00
eGFR (ml/min)	58.8±20.9	59.9±22.0	0.675
STS-PROM (%)	7.4±4.3	6.0±3.3	0.313
Echocardiographic variables			
LVEF (%)	55±14	55±15	0.974
Mean aortic gradient (mmHg)	42.6±15.6	42.2±20.3	0.864
Aortic valve area (cm^2)	0.63±0.21	0.70±0.37	0.643
PSAP (mmHg)	39.5±14.8	42.8±13.8	0.537
Moderate/severe mitral regurgitation	9 (25.0)	16 (24.6)	1.00
Moderate/severe aortic regurgitation	4 (10.8)	9 (13.9)	0.765

Values are n (%), mean (±SD) or median [IQR].
NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; LVEF: left ventricular ejection fraction; PSAP: pulmonary systolic arterial pressure.

6.5.2 Biomarkers of myocardial injury post-TAVR

Figure 6-1 describes the median CK-MB and cTnT values at each time point during the initial 72-hour period post-TAVR in the entire study population as well as for the TAo and TA groups. Overall, CK-MB levels remained within normal limits in all but 2 patients (99.2%) at baseline and increased above the upper normal limit in 88% of all patients with a median peak of 20.1 µg/l (IQR: 14.3 to 31.6 µg/l) at 12-24 hours following the procedure. In the TA group, CK-MB levels rose above the upper normal values in 95.6% of patients compared with 51.1% of patients in the TAo group (p<0.001), with median peak values of 21.5 µg/l [IQR: 16.1 to 32.7] and 10.7 [IQR: 7.3 to 17.3], respectively (p<0.001). Baseline

cTnT levels were within normal limits in 87.6% of the overall population, increasing beyond the upper normal range in all patients following TAVR, with a median peak of 0.64 µg/l (IQR: 0.39 to 1.03 µg/l) at 48 hours following TAVR (**Figure 6-1B**). In the TAo group, the peak cTnT level occurred at 24 hours post-TAVR, whereas in the TA group, peak cTnT levels occurred at 48 hours post-TAVR. The maximal cTnT levels in the TAo group within 72 hours post-TAVR was 0.22 µg/l (IQR: 0.14 to 0.37 µg/l) compared with 0.71 µg/l (IQR: 0.51 to 1.09 µg/l) in the TA group ($p< 0.001$) (Figure 1D). **Figure 6-2** describes the overall degree of cardiac biomarker increase (peak values) as well as stratified according to the anatomical approach (TAo vs. TA). An additional analysis for the TA group according to the sheath size is shown in **Table 6-3**. **Figure 6-3** describes the degree and time course of cardiac biomarker response post-TAVR within the propensity score-matched cohort.

The baseline and procedural variables associated with a greater degree of myocardial injury in the entire study population are shown in **Table 6-4**. In the multivariate analysis, the independent predictors of a higher rise in cTnT levels were the transapical approach ($r^2 = 0.230$, $p<0.001$), baseline renal function ($r^2 = 0.042$; $p<0.001$), diabetes ($r^2 = 0.023$; $p=0.004$), and baseline LVEF ($r^2 = 0.028$; $p=0.002$).

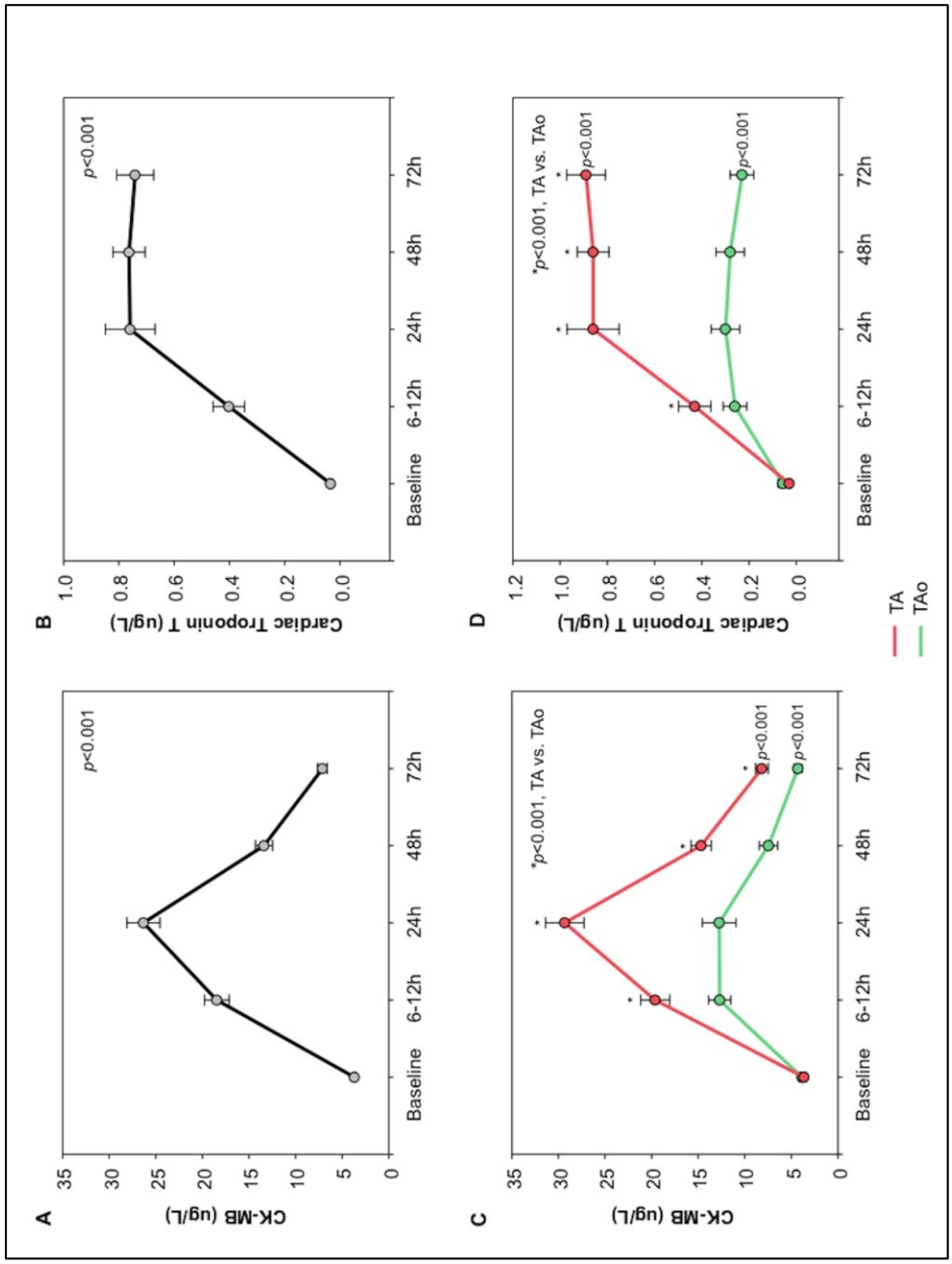

Figure 6-1: Changes in serum markers of myocardial injury following TAVR

Changes in creatine kinase-myocardial band (CK-MB) and cardiac troponin T levels within the 72 h following transcatheter aortic valve replacement (TAVR) in all patients (A and B, respectively) and grouped according to the approach (transaortic [TAo] and transapical [TA]) (C and D, respectively). Values are expressed as median (25th to 75th interquartile range).

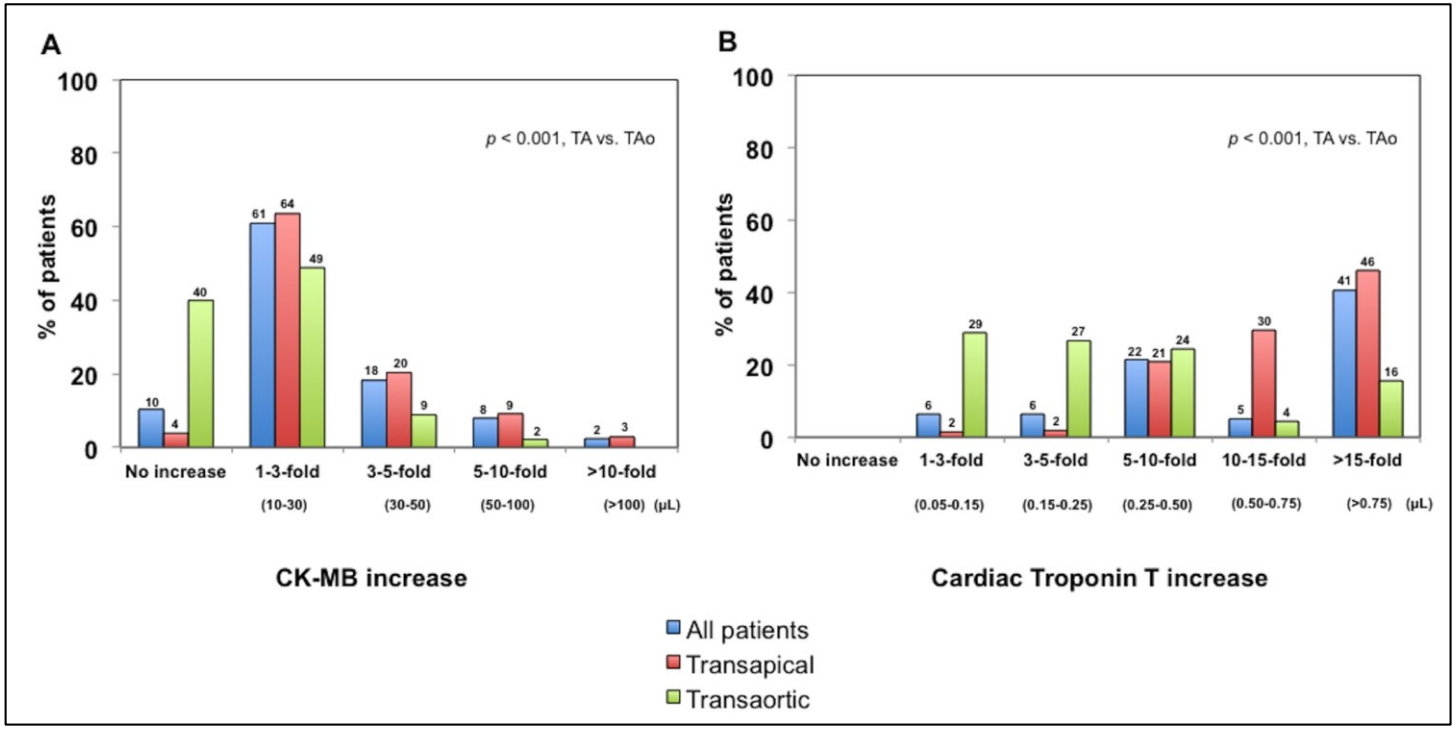

Figure 6-2: Degree of increase in CK-MB and cTnT levels following TAVR

Cardiac biomarker changes following TAVR are grouped according to the degree of creatine kinase-myocardial band (CK-MB) (A) and cardiac troponin T (B) increase in all patients and in the transaortic (TAo) and transapical (TA) approach groups.

Table 6-3: Clinical, echocardiography, and procedural characteristics of the transapical study population according to sheath size

Variable	≤ 24 F (n = 38)	≥ 26-F (n = 168)	p value
Clinical variables			
Age (years)	77 ± 8	78 ± 8	0.295
Male sex	23 (60.5)	77 (45.8)	0.102
NYHA class			0.142
I-II	11 (28.9)	26 (15.5)	
III-IV	27 (71.1)	142 (84.5)	
Diabetes mellitus	13 (34.2)	60 (35.7)	0.861
Dyslipidemia	32 (84.2)	142 (84.5)	0.962
Hypertension	36 (94.7)	154 (91.7)	0.523
Coronary artery disease	32 (84.2)	116 (69.0)	0.061
Previous myocardial infarction	8 (21.1)	73 (43.5)	0.011
History of atrial fibrillation	12 (31.6)	47 (28.0)	0.352
Cerebrovascular disease	22 (57.9)	40 (23.8)	0.987
Peripheral vascular disease	22 (57.9)	88 (52.4)	0.538
COPD	16 (42.1)	57 (33.9)	0.341
eGFR (mL/min)	66.7± 24.6	54.4 ± 22.0	0.003
STS-PROM (%)	7.6 ± 4.0	7.4 ± 4.6	0.793
Echocardiographic variables			
LVEF (%)	51 ± 14	52 ± 14	0.796
Mean aortic gradient (mmHg)	38.4 ± 15.8	39.2 ± 16.5	0.786
Aortic valve area (cm^2)	0.65 ± 0.29	0.65 ± 0.23	0.976
PSAP (mmHg)	39.2 ± 10.7	44.1 ± 13.9	0.075
Moderate/severe mitral regurgitation	6 (20.7)	26 (16.6)	0.588
Procedural variables			
Success*	35 (92.1)	141 (83.9)	0.197
Balloon post-dilatation	11 (28.9)	36 (21.4)	0.319
Time of procedure "skin to skin" (min)	70 [59-92]	70 [60-80]	0.612
Contrast amount (ml)	28 [20-60]	13 [10-28]	<0.001
Number of pace runs	4.8 ± 2.1	5.8 ± 1.9	0.003
Cardiac biomarker rise (µg/l)			
Cardiac kinase-MB	19.5 [15.0-31.0]	22.4 [16.4-32.8]	0.234
Cardiac troponin T	0.62 [0.39-1.02]	0.76 [0.52-1.13]	0.056
30-day clinical outcomes			
Myocardial infarction	1 (2.6)	5 (3.0)	0.909
New onset atrial fibrillation	3 (7.9)	43 (25.6)	0.018
New pacemaker	4 (10.5)	15 (8.9)	0.759
Major vascular complications	1 (2.9)	13 (7.8)	0.261
Major or life-threatening bleeding	5 (13.2)	42 (25.0)	0.083
Stroke	1 (2.9)	6 (3.6)	0.878
Death	-	20 (11.9)	0.025
Hospitalization length (days)	8 [6-10]	8 [7-13]	0.954

*Values are n (%), mean (±SD) or median [IQR]. * Following VARC-2 criteria [196]*
NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; LVEF: left ventricular ejection fraction; PSAP: pulmonary systolic arterial pressure.

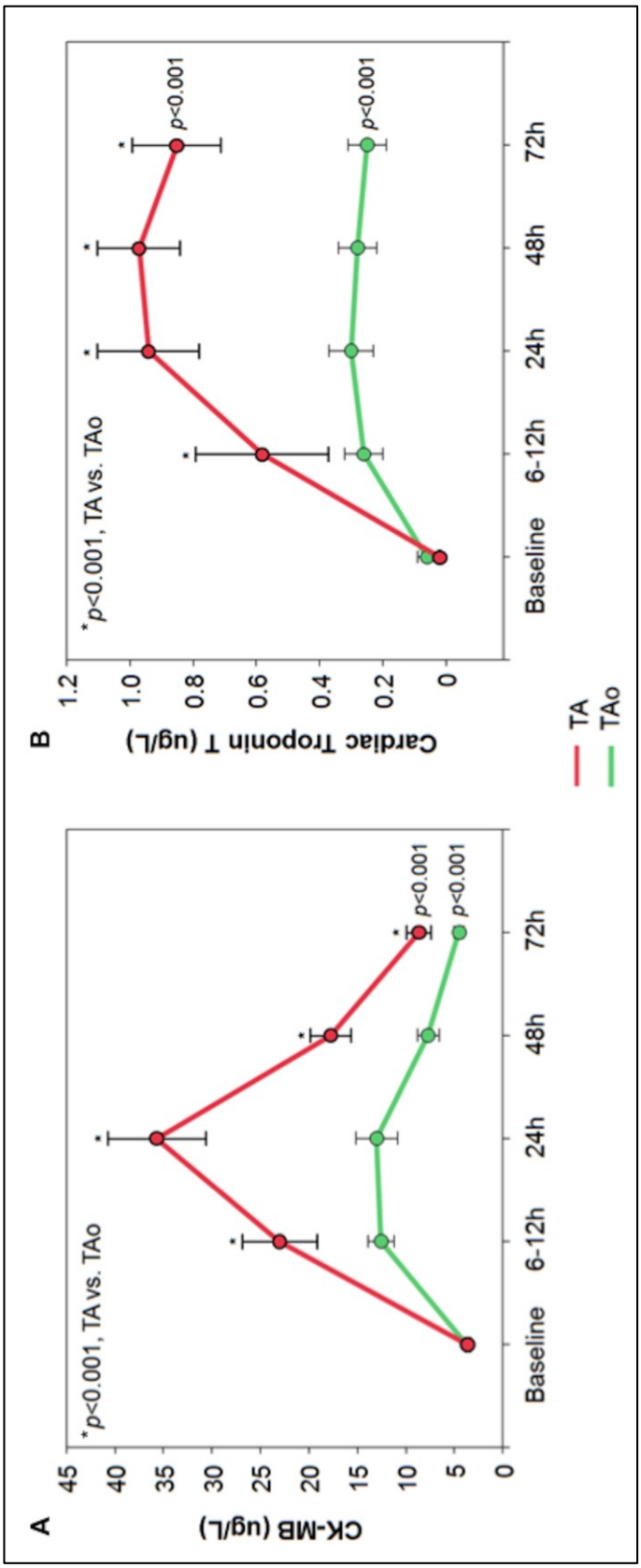
A
CK-MB (ug/L)
45
40
35
30
25
20
15
10
5
0
*p<0.001, TA vs. TAo
*
*
*
*
p<0.001
p<0.001
Baseline
6-12h
24h
48h
72h
B
Cardiac Troponin T (ug/L)
1.2
1.0
0.8
0.6
0.4
0.2
0
*p<0.001, TA vs. TAo
*
*
*
*
p<0.001
p<0.001
Baseline
6-12h
24h
48h
72h
TA
TAo

Table 6-4: Degree of cTnT increase following TAVR depending on baseline and procedural characteristics

Variable	Univariate		Multivariate Model	
	R^2	p value	R^2	p value
Clinical variables				
Age ≥ Median (80 years)	<0.003	0.374		
Sex Male	<0.001	0.747		
Diabetes mellitus	0.031	0.005	0.023	0.004
Dyslipidemia	0.014	0.063		
Hypertension	<0.001	0.949		
Coronary artery disease	<0.001	0.913		
Complete revascularization before TAVR	<0.001	0.762		
History of Atrial fibrillation				
Peripheral vascular disease	0.008	0.162		
COPD	0.005	0.255		
eGFR < Median (56 mL/min)	0.054	<0.001	0.042	<0.001
STS-PROM ≥ Median (6%)	<0.001	0.971		
Echocardiographic variables				
LVEF < 60%	0.018	0.035	0.028	0.002
Mean aortic gradient ≥ Median (38 mmHg)	<0.001	0.817		
Aortic valve area < Median (0.6 cm^2)	0.015	0.051		
PSAP ≥ Median (40 mmHg)	0.009	0.135		
Procedural variables				
Approach Transapical	0.230	<0.001	0.230	<0.001
Balloon Post-Dilatation	0.003	0.412		
Number of pace runs ≥ Median (5)	0.014	0.059	0.057	0.152

Cardiac troponin T (cTnT).
TAVR: transcatheter aortic valve replacement; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; LVEF: left ventricular ejection fraction; PSAP: pulmonary systolic arterial pressure.

6.5.3 Clinical outcomes and prognostic significance of myocardial injury

Table 6-5 describes 30-day and late outcomes of the overall study population as well as stratified according to the procedural approach (TAo vs. TA). A total of 24 patients (9.7%) had died within the 30 days following TAVR, and 49 patients (19.5%) died during a median follow-up of 12 [9-12] months. Early (30-day post-TAVR) or late clinical outcomes did not differ between the TAo and TA groups in either the overall (**Table 6-5**) or propensity-matched cohorts (**Table 6-6**).

Table 6-7 describes factors associated with clinical events at various time-point intervals post-TAVR. In a multivariate analysis, peak post-TAVR cTnT levels independently associated with 30-day all-cause mortality (p=0.043), late overall mortality (p =0.005), and late cardiac mortality (p=0.001). Greater increments of post-TAVR cTnT levels independently associated with late cardiac death or re-hospitalization due to cardiac causes (p<0.001). A 15-fold increase in cTnT levels after TAVR, irrespective of procedural approach, best identified patients at greater risk for 30-day mortality (AUC of 0.76 [95%CI: 0.64-0.87], p<0.001), as well as late mortality (AUC of 0.69 [95%CI: 0.61-0.78], p<0.001).

Table 6-5: Thirty-day and late clinical outcomes

Variable	All Patients (n=251)	TAO (n=45)	TA (n=206)	p value
30-day clinical outcomes				
Myocardial Infarction	7 (2.8)	1 (2.2)	6 (2.9)	0.799
New onset atrial fibrillation	57 (22.7)	11 (24.4)	46 (22.3)	0.759
New pacemaker	24 (9.6)	5 (11.1)	19 (9.2)	0.696
Major vascular complications	18 (7.3)	4 (9.1)	14 (7.0)	0.624
Major or life-threatening bleeding	62 (24.7)	15 (33.3)	47 (22.8)	0.138
Stroke	10 (4.1)	2 (4.5)	8 (4.0)	0.846
Death	24 (9.6)	5 (11.1)	19 (9.2)	0.696
Hospitalization length (days)	8 [7-12]	8 [7-10]	8 [6-12]	0.607
Echocardiographic post-procedure				
LVEF (%)	52±14	52±16	50±15	0.297
Mean aortic gradient (mmHg)	11.5±6.6	11.3±4.0	11.6±7.1	0.849
Aortic valve area (cm^2)	1.44±0.38	1.37±0.42	1.45±0.37	0.206
PSAP (mmHg)	42.8±13.0	38.0±13.0	43.8±12.8	0.021
Moderate/severe mitral regurgitation	40 (17.6)	8 (19.5)	32 (17.2)	0.726
Moderate/severe aortic regurgitation	9 (3.6)	4 (9.1)	5 (2.5)	0.055
Late clinical outcomes				
Cumulative mortality	49 (19.5)	7 (15.6)	42 (20.4)	0.459
Cardiac mortality	36 (14.3)	6 (13.3)	30 (14.6)	0.831
Cumulative cardiac mortality and/or cardiac rehospitalization	77 (30.7)	13 (28.9)	64 (31.1)	0.774

Values are n (%), mean (±SD) or median [IQR].
LVEF: left ventricular ejection fraction; PSAP: pulmonary systolic arterial pressure.

Table 6-6: Thirty-day and late clinical outcomes of the propensity-matched population

Variable	TAO (n=37)	TA (n=65)	p value
30-day clinical outcomes			
Myocardial Infarction	1 (2.8)	2 (3.1)	1.00
New onset atrial fibrillation	7 (18.9)	18 (27.7)	0.351
New pacemaker	5 (13.5)	7 (10.8)	0.753
Major vascular complications	3 (8.3)	4 (6.2)	0.698
Major or life-threatening bleeding	2 (6.3)	7 (11.1)	0.713
Stroke	2 (5.6)	1 (1.5)	0.545
Death	3 (8.1)	6 (9.2)	1.00
Hospitalization length (days)	8 [7-11]	8 [7-10]	0.297
Echocardiographic post-procedure			
LVEF (%)	53±13	53±12	0.873
Mean aortic gradient (mmHg)	11.5±3.3	11.5±7.0	0.966
Aortic valve area (cm2)	1.42±0.31	1.46±0.41	0.675
PSAP (mmHg)	40.9±8.3	43.4±12.2	0.372
Moderate/severe mitral regurgitation	7 (21.2)	7 (12.1)	0.365
Moderate/severe aortic regurgitation	3 (8.3)	3 (4.6)	0.663
Late clinical outcomes			
Cumulative mortality	5 (13.5)	13 (20.0)	0.409
Cardiac mortality	4 (10.8)	10 (15.4)	0.519
Cumulative cardiac mortality and/or cardiac rehospitalization	10 (27.0)	23 (35.4)	0.386

Values are n (%), mean (±SD) or median [IQR].
LVEF: left ventricular ejection fraction; PSAP: pulmonary systolic arterial pressure.

Table 6-7: Predictors of clinical outcomes following TAVR

	Univariate		Multivariate Model	
	OR/HR (95% CI)	p value	HR (95% CI)	p value
30-day mortality (n=24)				
eGFR (mL/min)*	1.03 (1.01-1.05)	0.011	1.23 (1.03-1.38)	0.025
Moderate/severe mitral regurgitation	2.66 (1.14-6.24)	0.024	-	-
Cardiac troponin T peak (µg/l)#	1.34 (1.03-1.75)	0.029	1.24 (1.01-1.54)	0.043
Cumulative mortality (n=49)				
Male Sex	1.67 (0.95-2.94)	0.075	1.81 (1.02-3.22)	0.044
eGFR (mL/min)*	1.02 (1.01-1.04)	0.001	1.20 (1.08-1.30)	0.001
Cardiac troponin T peak (µg/l)#	1.13 (1.05-1.22)	0.001	1.16 (1.07-1.26)	0.001
Cumulative cardiac mortality (n=36)				
Chronic atrial fibrillation	2.51 (1.26-5.03)	0.009	2.38 (1.18-4.79)	0.015
eGFR (mL/min)*	1.03 (1.01-1.04)	0.002	1.23 (1.09-1.35)	0.002
Cardiac troponin T peak (µg/l)#	1.14 (1.06-1.23)	0.001	1.17 (1.07-1.28)	0.001
Cumulative cardiac mortality and/or cardiac rehospitalization (n=77)				
Age	1.04 (1.01-1.08)	0.011	1.04 (1.01-1.07)	0.011
eGFR (mL/min)*	1.02 (1.01-1.03)	0.028	-	-
Cardiac troponin T peak (µg/l)#	1.20 (1.11-1.32)	<0.001	1.22 (1.11-1.33)	<0.001

**Per 10 mL/min decrease in eGFR. #Per 1 µg/L increase in cardiac troponin T.*
eGFR: estimated glomerular filtration.

6.5.4 Changes in left ventricular function over time

In the overall study population, compared with immediate post-TAVR measurements, LVEF at 6- to 12-month post-TAVR remained similar (52± 14 vs. 51 ± 14%, p=0.10). No significant changes in global strain were observed over time (hospital discharge: 16.2 ± 5.0%; 6- to 12-month follow-up: 15.7 ± 4.5%, p=0.86). **Figure 6-4** shows changes in ventricular function over time stratified according to TAo versus TA access. In the TAo group, there was a significant increase in LVEF over time (Δ LVEF: +3% [0; 13]), whereas no changes in LVEF over time were observed in the TA group (Δ LVEF 0 [-10; 7], p=0.058 vs. the TAo group) (**Figure 6-4A**). In the propensity score-matched cohort, significant differences in the changes of LVEF over time were observed between groups, with a greater improvement in LVEF over time observed in the TAo group (p=0.015) (**Figure 6-4C**).

A greater increase in left ventricular strain over time was observed in the TAo group compared to the TA group (Δ strain 2.06% [-0.23; 5.28] vs. 0.22% [-2.20; 2.58],

respectively; p=0.039) (**Figure 6-4B**). In the propensity-matched cohort, the improvement in ventricular strain in the TAo group was similar to the TA group (p=0.080) (**Figure 6-4D**). The correlation between changes in CK-MB and cTnT levels with the changes in LVEF between baseline and follow-up for the entire population are shown in **Figure 6-5**. Increases of cTnT levels post-TAVR had a significant, yet modest inverse correlation with the changes in LVEF and GLS over time (r = -0.24, p=0.001 for LVEF; r = -0.27, p= 0.004 for GLS). Also, a 13-fold increase in cTnT value best identified the patients at higher risk for LVEF and GLS decrease following TAVR (AUC 0.611 [95%CI: 0.53-0.70], p=0.013).

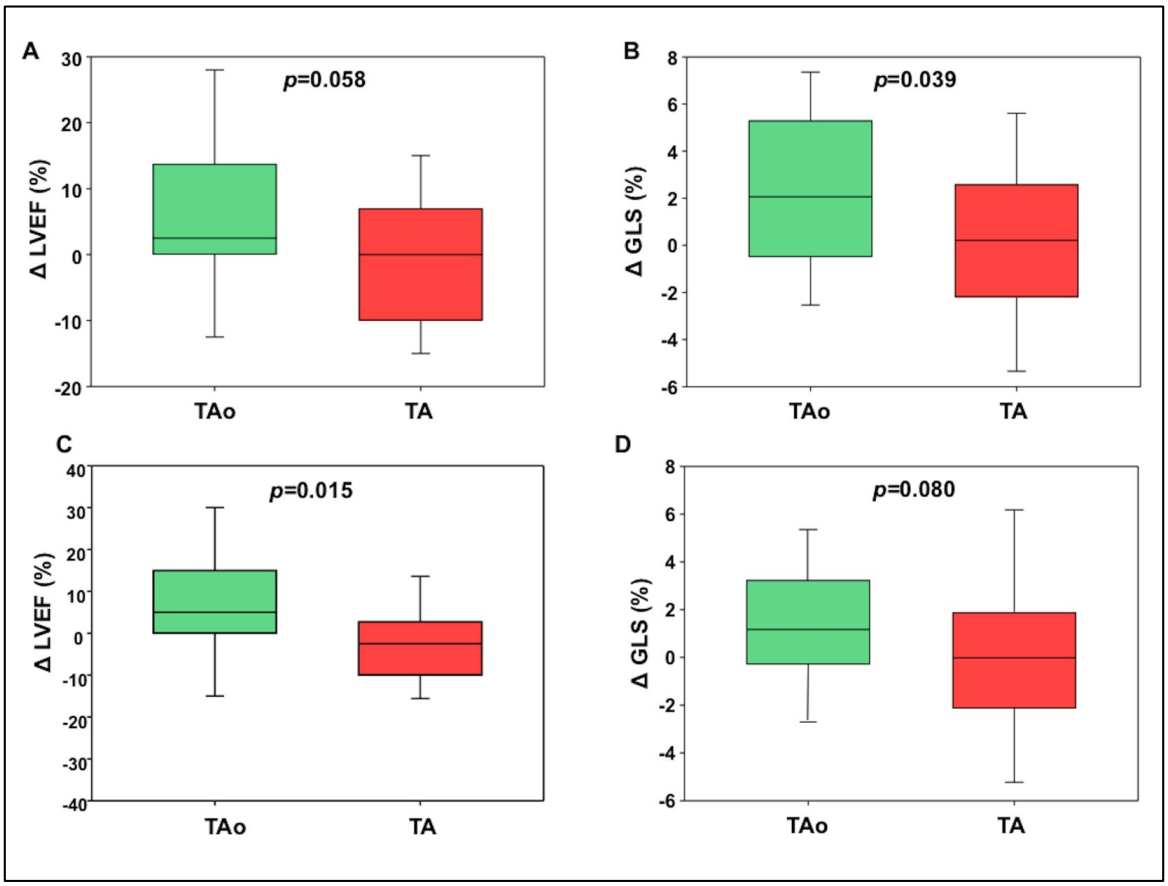

Figure 6-4: Delta (Δ) in LVEF and GLS after tAVR according to the approach

Change (delta [D]) in left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) after transcatheter aortic valve replacement (TAVR) according to the approach: transapical (TA [red bars]) versus transaortic (TAo [green bars]). (A) Changes in LVEF and (B) GLS between the baseline and 6- to 12-month echocardiography after TAVR for the overall population and for the propensity matched cohort (Figures C and D, respectively).

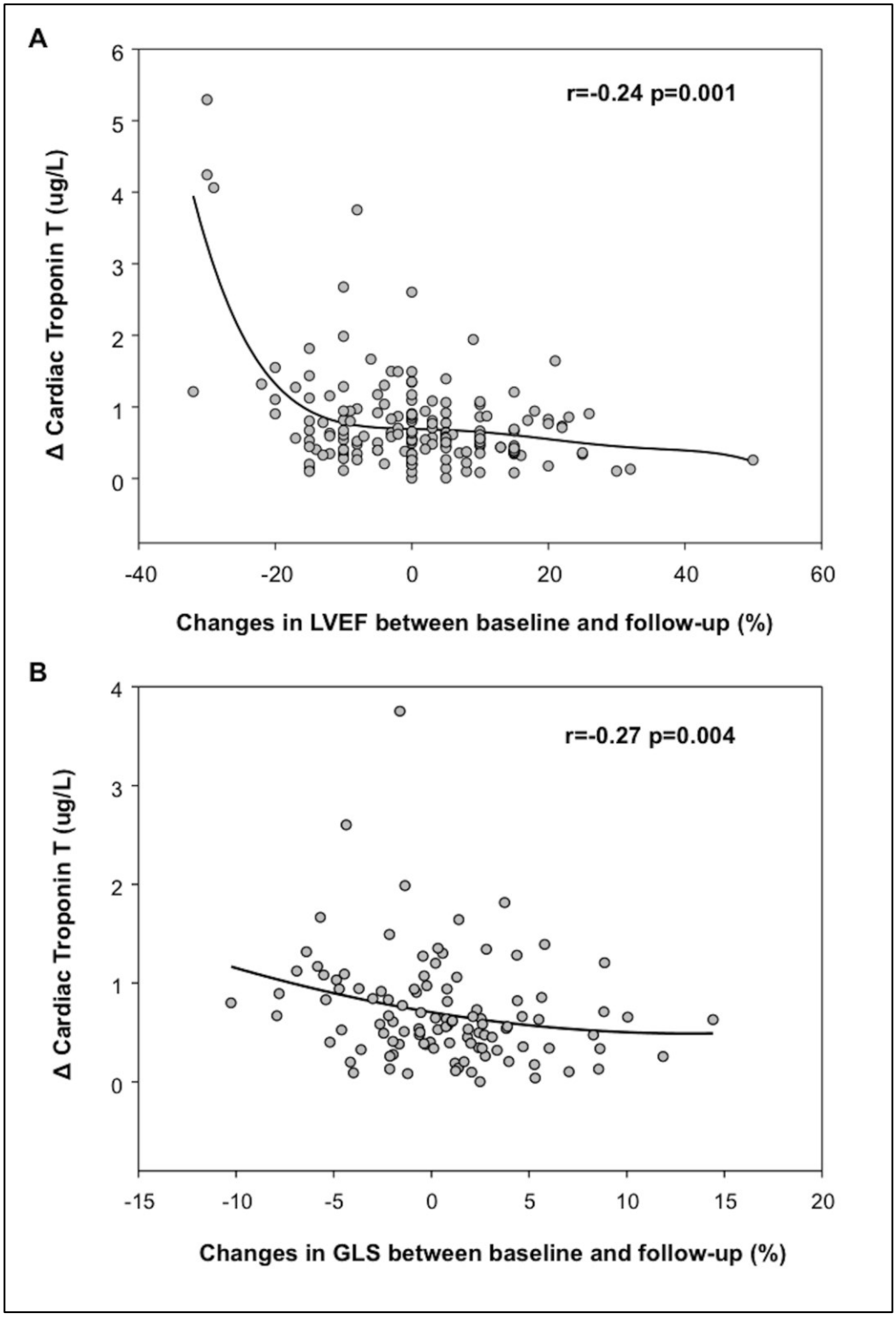

Figure 6-5: Delta (Δ) in LVEF and GLS After TAVR according to the approach

Relationship between the maximal increase in cardiac troponin T and the changes in left ventricular ejection fraction (LVEF) (A) and in global longitudinal strain (GLS) following transcatheter aortic valve replacement (TAVR).

6.6 DISCUSSION

TAVR in patients deemed unsuitable for TF approach was systematically associated with some degree of myocardial injury as determined by an increase in CKMB and cTnT levels. The TA approach was associated with a 2- to 3-fold greater increase in cardiac biomarkers of myocardial injury as compared to the TAo approach. A greater rise in cTnT levels was associated with poorer outcomes as determined by an increase in 30-day and 1-year mortality, as well as an increase in the combined endpoint of cardiac mortality/rehospitalization. The higher degree of myocardial injury in the TA group was also associated with impaired ventricular function at 6- to 12-month follow-up as evaluated by LVEF and GLS.

*6.6.1 **Incidence and degree of myocardial injury***

Previous studies have demonstrated the systemic release of myocardial proteins during TAVR, reflecting myocardial injury.[136,214-217] These peri-procedural cTnT and CKMB elevations are thought to reflect a variety of patient- and procedural-related factors. Indeed, TA-TAVR, involving the introduction of large-bore catheters through the ventricular apex has been postulated as a dominant factor promoting myocardial injury.[167,216] The present study confirms this notion, yet further describes a unique comparison to the more novel TAo-TAVR approach. Of interest is the 2- and 3-fold greater rise in CKMB and cTnT levels following TA- compared with TAo-TAVR, with such differences persisting following adjustment for between-group baseline differences in clinical characteristics. Intriguingly, differences in the degree of myocardial injury between the TA- and TAo-TAVR groups were similar to previous comparisons between TA- and TF-TAVR.[167,216,217] Collectively, these data strongly suggest that left ventricular apical perforation contributes most to peri-procedural TAVR-related myocardial injury. Similar to prior studies (2-4, 11), TA approach and baseline renal function were the most important predictors of myocardial injury post-TAVR, followed by diabetes and LVEF.[136,214,216,217]

6.6.2 Prognostic significance of peri-procedural TAVR-related myocardial injury

The extent of myocardial biomarker release post-TAVR has previously been linked to poorer short and mid-term clinical outcomes.[167,196,214,216] However, apart from evaluating the incidence and clinical importance of cardiac biomarker elevation post-TAVR, no study to date assessed the prognostic significance of myocardial injury in patients deemed unsuitable for TF-TAVR, including those undergoing the more novel TAo-TAVR approach. The results of the present study demonstrate a significant association between greater increments of cTnT levels with early (30-day) and late morbidity and mortality. We found that a 15-fold increase in cTnT was the optimal threshold for predicting adverse clinical outcomes. This level of post-TAVR cTnT rise is consistent with the VARC-2 criteria's proposed threshold for defining peri-procedural TAVR-related myocardial infarction.[196]

A TA-TAVR approach was associated with impaired LV systolic function at mid-term follow up compared with the TAo-TAVR approach, demonstrated by both LVEF and speckle-tracking echocardiography. The LVEF was reduced (defined as LVEF <50%) in one third of patients in the present study, however this rate increased up to 50% when left ventricular function was evaluated by GLS (defined as GLS < -15%). This is consistent with previous studies of mainly TF-TAVR patients.[265] Importantly, only those patients undergoing TAo-TAVR demonstrated significant improvements in left ventricular function over time as evaluated by both LVEF and longitudinal strain in the present study. Although small, such improvements in LVEF have been associated with improved clinical outcomes after TAVR and SAVR in previous studies.[233,266,267] There however remains controversy as to whether such improvements are chiefly a result of reduced left ventricular afterload post-TAVR[268] or via intrinsic alterations of myocardial structure and function.[255,265,269] Indeed, TA-TAVR significantly associates with left ventricular apical fibrosis involving ~5% of myocardium,[226] contributing to significant apical wall motion abnormalities.[220] This may in turn adversely affect myocardial recovery post-TAVR.

Poorer outcomes following TA- (vs. TF) –TAVR have been demonstrated in a number of large registries, with a 1.5- to 2-fold greater mortality for the TA- vs. TF-TAVR;[226,270] recently confirmed in a meta-analysis.[270] Some have postulated that the higher-risk profile

of patients undergoing TA-TAVR (vs. TF-TAVR), despite difficulties in accurately accounting for a number of confounding factors, could partially explain such prognostic differences.[233,270] As we await further data amongst patients with low LVEF deemed unsuitable for TF-TAVR, current data suggests that alternative anatomical approaches to TAVR, such as the TAo approach, may be preferable over the more established TA-TAVR approach in such patients.

The TA-TAVR approach has been key in the overall development of the TAVR field, currently accounting approximately 20-30% of all balloon-expandable TAVR procedures.[136] Moreover, many novel devices and improved iterations of TAVR-delivery systems, as well as for the transcatheter mitral valve replacement, are currently in development for performing transapical procedures.[136] Therefore, the importance of improving TA delivery systems and apical closure techniques for minimizing apical trauma and subsequent myocardial injury is paramount. Newer generation devices with lower profile, such as the new 18F Certitude delivery system for the TA placement of the SAPIEN 3 valve (Edwards Lifesciences Inc., Irvine, CA) may associate with even further reductions in peri-procedural TAVR-related biomarkers elevation.[154]

6.6.3 Study Limitations

Despite the present analysis comprising one of the largest cohort of patients undergoing TAo-TAVR and involving systematic measurements of cardiac biomarkers, patients were non-randomized to either a TA or TAo approach. Consequently, even the propensity-matched sensitivity analysis may not have sufficiently accounted for unmeasured between-group confounding factors unduly influencing study conclusions. Moreover, the number of patients who had TAo-TAVR was limited, and this precluded drawing definitive conclusions regarding clinical outcomes. Future studies with larger sample size and longer follow-up are needed to determine whether or not differences in myocardial injury and LVEF recovery between groups (TAo vs. TA) translate into significant differences in mortality and re-hospitalization rates. The results of this study were obtained in patients undergoing TAVR mostly with a balloon-expandable valve, and may not apply to those patients receiving a self-expandable valve through the TA approach.

6.7 CONCLUSION

Peri-procedural TAVR-related myocardial injury in non-transfemoral candidates was demonstrated in all patients, but transapical approach was associated with significantly greater myocardial injury compared with transaortic approach. A higher degree of myocardial injury translated into reduced left ventricular function improvement and lower early- and mid-term survival rates.

6.8 SOURCES OF FUNDINGS

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6.9 DISCLOSURE

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

CHAPTER 7: ARTICLE 4

Myocardial Injury Following Transcatheter Aortic Valve Implantation: Insights from Delayed-Enhancement Cardiovascular Magnetic Resonance

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7.1 RÉSUMÉ

LÉSIONS MYOCARDIQUES APRÈS L'IMPLANTATION DE VALVE AORTIQUE PAR CATHÉTER : APERÇUS DE LA RÉSONANCE MAGNÉTIQUE CARDIAQUE AVEC REHAUSSEMENT TARDIF

Objectif : Évaluer la présence, la localisation et l'étendue des lésions myocardiques déterminées par la résonance magnétique cardiaque avec rehaussement tardif (RMC), chez des patients subissant une implantation de valve aortique par cathéter (TAVI).

Méthodes et résultats : Un total de 37 patients, ayant subi une procédure TAVI réussie avec une valve expansible par ballonnet (transapicale [TA], n=11; non-TA, n=26), ont été inclus. Les concentrations de biomarqueurs cardiaques (CK-MB et cTnT) ont été mesurées initialement et à la suite de la procédure TAVI. La RMC a été effectuée dans la semaine précédant la procédure TAVI ainsi que dans les 30 jours suivant cette procédure. Des augmentations des biomarqueurs cardiaques ont été détectées chez 97 % des patients tel que déterminé par une augmentation des cTnT, et chez 49 % des patients tel que déterminé par une augmentation des CK-MB. À la suite de la procédure TAVI, aucune nouvelle nécrose myocardique n'a été observée avec l'approche non-transapicale. Cependant, tous les patients ayant eu une procédure TAVI par l'approche TA présentaient une nouvelle nécrose focale myocardique dans l'apex, avec une étendue myocardique médiane de 5 [2,0-7,0] % et une masse nécrotique de 3,5 [2,3-4,5] g.

Conclusion : Bien que des augmentations de certains biomarqueurs de lésions myocardiques ont systématiquement été observées à la suite des procédures TAVI, de nouvelles nécroses myocardiques, évaluées par RMC ont été observées seulement chez les patients subissant la procédure par l'approche transapicale. Ces nécroses impliquaient ~5 % du myocarde et ce, au niveau de l'apex.

Mots clés : Implantation de valve aortique par cathéter; Biomarqueur cardiaque; Lésion myocardique; Résonance magnétique cardiaque; Rehaussement tardif avec gadolinium.

Ces travaux ont été présentés lors du congrès Transcatheter Cardiovascular Therapeutics (TCT) (Washington-DC, EUA; octobre 2014).

7.2 ABSTRACT

Aims: To evaluate the presence, localization and extent of myocardial injury as determined by late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) in patients undergoing transcatheter aortic valve implantation (TAVI).

Methods and results: A total of 37 patients, who underwent successful TAVI with a balloon-expandable valve (transapical [TA], n=11; non-TA, n=26), were included. Cardiac biomarkers (CK-MB and cTnT) levels were determined at baseline and following TAVI. CMR was performed within a week before and within 30 days following TAVI. Some increase in cardiac biomarkers was detected in 97% of the patients as determined by a rise in cTnT, and in 49% of the patients as determined by a rise in CK-MB. Following TAVI, no new myocardial necrosis defects were observed with the non-TA approach. Nonetheless, all of the patients who underwent TAVI through the TA approach had new focal myocardial necrosis in the apex, with a median myocardial extent and necrotic mass of 5 [2.0-7.0]% and 3.5 [2.3-4.5]g, respectively.

Conclusions: Although some increase in cardiac biomarkers of myocardial injury was systematically detected following TAVI, new myocardial necrosis as evaluated by CMR was observed only in patients undergoing the procedure through the TA approach, involving ~5% of the myocardium in the apex.

Key word: Transcatheter aortic valve implantation; Cardiac biomarkers; Myocardial injury; Cardiac magnetic resonance imaging; Late gadolinium enhancement.

7.3 INTRODUCTION

A mild rise in cardiac biomarkers of myocardial injury is frequently observed following transcatheter aortic valve implantation (TAVI),[167,214,216,217] and a greater rise in these cardiac biomarkers has been associated with a negative effect on left ventricular ejection fraction (LVEF) and acute and midterm mortality.[167,196,214,216] However, the mechanisms associated with this increase in cardiac biomarkers of myocardial injury are not well understood and very few data exist on the presence, location and extent of new myocardial necrosis following TAVI.

Contrast-enhanced cardiovascular magnetic resonance (CMR) imaging permits the accurate detection and quantification of irreversible myocardial injury, and it can detect very small areas of myocardial necrosis,[271,272] of which even minor necrosis of the order of 1.4% of LV myocardium are associated with seven-fold increase in major cardiac events.[273] In the context of percutaneous coronary interventions, it has been shown that even mild increases in cardiac biomarkers were associated with new focal defects of myocardial necrosis,[272] but data in the context of TAVI are lacking. The objectives of the present study were therefore to evaluate the presence, location, and extent of myocardial injury following TAVI as determined by CMR.

7.4 METHODS

7.4.1 ***Patient Population***

We prospectively screened 75 consecutive patients for the study, so that 45 patients diagnosed with severe symptomatic aortic stenosis who were accepted for a TAVI with a balloon-expandable valve were enrolled. A total of 30 patients were not included in the study due to the following reasons: critical state (n=12), previous pacemaker (n=5), and logistic reasons (n=13). Forty-five patients had therefore a CMR performed within 7 days (median: 1 [1-2] days) before TAVI, and 37 of them had a repeat CMR exam performed within 30 days (median: 6 [3-27] days) following TAVI. The reasons to not repeat the CMR exam after TAVI were: pacemaker implantation post-TAVI (n=4), death (n=2), and logistic reasons (n=2). The actual analysis included 37 patients submitted to uncomplicated

TAVI (transfemoral [TF] approach: 22 patients; transaortic [TAo] approach: 4 patients; transapical [TA] approach: 11 patients). Patients undergoing TAVI through retrograde approach (TF and TAo) were pooled together for analysis. The baseline characteristics and outcomes of the non-included patients are shown in **Table 7-1**.

Selection of the approaches was based on the appropriateness of the iliofemoral arteries as previously described,[136] and details about the TAVI procedure have been provided elsewhere.[136] In TA-TAVI cases, the technique used for apical closure consisted of two large purse string sutures using Ethibond 2-0 large needle sutures with pledges. All baseline and procedural characteristics were prospectively collected on pre-set data collection forms. Baseline co-morbidities were defined according to the Society of Thoracic Surgeons (STS) criteria, and periprocedural events according to the VARC (Valve Academic Research Consortium)-2 criteria.[196] Coronary artery disease was defined as the presence of coronary lesion with a diameter stenosis ≥ 50% in vessels ≥ 2.0mm, or prior coronary revascularization. The procedures were performed under a compassionate clinical use program approved by Health Canada, and all patients provided signed informed consent for the procedures.

7.4.2 Laboratory and Doppler echocardiographic data

All patients underwent a Doppler echocardiographic examination at baseline, before the intervention, and at 6-month to 1-year follow-up, and LVEF was calculated using the biplane Simpson method. Blood samples were collected at baseline, 6 to 12, 24, 48, and 72 h following the procedure. Creatine kinase-myocardial band (CK-MB) mass and cardiac troponin T (cTnT) levels were measured at each point time, by electrochemiluminescence immunoassay (Roche, Minneapolis, Minnesota). Based on the 99th percentile in a healthy population and the requirement of a ≤ 10% coefficient variation, the upper normal limits for CK-MB and cTnT levels in our institution were 10 and 0.05 μg/l, respectively. Myocardial injury was defined as a CK-MB level >10 μg/l or a cTnT level > 0.05 μg/l. In those patients with elevated CK-MB or cTnT levels at baseline, myocardial injury was defined as any increase >20% after the procedure.

7.4.3 Cardiac magnetique resonance

The CMR studies were performed using a 1.5 Tesla Philips Achieva scanner operating release 2.6 level 3, dedicated 32-channel phased-array cardiac coil, and vectorcardiographic gating during successive end-expiratory breath-holds (Philips Healthcare, Best, The Netherlands). Cine imaging of cardiac volumes and function was performed by steady-state free precession technique, at 30 phases per cardiac cycle, in 8-14 parallel short-axis (full coverage) and 2-chamber, 4-chamber, and 2 orthogonal left ventricular outflow tract (LVOT) planes (8 mm thickness, 0 mm gap). Typical parameters included TR/TE of 3.4/1.2 ms, flip angle 40°, NEX of 1, yielding in-plane spatial resolution of 1.6 × 2 mm.

Late gadolinium enhancement (LGE) images were acquired in 2D using an inversion recovery fast gradient echo sequence triggered every other heartbeat, 10 minutes after intravenous injection of 0.2 mmol/kg gadolinium diethyltriaminepenta- acetic acid. The in-plane image resolution was typically 2.5 mm, and each imaging voxel represented approximately 42 µl of tissue. Volumetric coverage of the entire LV was achieved using 2 long-axis planes (2-chamber and 4-chamber) and the short-axis plane matching functional imaging to ensure precise co-registration between cine CMR and infarct measurements.

All CMR images were analyzed in a central core laboratory by experienced technicians blinded to patient data and supervised by an experienced CMR reader cardiologist using a commercially available software (QMass version 7.2, Medis, Leiden, The Netherlands). Briefly, LV volumes and ejection fraction were measured from semi-automated tracings of endocardium and epicardium performed on all 30 phases of the RR cycle in short axis SSFP images. To determine infarct size, quantitative assessment of LGE volume was performed on short axis inversion recovery images by semi-automated signal intensity analysis, using the full width at half-maximum technique on the 17-segment model.

Reproducibility on LGE data was evaluated in 10 patients and revealed excellent inter- and intra-observer agreement with Lin's concordance correlation coefficient of 0.92 ($p < 0.0001$; Bland & Altman 95%CI: -2.43 to 2.48) and of 0.98 ($p < 0.0001$; Bland & Altman 95%CI: -1.96 to 2.55), respectively.

7.4.4 ***Statistical Analysis***

Categorical variables are reported as n (%). Continuous variables are expressed as median (25th to 75th interquartile range [IQR]). Group comparisons were analyzed using the Wilcoxon rank sum test for continuous variables, and chi-square test for categorical variables. An analysis of variance for repeated measures was performed to test for equal means at different times (baseline, 6 to 12, 24, 48, and 72 h) for the cardiac enzyme values and LVEF. For the comparison of the continuous variables before and after TAVI (including LGE as determined by CMR) paired data were compared using the paired Student t test or Wilcoxon signed- rank test, according to variable distribution. The results were considered significant with p values < 0.05. All analyses were conducted using the statistical package SPSS 19 (SPSS, Chicago, IL).

7.5 RESULTS

The main baseline and procedural characteristics of the study population are shown in **Table 7-2**. The TF/TAo patients presented baseline characteristics similar to those of the TA approach patients, except for an increased age ($p=0.040$), and reduced incidence of coronary artery disease ($p =0.001$), and peripheral arterial disease ($p =0.008$). Additionally, in the TA group the Edwards Sapien valve was more frequently implanted and there was an increased number of pace runs an increased hospital stay (all with $p <0.001$).

Table 7-1: Clinical characteristics of patients who underwent cardiac magnetic resonance (CMR) exam at baseline, according to the performance or not of CMR following TAVI

Variable	All Patients (n = 37)	Non-included Patients (n=8)	p Value
Clinical variable			
Age, years	81 [77-84]	80 [74-84]	0.760
Men	21 (56.8%)	6 (75.0%)	0.340
Body mass index, kg/m^2	27.5 [23.0-31.5]	29.4 [27.9-32.4]	0.180
New York Heart Association functional class			0.462
I-II	13 (35.1%)	2 (25.0%)	
III-IV	24 (64.9%)	6 (75.0%)	
Diabetes	11 (29.7%)	4 (50.0%)	0.270
Dyslipidemia	24 (64.9%)	7 (87.5%)	0.259
Hypertension	31 (83.8%)	6 (75.0%)	0.556
Coronary artery disease	22 (59.5%)	5 (62.5%)	0.874
Previous myocardial infarction	10 (27.0%)	2 (25.0%)	0.906
Prior coronary artery bypass graft	17 (45.9%)	3 (37.5%)	0.663
Atrial fibrillation (by history)	13 (35.1%)	1 (12.5%)	0.210
Cerebrovascular Disease	6 (16.2%)	-	0.221
Peripheral vascular disease	12 (32.4%)	1 (12.5%)	0.259
Chronic obstructive pulmonary disease	13 (35.1%)	1 (12.5%)	0.210
Porcelain Aorta	11 (29.7%)	2 (25.0%)	0.789
Valve-in-Valve	7 (18.9%)	1 (12.5%)	0.667
Estimated glomerular filtration, mL/min	63 [55-82]	58 [41-63]	0.047
Society of Thoracic Surgeons predicted risk of mortality, %	5.5 [3.4-8.3]	4.1 [2.9-6.2]	0.327
Echocardiographic variable			
Left ventricular ejection fraction, %	60 [47-60]	51 [35-60]	0.271
Mean aortic gradient, mmHg	40 [30-52]	41 [25-51]	0.622
Aortic valve area, cm^2	0.70 [0.55-0.87]	0.60 [0.52-0.76]	0.575
Pulmonary systolic arterial pressure, mmHg	40 [31-55]	38 [34-45]	0.825
Moderate/severe mitral regurgitation	7 (18.9%)	2 (25.0%)	0.779
Procedural variable			
Success*	33 (89.2%)	7 (87.5%)	0.692
Prosthesis type			0.207
Edwards Sapien	9 (24.3%)	-	
Sapien XT	26 (70.3%)	8 (100%)	
Sapien 3	2 (5.4%)	-	
Prosthesis size, mm			0.040
23 mm	17 (45.9%)	2 (25.0%)	
26 mm	13 (35.1%)	1 (12.5%)	
29 mm	7 (18.9%)	5 (62.5%)	
Balloon Post-Dilatation	11 (29.7%)	-	0.207

Continued

Conclusion

Variable	All Patients (n = 37)	Non-included Patients (n=8)	p Value
30-day outcomes*			
Major vascular complications	2 (5.4%)	-	1.0
Major or life-threatening bleeding	4 (10.8%)	2 (25.0%)	0.286
Acute renal failure	1 (2.7%)	-	1.0
Stroke	-	1 (12.5%)	0.178
Death	-	2 (25.0%)	0.028
Hospitalization length, days	6 [4-9]	13 [5-21]	0.161

Data are presented as median [IQR] or n (%).
** Following VARC-2 criteria[196]*

Table 7-2: Clinical, echocardiography, and procedural characteristics of the study population

Variable	All Patients (n = 37)	Transfemoral/ Transaortic (n = 26)	Transapical (n = 11)	p Value
Clinical variable				
Age, years	81 [77-84]	83 [79-85]	78 [71-79]	0.040
Men	21 (56.8%)	14 (53.8%)	7 (63.6%)	0.583
New York Heart Association functional class				0.593
I-II	13 (35.1%)	8 (30.8%)	5 (45.5%)	
III-IV	24 (64.9%)	18 (69.2%)	6 (54.5%)	
Diabetes	11 (29.7%)	7 (26.9%)	4 (36.4%)	0.566
Hypertension	31 (83.8%)	21 (80.8%)	10 (90.9%)	0.444
Coronary artery disease	22 (59.5%)	11 (42.3%)	11 (100.0%)	0.001
Complete revascularization	12 (54.5%)	8 (72.7%)	4 (36.4%)	0.087
Incomplete revascularization	10 (45.5%)	3 (27.3%)	7 (63.6%)	
Previous myocardial infarction	10 (27.0%)	4 (15.4%)	6 (54.5%)	0.014
Prior coronary artery bypass graft	17 (45.9%)	10 (38.5%)	7 (63.6%)	0.160
Prior percutaneous coronary intervention	8 (21.6%)	3 (11.5%)	5 (45.5%)	0.022
Atrial fibrillation (by history)	13 (35.1%)	10 (38.5%)	3 (27.3%)	0.515
Cerebrovascular disease	6 (16.2%)	5 (19.2%)	1 (9.1%)	0.444
Peripheral vascular disease	12 (32.4%)	5 (19.2%)	7 (63.6%)	0.008
Estimated glomerular filtration, mL/min	63 [55-82]	65.4 [55.6-81.6]	60.4 [53.0-94.5]	0.781
Society of Thoracic Surgeons predicted risk of mortality, %	5.5 [3.4-8.3]	5.6 [3.4-8.6]	5.5 [3.1-7.8]	0.806
Echocardiographic variable				
Left ventricular ejection fraction, %	60 [47-60]	60 [42-60]	60 [47-60]	0.987
Mean aortic gradient, mmHg	40 [30-52]	42 [35-51]	32 [28-53]	0.374
Aortic valve area, cm^2	0.70 [0.55-0.87]	0.65 [0.55-0.81]	0.78 [0.51-0.93]	0.341
Pulmonary systolic arterial pressure, mmHg	40 [31-55]	37 [31-60]	42 [33-48]	0.947
Procedural variable				
Success*	33 (89.2%)	23 (88.5%)	10 (90.9%)	0.827

Continued

Conclusion

Variable	All Patients (n = 37)	Transfemoral/ Transaortic (n = 26)	Transapical (n = 11)	p Value
Prosthesis type				<0.001
Edwards Sapien	9 (24.3%)	2 (7.7%)	7 (63.6%)	
Sapien XT	26 (70.3%)	23 (88.5%)	3 (27.3%)	
Sapien 3	2 (5.4%)	1 (3.8%)	1 (9.1%)	
Prosthesis size, mm				0.589
23 mm	17 (45.9%)	11 (42.3%)	6 (54.5%)	
26 mm	13 (35.1%)	9 (34.6%)	4 (36.4%)	
29 mm	7 (18.9%)	6 (23.1%)	1 (9.1%)	
Balloon Post-Dilatation	11 (29.7%)	10 (38.4%)	1 (9.1%)	0.119
Number of pace runs	3 [3-5]	3 [2-4]	5 [4-7]	<0.001
Cardiac biomarker rise, µg/l				
Cardiac kinase-MB	9.10 [4.4-16.10]	6.25 [2.40-12.6]	12.40 [9.10-22.6]	0.016
Cardiac troponin T	0.18 [0.12-0.52]	0.13 [0.11-0.20]	0.61 [0.36-0.79]	<0.001
30-day outcomes*				
Major vascular complications	2 (5.4%)	2 (7.7%)	-	0.999
Major or life-threatening bleeding	4 (10.8%)	2 (7.7%)	2 (18.2%)	0.266
Acute renal failure	1 (2.7%)	-	1 (9.1%)	0.231
Stroke	0	0	0	-
Death	0	0	0	-
Hospitalization length, days	6 [4-9]	5 [4-8]	10 [8-13]	<0.001

Data are presented as median [IQR] or n (%).
** Following VARC-2 criteria[196]*

7.5.1 Cardiac biomarkers after TAVI

The mean values of CK-MB and cTnT at each time point within the 72 h following the procedure for the entire study population and for the TF/TAo and TA groups are shown in **Figure 7-1**. CK-MB levels were within normal limits in all patients at baseline and increased to above the upper normal limit in 49% of the patients with a median peak of 9.10 µg/l (4.4 to 16.10 µg/l) at 12-24 h following the procedure and returned to baseline values at 72 h after TAVI. In the TA group, the CK-MB levels were above the upper normal values in 73% of the patients compared to 35% of the patients in the TF/TAo group, with median peak values of 12.40 (9.10 to 22.6) µg/l and 6.25 (2.40 to 12.6) µg/l, respectively ($p = 0.023$ vs TF/TAo). The cTnT levels were within the normal limits at baseline in all patients and increased to above the upper normal limit in all patients but 1 (97.3%) following TAVI, with a median peak of 0.18 (0.12 to 0.52) µg/l at 48 h following the procedure (**Figure 7-1A**). The cTnT values continued to be above baseline values at 72 h following TAVI (**Figure 7-1A**). In the TF-TAVI group, peak cTnT was at 6 to 12 h after the procedure, whereas in the TA-TAVI group, it occurred at 24 h after the procedure, cTnT levels increased to above the upper normal values in all patients in the TA-TAVI group compared to 96% of the patients in the TF-TAVI group ($p = 0.518$). The degree of cTnT increase was higher in the TA-TAVI group compared to the TF-TAVI group at all time points following the procedure ($p < 0.001$) (**Figure 7-1B**). The median maximal cTnT value in the TF-TAVI group within the 72 h following the procedure was 0.13 (0.11 to 0.20) µg/l compared to 0.61 (0.36 to 0.79) µg/l in the TA-TAVI group ($p < 0.001$).

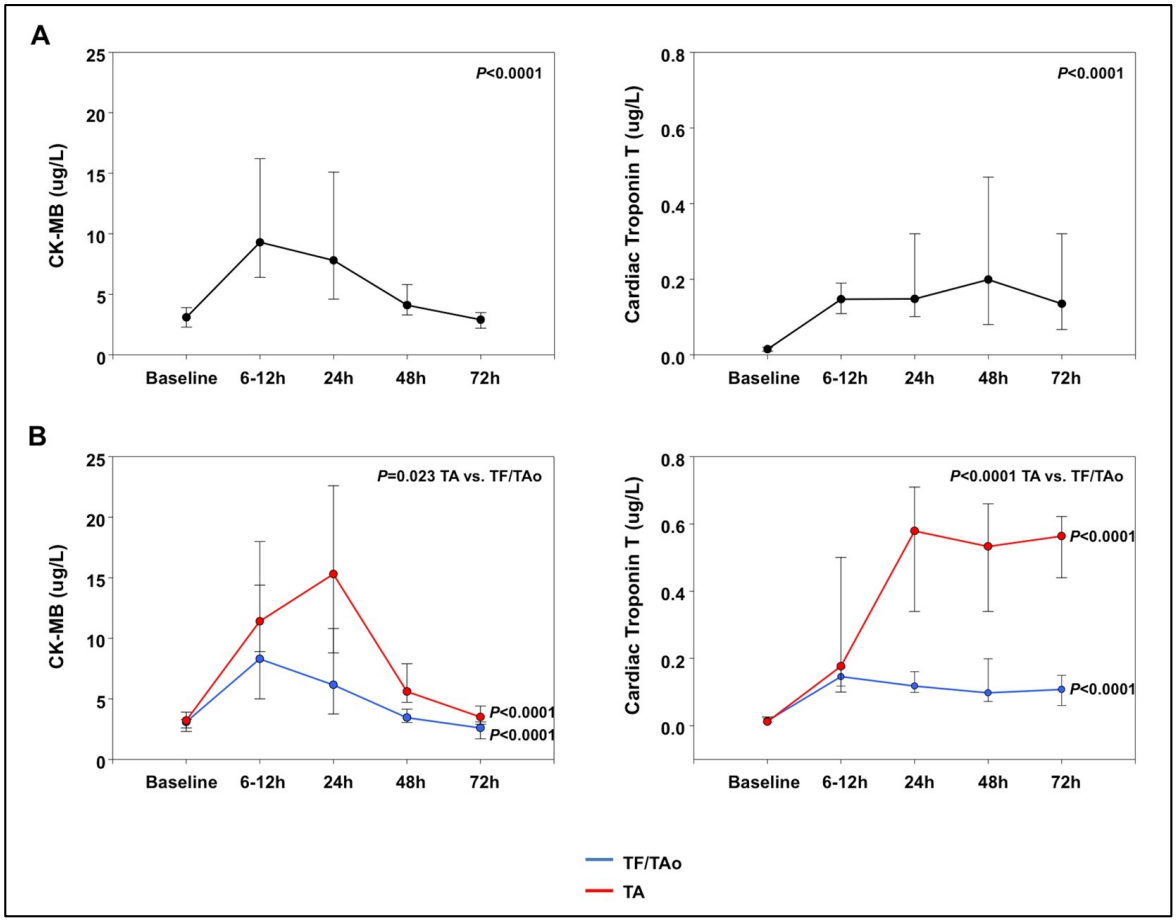

Figure 7-1: Changes in creatine kinase-myocardial band (CK-MB) and cardiac troponin T (cTnT) levels within the 72 h following transcatheter aortic valve implantation (TAVI) in all patients (A) and grouped according to the approach (transfemoral [TF] / transaortic [TAo] grouped and transapical [TA]) (B)

7.5.2 CMR and echocardiographic data

Baseline and post-TAVI CMR data are shown in **Tables 7-3, 7-4 and 7-5**. There were no significant changes in left and right ventricles dimensions and functions parameters following TAVI, except for an increase in left and right ventricular cardiac output, and a trend towards a reduced LVEF in the TA group after TAVI (61.8 ± 14.8 vs. 54.1 ± 11.7, respectively; p=0.148). There were no significant differences between the TF/TAo and TA approach.

Echocardiography data at 6- to 12-months follow-up were available in 33 patients (89%), being 9 in the TA group (82%). Regarding the differences in LVEF by echocardiography at 6- to 12-months in relation to the baseline values (Delta), there was an overall increase in

LVEF: Delta of +5 [0-19] (p=0.0072). However, when analyzed according to the approach this was only statistically significant for the TF/TAo group (Delta LVEF: +5 [0-10], p=0.0374) as compared to TA (Delta LVEF: 0 [0-10], p=0.0921).

Myocardial necrosis was detected by LGE in 12 patients (32.4%) at baseline, with an ischemic pattern in all of them (transmural in 7 patients [58%] and subendocardial in 5 patients [42%]). The distribution and frequency (%) of myocardial necrosis defects at baseline is shown in **Figure 7-2**. LGE pre-TAVI was similar between TF/TAo and TA groups (median 0g [0 to 1.5] versus 1.1g [0 to 4.0], respectively; p =0.475), with an overall median of 0% (0 to 3.8) of the myocardium, and with a median of 0g (0 to 3.3) of necrosis. After the TAVI procedure, new focal myocardial necrosis was detected only in the TA group, and it was restricted to the apical segments in all patients, as shown in the examples in **Figure 7-3** and **Table 7-6** (individual data). The median extent of LGE after TAVI was of 5% (2.0 to 7.0) of the myocardium (versus 1.0% [0 to 5.0] before TAVI; p =0.031), and with a median of 3.5g (2.3 to 4.6) of necrosis (versus 1.1g [0 to 4.0] before TAVI; p=0.031) (**Figure 7-4**). All tracings were manually reviewed for accurate myocardial necrosis measurements in orthogonal axis, as short axis could be unsuitable to evaluate the apex, and showed 3.5 g (2.3 to 4.5) of new necrosis after TA-TAVI. No patient presented new focal defects in the LVOT septum at the level of the conduction system tract. The LGE distribution in the apex after TAVI is shown in **Figure 7-3**.

Table 7-3: Cardiac magnetic resonance (CMR) variables of the study population overall and according to the approach

Variable	All Patients (n = 37)	TF/TAo (n = 26)	Transapical (n = 11)	p Value
Functional variables (Pre-TAVI)				
LV end diastolic volume, ml	152.3±55.7	153.5±62.6	149.3±36.8	0.835
LV end systolic volume, ml	71.5±59.3	76.0±66.7	61.0±37.0	0.491
LV stroke volume, ml/min	80.6±18.7	77.4±19.1	88.2±16.2	0.111
LV cardiac output*, L/min	5.59±1.26	5.58±1.33	5.64±1.12	0.898
LV ejection fraction♮, %	57.4±16.0	55.5±16.5	61.8±14.6	0.282
LV mass, g	117.4±34.0	117.8±33.1	116.5±37.7	0.914
Functional variables (Post-TAVI)				
LV end diastolic volume, ml	157.9±60.5	157.5±65.8	159.0±44.8	0.949
LV end systolic volume, ml	75.1±56.2	75.2±62.7	74.6±33.9	0.976
LV stroke volume, ml/min	82.8±20.5	82.3±19.0	84.4±25.5	0.788
LV cardiac output*, L/min	6.09±1.31	6.04±1.28	6.22±1.48	0.724
LV ejection fraction♮, %	56.3±14.4	57.0±15.4	54.1±11.7	0.613
LV mass, g	123.6±31.7	120.7±32.7	132.0±28.6	0.365

*Values are mean (±SD). TF: transfemoral; TAo: transaortic; LV: left ventricular. *p=0.58, for comparison between pre and post-TAVI values; ♮ p=0.148, for comparison between pre- and post-TAVI values in the transapical group.*

Table 7-4: Cardiac magnetic resonance (CMR) variables of the study population overall and according to the approach for the right ventricle (RV) analysis

Variable	All Patients (n = 37)	TF/TAo (n = 26)	Transapical (n = 11)	p Value
Functional variables (Pre-TAVI)				
RV end diastolic volume, ml	118.1±39.4	122.2±43.1	108.5±28.0	0.344
RV end systolic volume, ml	56.5±34.0	61.5±38.4	44.6±15.7	0.170
RV stroke volume, ml/min	61.5±17.2	60.5±17.0	63.9±18.4	0.586
RV cardiac output#, L/min	4.22±1.18	4.31±1.23	4.00±1.10	0.477
RV ejection fraction, %	54.5±12.8	52.5±13.8	59.3±8.8	0.144
Functional variables (Post-TAVI)				
RV end diastolic volume, ml	126.1±46.4	130.9±51.7	112.3±22.2	0.308
RV end systolic volume, ml	61.5±42.7	65.7±47.4	49.2±22.0	0.324
RV stroke volume, ml/min	64.7±18.8	65.2±20.1	63.1±15.5	0.780
RV cardiac output#, L/min	4.86±1.38	4.85±1.38	4.89±1.45	0.937
RV ejection fraction, %	54.2±13.3	53.2±13.6	57.1±12.8	0.454

Values are mean (±SD). TF: transfemoral; TAo: transaortic. #p=0.025, for comparison between pre- and post-TAVI values

Table 7-5: Cardiac magnetic resonance (CMR) variables of the study population pre and post-TAVI for the transapical approach

Variable	Pre-TAVI	Post-TAVI	p Value
Functional variables (Pre-TAVI)			
LV end diastolic volume, ml	149.3 ± 36.8	159.0 ± 44.8	0.848
LV end systolic volume, ml	61.0 ±37.0	74.6 ± 33.9	0.497
LV stroke volume, ml/min	88.2 ± 16.2	84.4 ± 25.5	0.471
LV cardiac output, L/min	5.64 ± 1.12	6.22 ± 1.48	0.384
LV ejection fraction, %	61.8 ± 14.6	54.1 ± 11.7	0.148
LV mass, g	116.5 ± 37.7	132.0 ± 28.6	0.280
RV end diastolic volume, ml	108.5 ± 28.0	112.3 ± 22.2	0.974
RV end systolic volume, ml	44.6 ± 15.7	49.2 ± 22.0	0.669
RV stroke volume, ml/min	63.9 ± 18.4	63.1 ± 15.5	0.625
RV cardiac output, L/min	4.00 ± 1.10	4.89 ± 1.45	0.228
RV ejection fraction, %	59.3 ± 8.8	57.1 ± 12.8	0.715

Values are mean (±SD). TF: transfemoral; TAo: transaortic; LV: left ventricular; RV: right ventricular.

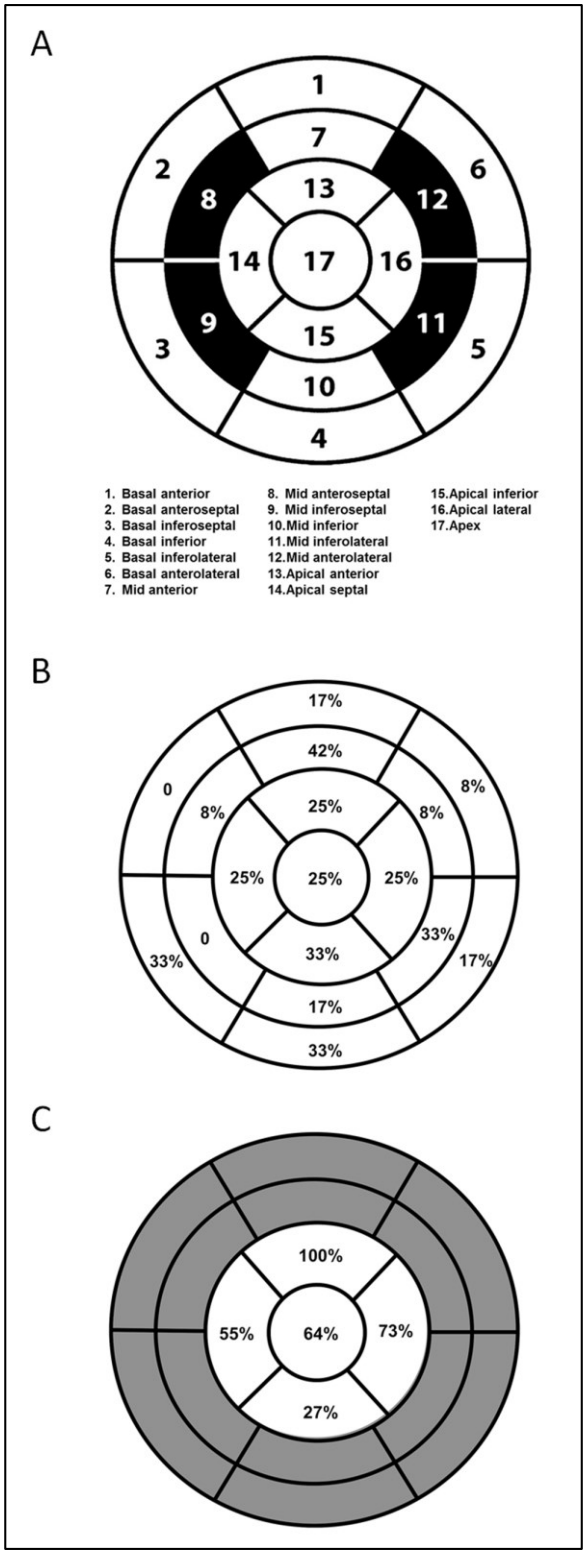

Figure 7-2: Schematic representations. A) 17-segment American Heart Association (AHA) model used to analyze myocardial necrosis distribution within the heart. B) Distribution and frequency (%) of focal myocardial necrosis before TAVI. C) Distribution and frequency (%) of focal myocardial necrosis after TAVI

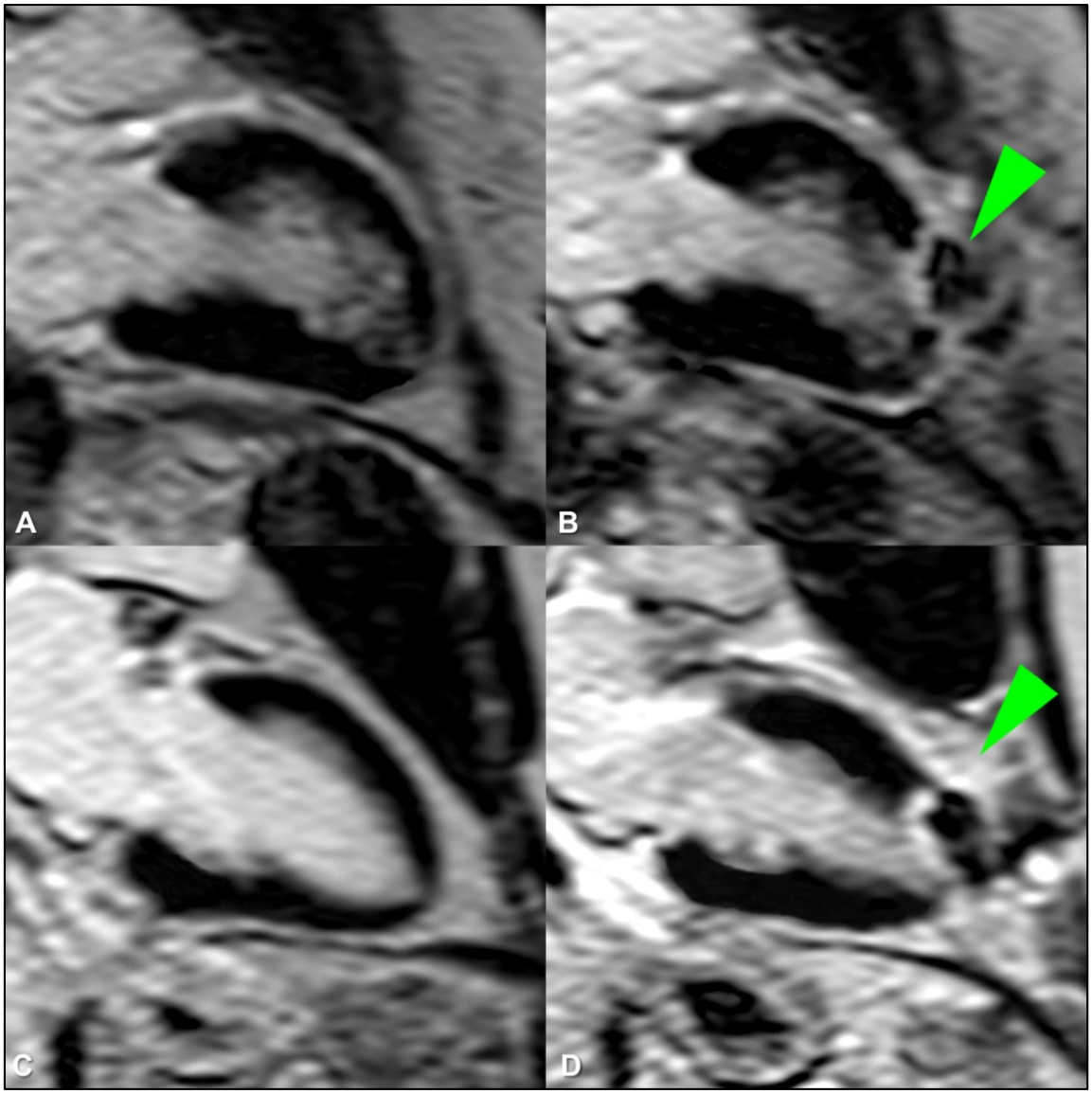

Figure 7-3: Representative cardiovascular magnetic resonance (CMR) before (A, C) and after transcatheter aortic valve implantation (B, D) through the transapical approach in 2 patients, showing the typical late gadolinium enhancement in the apex of the left ventricle (arrows)

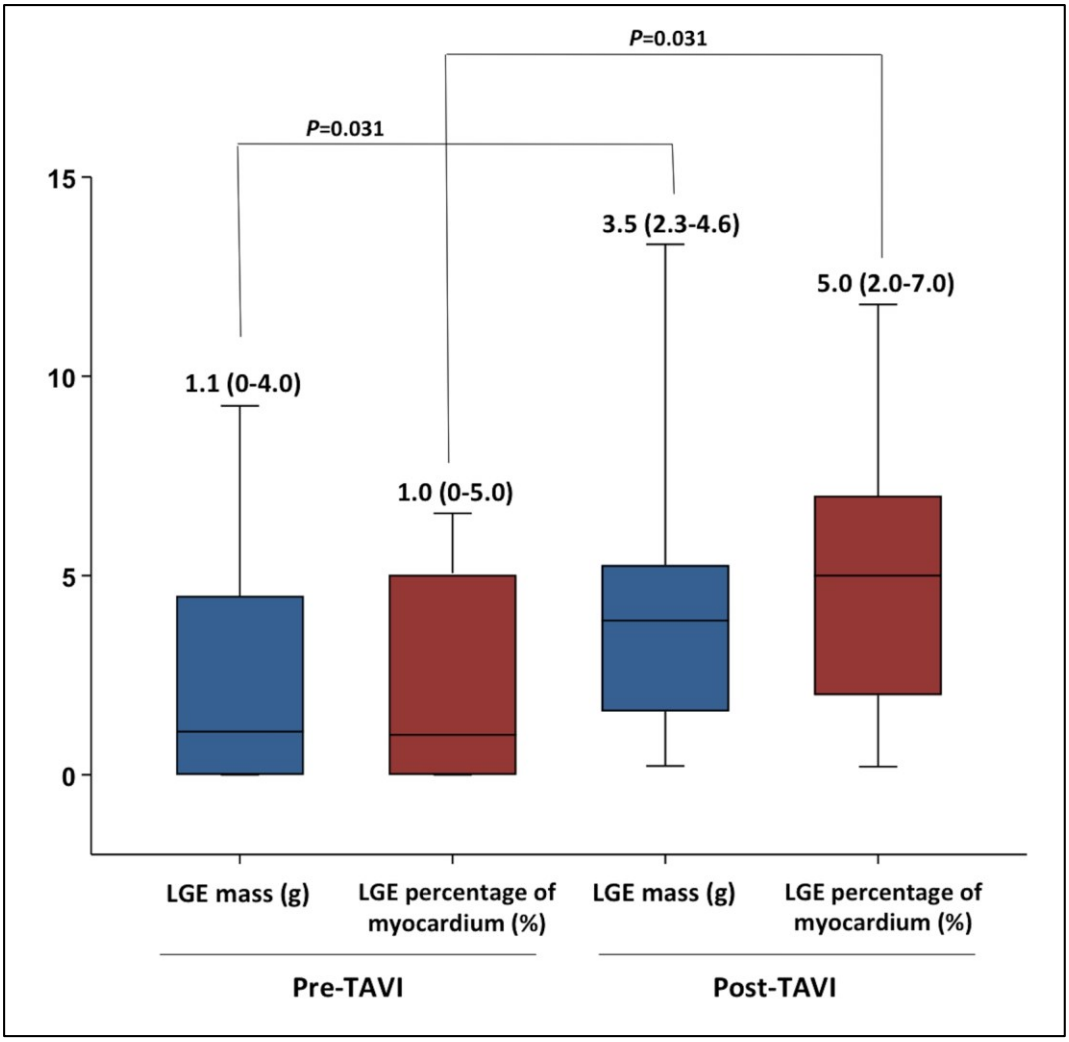

Figure 7-4: Degree and extent of myocardial necrosis at the apex before and after TAVI (transapical approach patients)

Table 7-6: Individual data for myocardial injury in the transapical approach after TAVI

Patient	Age	Gender	Transcatheter Heart Valve		Sheath Diameter (OD)	New Myocardial Injury (LGE)	
			Type	Size		Mass (g)	Volume (ml)
1	65	Female	Edwards Sapien	23	30F	2.28	2.18
2	69	Male	Sapien XT	26	24F	0.96	0.91
3	71	Female	Edwards Sapien	23	30F	2.06	1.96
4	73	Female	Edwards Sapien	23	30F	3.88	3.69
5	77	Male	Sapien 3	26	18F	2.38	2.26
6	78	Male	Edwards Sapien	26	30F	3.48	3.31
7	78	Male	Sapien XT	26	24F	4.86	4.63
8	79	Female	Edwards Sapien	23	30F	3.00	2.85
9	79	Male	Sapien XT	29	26F	4.45	4.23
10	83	Male	Edwards Sapien	23	30F	8.80	8.38
11	88	Male	Edwards Sapien	23	30F	4.60	4.38

LGE: late gadolinium enhancement; OD: outer diameter in French (F).

7.6 DISCUSSION

Several previous studies have shown that TAVI is associated with some increase in the biomarkers of myocardial injury in most patients.[167,214,216,217] This rise in such cardiac biomarkers has been observed following TAVI with both balloon-expandable and self-expandable valves, and consistent with the results of the present study, a greater rise has been detected in those patients undergoing the procedure by the TA compared to the TF approach. Several mechanisms have been proposed to explain this systematic rise in cardiac biomarkers following TAVI. First, the lower (ventricular) part of the transcatheter valve usually sits within the LVOT and mechanical compression of the myocardial septum at this level by the transcatheter valve can cause some myocardial injury. In fact, previous CMR studies have shown that myocardial necrosis can be detected in the LVOT septum at the level of the conduction tract system in patients undergoing TAVI with a self-expandable valve, which indeed may be responsible for some conduction disturbances after valve implantation.[274] In the present study, CMR studies failed to detect any focal myocardial necrosis at the level of the septum, suggesting that this mechanism is not responsible for the rise in cardiac biomarkers observed following TAVI with a balloon-expandable valve. Indeed, this could partially explain the lower incidence of conduction disturbances and need for pacemaker implantation associated with balloon-expandable compared to self-expandable valve implantation.[190] However, it must be borne in mind that as much as 9% of the patients were unable to undergo a repeated CMR in the days following TAVI due to pacemaker implantation, precluding to rule out the presence of new focal myocardial necrosis at the level of the septum in such patients.

It is well known that TAVI is associated with a high number of cerebral microemboli during the procedure, particularly during valve positioning and implantation,[136,275] and up to 70% of patients undergoing TAVI with a dual carotid filter protection had some debris at the level of the filter at the end of the procedure.[275] Therefore, the occurrence of coronary emboli during the procedure may contribute to myocardial injury following TAVI. In the setting of PCI, irreversible myocardial injury as evaluated by CMR is related to either epicardial side-branch occlusion in areas adjacent to the intervention site, or to micro-vascular circulation compromise, downstream to the intervened artery segment.[276] In the present study, the CMR

data showing the absence of new focal myocardial necrosis in all TF/TAo patients does not support the coronary emboli hypothesis as a factor involved in myocardial injury in TAVI patients. Finally, TAVI is associated with episodes of severe hypotension and potential global myocardial ischemia (rapid pacing runs, balloon valvuloplasty, valve implantation), which in turn can translate into diffuse myocardial injury. While no diffuse necrosis was detected in any patient in our study, the fact that the quantification of myocardial necrosis on LGE images was analyzed using a semi-automatic, signal intensity threshold method, rather than the assessment of diffuse interstitial fibrosis accumulation as determined by myocardium T1 mapping,[277] may have been associated with an underdiagnosis of diffuse patterns of subendocardial myocardial necrosis, associated with episodes of severe hypotension or global ischemia. The presence of diffuse myocardial necrosis as evaluated by myocardial T1 mapping will have to be evaluated in future studies.

The use of the TA approach involves the puncture and the introduction of a large catheter through the ventricular apex (≥ 24-F, with external diameter ≥ 7.9 mm). This has been associated with a greater increase in cardiac biomarkers of myocardial injury, and the present study confirms the presence of significant myocardial necrosis at the level of the left ventricular apex in such patients. The CMR analysis also revealed that apical lesions extended beyond the puncture site in the apex, showing that both the puncture itself but also the purse strings from the suture may explain the damage. This is also supported by previous study in an experimental model showing that apical puncture closure with a device (without the sutures) did not cause LV myocardial fibrosis beyond the access site.[278] Importantly, the necrotic mass was ~3 g and represented ~5% of the left ventricular myocardial mass. This amount of necrosis is similar to that observed in the context of percutaneous coronary intervention (PCI),[276] where new myocardial necrosis is detected in ~25% of the cases, also extending to a mean of 5% of the LV mass.[276] This amount of myocardial injury by LGE is however lower than that reported in patients undergoing open-heart surgery, where certain degree of cardiac biomarkers elevation occurs almost invariably,[279] leading to irreversible myocardial injury as evaluated by CMR in more than one third of the patients.[279]

Studies in the context of coronary artery disease have shown that even small amounts of myocardial necrosis (as low as 1 g) were associated with a 5% increase in major cardiac events.[280] Azevedo et al.[112] showed that new myocardial necrosis following surgical aortic

valve replacement extending to ≥ 5% of the myocardium as determined by CMR was associated with increased mortality and decreased LVEF at 2-year follow-up. Interestingly, in patients undergoing TAVI with a balloon-expandable valve, the degree and extent of cardiac biomarker elevation (also more frequent for the TA approach) have also been associated with less improvement in LVEF at 1-year follow-up.[167] Also in accordance with these results, Barbash et al.[220] showed the presence of apical wall motion abnormalities in about one third of the patients treated through the TA approach, which translated into a lower LVEF at follow-up. While the poorer outcomes associated with the TA approach have been mainly related to the higher risk profile of the patients treated through this approach (usually patients with inadequate iliofemoral access),[281] the TA approach was found to be an independent predictor of mortality in 2 large TAVI studies (FRANCE-2 and the UK registries)[282,283] as well as in a recent meta-analysis.[270] The present study showing that this approach is systematically associated with significant irreversible myocardial injury suggests that the loss of ~5% of the myocardium associated with this approach (>1g of necrotic mass in all cases) may contribute to these poorer clinical outcomes. However, the small sample size of the present study precluded any evaluation of the correlation between the severity of myocardial necrosis as determined by CMR and clinical outcomes, and this will have to be evaluated in future studies with a larger number of patients.

7.6.1 ***Study Limitations***

This study had some limitations. The patients were not consecutive and a selection bias might have influenced the results. The limited number of patients and the lack of long-term follow-up do not allow us to determine a cut-off for the amount of myocardial necrosis associated with poorer clinical outcomes, evaluate the changes in LV function, or to establish a correlation between cardiac biomarkers elevation and new focal necrosis. The oedema-weighted T2 imaging was not analyzed in the present study, and this would have helped to further clarify the effect of TAVI procedure on myocardial damage in the LVOT septum. These aspects will have to be evaluated in future larger studies. The results of this study were obtained in patients undergoing TAVI with a balloon-expandable valve, and may not apply to those patients receiving a self-expandable valve.

7.7 CONCLUSION

In conclusion, while some increase in the biomarkers of myocardial injury was systematically detected in patients undergoing TAVI with a balloon-expandable valve, the presence of new myocardial necrosis as evaluated by CMR was detected only in patients undergoing TAVI through the TA approach. New myocardial necrosis was limited to the left ventricular apex, and affected about 5% of the ventricular mass. No other new myocardial necrosis defects were detected outside the ventricular apex. These results provide important insight into the mechanisms of myocardial injury following TAVI and invite us to further evaluate the clinical impact of new myocardial necrosis on clinical outcomes.

7.8 SOURCES OF FUNDINGS

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7.9 DISCLOSURE

Dr. Robert DeLarochellière is consultant for St. Jude Medical. Dr. Eric Dumont is consultant for Edwards Lifesciences. Dr. Josep Rodés-Cabau is consultant for Edwards Lifesciences and St. Jude Medical. The other authors have no conflicts of interest to declare.

CHAPTER 8: ARTICLE 5

Coronary Obstruction Following Transcatheter Aortic Valve Implantation: A Systematic Review

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8.1 RÉSUMÉ

OBSTRUCTION CORONAIRE APRÈS L'IMPLANTATION DE VALVE AORTIQUE PAR CATHÉTER : UN REVUE SYSTÉMATIQUE

Objectif : Évaluer, par une revue systématique de la littérature, les caractéristiques initiales, la prise en charge et les résultats cliniques de patients présentant une obstruction coronarienne comme complication en lien avec une implantation de valve aortique par cathéter (TAVI).

Contexte : Très peu de données existent sur l'obstruction coronarienne en lien avec une procédure TAVI.

Méthodes : Toutes les études publiées entre 2002 et 2012, portant sur l'obstruction coronarienne comme complication survenant en lien avec une procédure TAVI ont été identifiées utilisant une recherche électronique systématique. Seules les études rapportant les résultats initiaux et les caractéristiques procédurales, la prise en charge des complications et les résultats cliniques ont été analysées.

Résultats : Un total de 16 publications décrivant 24 patients ont été identifiées. La majorité des patients étaient des femmes (83%) avec un âge moyen de 83±7 ans et un euroSCORE logistique moyen de 25,1±12,0%. La hauteur moyenne de l'ostium de l'artère coronarienne gauche (ACG) et la largeur de la racine aortique étaient de 10,3±1,6 mm et 28,1±2,8 mm, respectivement. La majorité des patients (88%) ont reçu une valve expansible par ballonnet et les obstructions coronariennes se sont produites plus fréquemment dans l'ACG (88%). Une intervention coronarienne percutanée (ICP) a été pratiquée lors de 23 cas (95,8%) et a été un succès pour la majorité des cas sauf deux (91,3%). Lors du suivi à 30 jours, aucun cas de thromboses des tuteurs ou de revascularisation n'a été observé et le taux de mortalité était de 8,3%.

Conclusion : L'obstruction coronarienne en lien avec une procédure TAVI se produit plus fréquemment chez les femmes, chez les patients recevant une valve expansible par ballonnet, et dans l'ACG, faisant de l'ICP un traitement faisable et fructueux dans la majorité des cas. Des efforts continuels devraient être faits afin d'identifier les facteurs

associés à cette complication potentiellement mortelle afin d'implémenter des mesures appropriées pour sa prévention.

Mots clés : Sténose aortique; Remplacement de valve aortique par cathéter; Valve cardiaque transcathéter; Sténose coronaire; Occlusion coronaire; Obstruction coronaire.

Ces travaux ont été présentés lors du congrès de la Société Américaine de Cardiologie de l'ACC (San Francisco, EUA; mars 2013), au Congrès de La Société Latino-Américaine de Cardiologie (SOLACI, São Paulo, 2013), où ils ont gagné le prix d'un des meilleurs abstracts présentés lors du Congrès.

8.2 ABSTRACT

Objective: To evaluate, through a systematic review of the literature, the main baseline characteristics, management and clinical outcomes of patients suffering coronary obstruction as a complication of transcatheter aortic valve implantation (TAVI).

Background: Very few data exist on coronary obstruction following TAVI.

Methods: Studies published between 2002 and 2012, with regards to coronary obstruction as a complication of TAVI, were identified using a systematic electronic search. Only the studies reporting data on the main baseline and procedural characteristics, management of the complication, and clinical outcomes were analyzed.

Results: A total of 18 publications describing 24 patients were identified. Most (83%) patients were women, with a mean age of 83±7 years, and a mean logistic EuroSCORE of 25.1±12.0%. Mean left coronary artery (LCA) ostium height and aortic root width were 10.3±1.6 mm and 27.8±2.8 mm, respectively. Most patients (88%) had received a balloon-expandable Edwards valve, and coronary obstruction occurred more frequently in the LCA (88%). Percutaneous coronary intervention (PCI) was attempted in 23 cases (95.8%) and was successful in all but 2 patients (91.3%). At 30-day follow-up, there were no cases of stent thrombosis or repeat revascularization, and the mortality rate was of 8.3%.

Conclusion: Coronary obstruction following TAVI occurred more frequently in women, in patients receiving a balloon-expandable valve, and in the LCA, being PCI a feasible and successful treatment in most cases. Continuous efforts should be made to identify the factors associated with this life threatening complication in order to implement the appropriate measures for its prevention.

Key words: Aortic stenosis; Transcatheter aortic valve replacement; Transcatheter heart valve; Coronary stenosis; Coronary occlusion; Coronary obstruction.

8.3 INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement in those patients considered at very high or prohibitive risk for surgery.[136] Despite its more widespread adoption as a treatment option and the increasing experience of the centers, TAVI is still associated with complications such as vascular/bleeding and cerebrovascular events, conduction abnormalities requiring permanent pacemaker implantation, and significant residual aortic regurgitation.[136] The relatively high rate of such complications has made possible an accurate evaluation of their predictive factors and clinical consequences, and this does indeed represent a first step on the way of implementing appropriate preventive measures and treatment. Nonetheless, TAVI has also been associated with very rare but life-threatening complications such as coronary ostia obstruction. Apart from some reports on its incidence (usually <1%) in some TAVI series,[144,146,164,165,186,219,284] specific clinical data on this important complication have been scarce and restricted to case reports and small case series, precluding any appropriate evaluation of the baseline characteristics of patients suffering this complication, as well as its management and clinical impact. The objective of the present study was to provide further insight into the baseline characteristics, management, and clinical outcomes of patients with coronary obstruction as a complication of TAVI through a systematic review of all the studies on TAVI and coronary obstruction published thus far.

8.4 METHODS

8.4.1 ***Patient Population***

All relevant articles in English about TAVI and coronary obstruction published between December 2002 and July 2012 were systematically searched in BioMedCentral (http://www.biomedcentral.com), Google Scholar (http://www.scholar.google.com), and PubMed (http://www.pubmed.gov). The following query terms were used: aortic stenosis, transcatheter aortic valve implantation, transcatheter aortic valve replacement, transcatheter heart valve, heart valve prosthesis implantation, coronary stenosis, coronary occlusion, and coronary obstruction. Further studies were sought by means of a manual search of

secondary sources, including references from primary articles (backward snowballing) and contacts with international experts.

Citations were first screened at the title/abstract level by two independent reviewers (H.B.R., L.N.F.), and retrieved as complete manuscripts if potentially pertinent. Divergences were resolved after consensus, in order to gather all of the pertinent case reports and case series concerning coronary obstruction in TAVI. Published articles that included only the incidence of the complication without any case description were excluded from this analysis.

Gathered data included baseline clinical, echocardiographic, and computed tomography (CT) characteristics. CT variables included data on left coronary artery (LCA) ostium height from aortic annulus, severity and distribution of valve calcification, and aortic root and annulus diameters. Procedural data on the type and size of the transcatheter valve, approach, and clinical presentation and management of coronary obstruction were recorded. Finally, data on in-hospital or 30-day mortality, and clinical status at follow-up including the need for repeat revascularization were also gathered.

8.4.2 ***Statistical Analysis***

Categorical variables were reported as n (%), and continuous variables as mean ± SD. Group comparisons were performed using the Chi-square test for categorical variables and Students' t-test adjusted for multiple comparisons (Bonferroni method) for continuous variables. The results were considered significant with p values <0.05. All analyses were conducted using the statistical package SAS, version 9.3 (SAS Institute Inc, Cary, NC, USA).

8.5 RESULTS

8.5.1 Study Population

Between January 2002 and May 2012, 19 publications describing a total of 27 patients who had experienced coronary obstruction related to a TAVI procedure were identified.[156,285-302] All studies referred to single case reports or small series, with a maximum of 5 reported cases of coronary obstruction. Three cases with previous surgical aortic valve prosthesis ("valve-in-valve" procedure) were excluded from this analysis,[299,302] leading to a final study population of 24 patients. The main baseline clinical characteristics were available in all patients. CT data on left main ostium height, and annulus and aortic root measurements were reported in 13, 12, and 8 patients, respectively. No data were reported on the severity and distribution of valve calcification. Procedural and clinical data on the clinical presentation, diagnosis, and management of the coronary obstruction were available in all patients. All studies reported data on in-hospital outcomes, 12 studies (including 16 patients) reported data on 30-day outcomes, and 11 studies (including 14 patients) reported data at follow-up.

8.5.2 Main clinical, echocardiographic, CT, and procedural characteristics

The main clinical, echocardiographic, CT, and procedural characteristics of the patients are shown in **Tables 8-1** (individual data) and **8-2** (mean data). Mean age of the study population was 83 ± 7 years and most patients were women (83.3%). The main baseline characteristics of the study population compared to those reported in the largest TAVI registries[138,139,142,144,164,165,187,219,284] (pooled data) and the PARTNER trial[145,146] are shown in **Figure 8-1**. CT data revealed a mean LCA ostia height of 10.3 ± 1.6 mm and aortic root width of 27.8 ± 2.8 mm. The mean values of LCA height and aortic root diameter compared to the values obtained in a previous population of patients with and without aortic stenosis,[303,304] as well as that of patients referred for TAVI[305] are shown in **Figure 8-2**. A balloon-expandable Edwards valve (Edwards Lifesciences, Irvine, CA) was used in most (87.5%) cases.

Table 8-1: Individual data on baseline clinical and procedural characteristics

Patient	Age	Sex	Previous CABG	Logistic EuroSCORE (%)	Mean Aortic Gradient (mmHg)	Aortic Annulus (mm)	Aortic Root (mm)	LCA Height (mm)	Approach	Valve Type	Valve Size
1 [287]	85	F	No	13.3	88	22.0	-	9.1	TA	SAPIEN®	26
2 [156]	87	-	No	-	-	-	-	-	TF	SAPIEN®	-
3 [288]	85	F	No	18.0	45	-	-	-	TF	SAPIEN®	23
4 [289]	81	F	No	21.0	-	-	-	>12	TA	SAPIEN®	26
5 [289]	85	F	No	23.8	-	-	-	>12	TF	SAPIEN XT®	23
6 [289]	80	M	No	31.0	-	-	-	>12	TA	SAPIEN XT®	29
7 [290]	86	F	No	24.3	51	22.4	31.3	9.7	TF	SAPIEN®	26
8 [290]	78	F	Yes	51.5	46	19.3	27.8	10.3	TA	SAPIEN®	23
9 [290]	80	F	No	25.3	58	20.9	26.4	9.0	TA	SAPIEN®	23
10 [290]	88	F	No	22.0	55	18.0	26.2	11.0	TA	SAPIEN®	23
11 [290]	82	M	No	20.7	43	22.1	33.0	9.0	TA	SAPIEN®	23
12 [291]	86	M	No	-	-	-	-	-	TF	SAPIEN®	23
13 [292]	87	F	No	-	60	20.0	-	-	TF	SAPIEN®	23
14 [293]	87	F	No	-	70	20.0	-	-	TA	SAPIEN®	23
15 [294]	58	F	No	-	57	-	-	-	TF	SAPIEN®	26
16 [295]	86	F	No	-	-	-	-	-	TF	SAPIEN®	23
17 [296]	82	F	No	-	-	-	-	7.0	TF	SAPIEN®	23
18 [297]	68	F	No	8.8	46	21.6	26.4	-	TA	SAPIEN®	26
19 [298]	86	F	No	31.2	55	-		10.2	TF	SAPIEN®	23
20 [299]	76	F	No	9.1	90	24.0	-	-	TF	SAPIEN XT®	26
21 [300]	86	F	No	-	68	-	-	-	TF	SAPIEN XT®	23
22 [301]	86	F	No	45.0	-	20.0	-	11.0	TF	CoreValve®	26
23 [302]	89	F	No	25.3	65	20.0	-	12.0	TF	CoreValve®	26
24 [303]	87	M	No	-	-	-	-	-	TF	CoreValve®	29

CAD: coronary artery disease; CABG: coronary artery bypass graft; F: female; M: male; LC: left coronary artery; TA: transapical; TF; transfemoral.

Table 8-2: Baseline clinical. echocardiographic, computed tomography, and procedural characteristics of the study population

	n = 24
Clinical variables	
Age, yrs	82.5 ± 7.0
Female	20 (83.3%)
NYHA functional class	
I-II	18.2%
III-IV	81.8%
Previous CABG	1 (4.2%)
Logistic EuroSCORE (%)	25.1 ± 12.0
Echocardiographic and CT Data	
Mean aortic gradient (mmHg)	59.8 ± 14.5
Indexed aortic valve area (cm^2/m^2)	0.43 ± 0.09
Aortic annulus (mm)	20.8 ± 1.6
Left main height (mm)	10.3 ± 1.6
Aortic root width (mm)	27.8 ± 2.8
Procedural Data	
Approach	
Transfemoral	15 (62.5%)
Transapical	9 (37.5%)
Valve type	21 (87.5%)
SAPIEN® and SAPIEN XT®	13 (54.2%)
23 mm	6 (25.0%)
26 mm	1 (4.2%)
29 mm	1 (4.2%)
Unknown	3 (12.5%)
CoreValve®	
26 mm	2 (8.3%)
29 mm	1 (4.2%)
Ratio valve/annulus	1.19 ± 0.07

PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; NYHA: New York Heart Association functional classification; CT: omputed tomography.

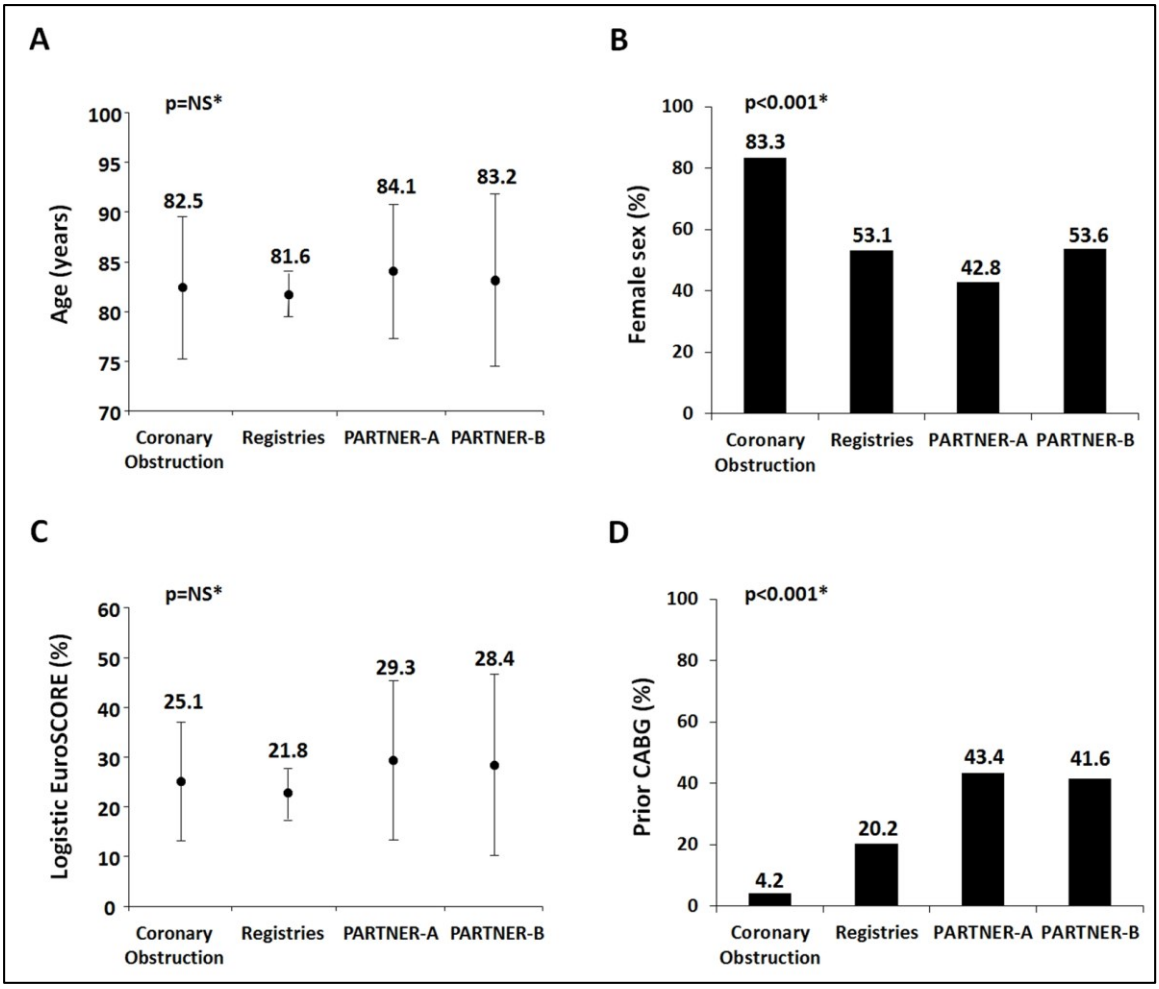

Figure 8-1: Main baseline clinical characteristics

*Main baseline characteristics of the study population compared to the largest transcatheter aortic valve implantation registries [138,139,142,144,164,165,187,219,284] (pooled data) and the PARTNER trials,[145,146] including mean age (A), female sex (B), logistic EuroSCORE (C), and prior coronary artery bypass graft (CABG; D). *Coronary obstruction vs. other groups*

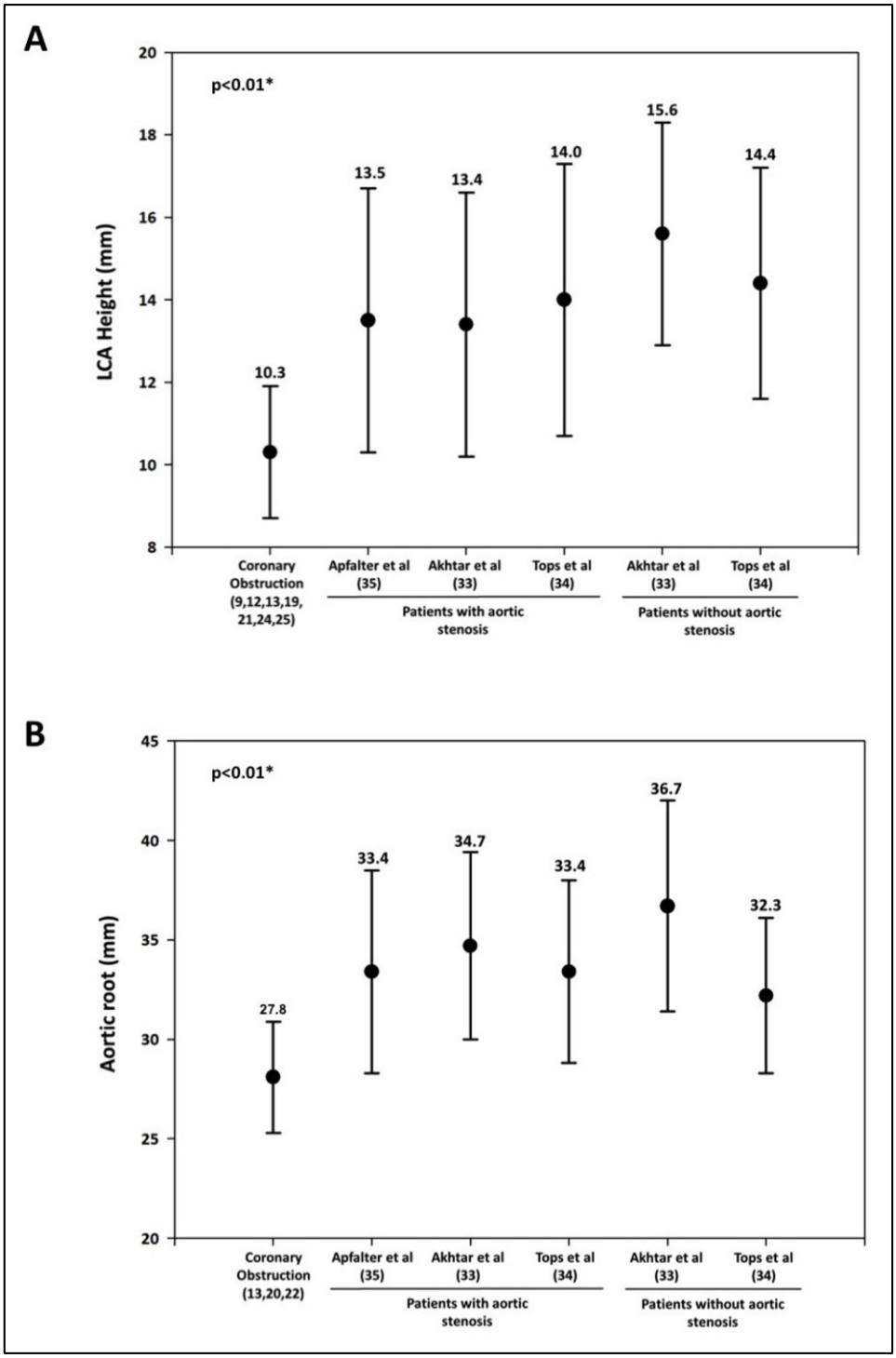

Figure 8-2: Computed tomography data

Mean values of the left coronary artery (LCA) height (A) and aortic root diameter (B) of patients with coronary obstruction following transcatheter aortic valve implantation compared to the values obtained from previous computed tomography studies including patients with and without aortic stenosis.[303-305] ***Coronary obstruction vs. other groups***

8.5.3 Clinical presentation and management

The main data on clinical presentation and management of coronary obstruction are shown in **Tables 8-3** (individual data) and **8-4** (mean data). Most (87.5%) cases presented with persistent severe hypotension. Onset of symptoms occurred immediately after valve implantation in 20 patients (83.3%), within the first few hours after the procedure in two patients (8.3%), and within the first 2 days after the procedure in another 2 patients (8.3%). Coronary obstruction occurred more frequently in the LCA (83.3%), and the diagnosis was made by coronary angiography in all patients but one (post-mortem). Coronary obstruction was related to the displacement of a calcified native aortic valve leaflet towards the coronary ostium in all patients, except for one patient with aortic valve cusp shearing and migration into the LCA.

Percutaneous coronary intervention (PCI) was attempted in 23 patients (95.8%), and was successful in all but 2 (91.3%). At least one stent was implanted at the coronary ostia in 20 patients. Significant compression of the stent requiring the implantation of a second stent occurred in 3 patients, whereas conversion to open heart surgery was required in 2 patients. The 2 unsuccessful PCI cases consisted of a failure to cross the obstruction with the coronary wire, requiring emergency CABG, and a failure to re-establish coronary flow despite successful stent implantation, leading to continuous cardiogenic shock and death.

8.5.4 Clinical outcomes

Hospital mortality rate was 8.3%, and all patients who had successful PCI survived and were discharged of the hospital at a mean of 7±4 days following the intervention, with no cases of stent thrombosis or repeat revascularization. Data at follow-up (mean of 10 ± 6 months) were available in 14 patients, and all of them were alive and in NYHA functional class I or II at that time. One patient needed repeat revascularization due to stent restenosis at 4-month follow-up.

Table 8-3: Individual data on clinical presentation and management of coronary obstruction

Patient	Coronary obstruction	Clinical Presentation			Treatment		Successful PCI	Stent type	Need for hemodynamic Support	Hospital stay (d)	In-hospital death
		Severe hypotension	ST-segment changes	Ventricular arrhythmias or CPR	PCI	CABG					
1 [287]	Both	Yes	Yes	No	Yes	No	Yes	BMS	No	11	No
2 [156]	LCA	Yes	No	No	No	No	-	-	No	5	Yes
3 [288]	LCA	Yes	Yes	Yes	Yes	No	Yes	DES	No	5	No
4 [289]	LCA	Yes	Yes	Yes	Yes	No	Yes	BMS	Yes	13	No
5 [289]	RCA	Yes	Yes	No	Yes	Yes	No	-	Yes	12	No
6 [289]	RCA	Yes	Yes	Yes	Yes	No	Yes	-	No	14	No
7 [290]	LCA	Yes	Yes	No	Yes	No	Yes	DES	No	4	No
8 [290]	LCA	Yes	No	Yes	Yes	No	No	BMS	Yes	0	Yes
9 [290]	LCA	Yes	No	Yes	Yes	No	Yes	BMS	No	5	No
10 [290]	LCA	Yes	Yes	No	Yes	No	Yes	BMS	No	4	No
11 [290]	LCA	No	No	No	Yes	No	Yes	-	No	3	No
12 [291]	LCA	Yes	No	No	Yes	No	Yes	BMS	No	-	No
13 [292]	LCA	Yes	No	Yes	Yes	No	Yes	BMS	Yes	5	No
14 [293]	LCA	Yes	No	Yes	Yes	No	Yes	BMS	No	5	No
15 [294]	RCA	Yes	Yes	No	Yes	No	Yes	BMS	No	4	No
16 [295]	LCA	Yes	Yes	No	Yes	No	Yes	DES	No	-	No
17 [296]	LCA	Yes	Yes	Yes	Yes	No	Yes	DES	Yes	8	No
18 [297]	LCA	Yes	Yes	No	Yes	No	Yes	BMS	No	5	No
19 [298]	LCA	Yes	No	Yes	Yes	No	Yes	BMS	No	-	No
20 [299]	LCA	Yes	No	Yes	Yes	No	Yes	DES	No	11	No
21 [300]	LCA	Yes	Yes	No	Yes	No	Yes	Both	No	-	No
22 [301]	LCA	No	Yes	No	Yes	No	Yes	BMS	No	-	No
23 [302]	LCA	No	No	No	Yes	No	Yes	BMS	No	-	No
24 [303]	LCA	Yes	No	Yes	Yes	No	Yes	DES	Yes	-	No

CPR = cardiopulmonary resuscitation; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; Hemo: hemodynamic; LCA: Left coronary artery; RCA: Right coronary artery; DES: drug eluting stent; BMS: bare metal stent.

Table 8-4: Clinical presentation and management of coronary obstruction

	n = 24
Obstructed coronary artery	
Left main	20 (83.3%)
Right	3 (12.5%)
Both coronary arteries	1 (4.2%)
Clinical Presentation	
Severe maintained hypotension	21 (87.5%)
ST-segment changes	13 (54.2%)
ST-segment elevation	6 (25.0%)
Ventricular arrhythmias	6 (25.0%)
Treatment	
PCI attempted	23 (95.8%)
Successful	21 (91.3%)
Stent successfully implanted	19 (82.6 %)
Guide-wire protection only	1 (4.4%)
Catheter manipulation removed the calcium	1 (4.4%)
Unsuccessful	2 (8.7%)
Wire crossing failure	1 (4.4%)
Stent implanted but no flow	1 (4.4%)
Post-mortem diagnosis	1 (4.4%)
Type of stent	
Bare Metal Stent only	13 (65.0%)
Drug eluting stent only	6 (30.0%)
Both	1 (5.0%)
Complications	
Need for cardiopulmonary resuscitation	9 (37.5%)
Need for hemodynamic support	6 (25.0%)
Compression requiring 2nd stent	3 (13.4%)
Conversion to Open Heart Surgery	2 (8.3%)
Restenosis	1 (4.2%)
In-hospital death	2 (8.3%)
Hospitalization length, days	7 ± 4

PCI: percutaneous coronary intervention

8.6 DISCUSSION

The main findings of this systematic review of the literature on symptomatic coronary obstruction following TAVI showed that this complication occurred more frequently in women and in patients with no prior CABG. In these cases, the mean height of the LCA ostium was ~10 mm (range 7 to >12 mm), and the mean diameter of the aortic root was ~28 mm (range 26 to 33 mm). Also, the vast majority of reported cases of coronary obstruction post-TAVI occurred in patients who had received a balloon-expandable valve. Clinical presentation included persistent severe hypotension, ST-segment changes, and ventricular arrhythmias, all of which occurred immediately after valve implantation in most cases. LCA ostia obstruction was more frequent than RCA obstruction, and most patients were treated with PCI, which was successful in about 90% of them. However, conversion to open heart surgery and mechanical hemodynamic support were required in about 8% and 25% of PCI attempts, respectively. Importantly, significant compression of the implanted stent was observed in 13% of the cases, requiring the implantation of a second stent in all of them. There were no cases of acute stent thrombosis or repeat revascularization, and the in-hospital mortality rate for the entire study population was 8.3% (0% in those patients with a successful PCI).

Coronary obstruction following TAVI was first described in the first TAVI experimental porcine model,[134] and this potential complication was subsequently confirmed by other authors in different experimental models.[306] The occurrence of coronary obstruction after TAVI in humans was first described in 2006,[156] and its reported incidence has usually been <1%, ranging from zero to up to 4.1% in contemporary series.[156,288,307-309] The rates of coronary obstruction in recent TAVI registries and in the PARTNER trial are summarized in **Table 8-5**.

Table 8-5: Data on coronary obstruction from large TAVI registries and the PARTNER trial

Study	n	Valve/Approach	Transfemoral	Transapical	All Procedures	Cases SAPIEN®	Cases CoreValve®
ADVANCE [286]	996	CoreValve	0.1%	-	0.1%	-	1
Canadian [164]	345	Cribier-Edwards, SAPIEN, SAPIEN XT / 49% TF, 51% TA	0.6%	1.1%	0.9%	3	-
FRANCE [186]	244	SAPIEN or CoreValve SAPIEN or CoreValve / 66% TF, TS 5%, 29% TA	SAPIEN (2.1%) CoreValve (1.5%)	0%	1.2%	2	1
German [144]	670	SAPIEN or CoreValve / 96% TF, 4% TA	-	-	0.1%	-	-
SOURCE [219]	1038	SAPIEN / 45% TF, 55% TA	0.7%	0.5%	0.6%	6	-
PARTNER [146]	348	SAPIEN / 70.1% TF, 29.9% TA	0%	0%	0%	-	-
SOURCE XT [165]	2600	SAPIEN XT/63% TF, 34% TA	0.3%	0.3%	0.3%	8	-
Pooled studies			13/3,726 (0.35%)	8/1,833 (0.44%)	22/6,241 (0.35%)	19	2
SAPIEN®					19/4,497 (0.42%)		
CoreValve®					2/1,074 (0.19%)		

8.6.1 Factors associated with coronary obstruction following TAVI

The most frequent mechanism associated with coronary obstruction following TAVI has been the displacement of the calcified native cusp over the coronary ostium, and this has also been confirmed by the present review of the literature. In fact, no cases of coronary obstruction related to the struts of the transcatheter valve frame or to the cuff/leaflets of the transcatheter valve itself have been reported to date. While the final mechanism leading to coronary obstruction after TAVI is well understood, the risk factors that predispose a patient to its occurrence remain largely unknown. A low position of the coronary ostia with respect to the aortic annulus has been highlighted as one of the most important factors contributing to this complication, and it has been suggested that a coronary ostia height cutoff ≤ 10 mm increases the risk of coronary obstruction during TAVI.[310,311] In a recent postmortem study including 51 normal hearts, the mean LCA height, as determined by the LCA distance to the bottom of the corresponding sinus, was 12.6 ± 2.6 mm.[312] In another study that evaluated the aortic root with multislice CT in 169 patients with and without aortic stenosis, the mean distance from the basal attachment point of the aortic valve leaflets to the ostium of the LCA was 14.4 ± 2.9 mm, with no differences between patients with and without aortic stenosis.[304] Akhtar et al.[303] found that aortic stenosis was associated with a shorter distance from the aortic valve annulus to the LCA ostium (13.4 ± 3.2 mm vs. 15.6 ± 2.7 mm; p = 0.01). The present study showed that mean height of the LCA ostium in the reported cases of coronary obstruction following TAVI was 10.3 mm (range 7 to up to >12 mm), a mean value that appears to be significantly lower (2 to 5 mm) compared to that reported in prior pathological and CT studies in patients with and without aortic stenosis (**Figure 8-2**). However, this mean coronary ostium height value was higher than the previously suggested 10-mm "safety" cutoff, and indeed, about 60% of the cases with coronary obstruction following TAVI had a coronary ostia height >10 mm. This suggests that factors other than a short distance between the aortic annulus and coronary ostia may also be involved in the occurrence of this complication.

The severity of valve calcification, and especially the presence of bulky calcium nodules on the left or right aortic leaflets have also been suggested as important predictive factors for coronary obstruction after TAVI. However, the degree of valve calcification or the presence of calcium nodules was not described in any of the reports included in the present review,

suggesting that this factor was either not evaluated or not taken into consideration. Also, a narrow aortic root with shallow sinuses of Valsalva leaving little room to accommodate the calcified native aortic leaflets after valve deployment may also be an important factor associated with coronary obstruction after TAVI. In this series, the mean aortic root diameter was ~28 mm, which was lower than the >30 mm diameter reported in previous studies evaluating aortic root geometry (**Figure 8-2**).[303,305] However, most reports included in the present review evaluated the aortic root diameter by echocardiography, and it has been shown that echocardiography tends to underestimate aortic root diameters compared with multislice CT.[304,313] Thus, we cannot draw firm conclusions about the role of aortic morphology, and in particular the degree of aortic root effacement, in relation to this complication.

Analysis of the clinical characteristics of the patients who suffered coronary obstruction after TAVI revealed a mean age (82.5 ± 7.0 years) and risk profile (mean logistic EuroSCORE: 25.1 ± 12.0) similar to those reported in most previous TAVI studies (**Figure 8-1**). However, up to 83% of the patients suffering this complication were women, and this is a significantly higher rate in comparison with the ~50% prevalence of women in most TAVI studies (**Figure 8-1**). Moreover, it has been shown previously in the literature that women have a smaller aortic root;[314] this, together with lower coronary ostia height may partially explain the increased incidence of this complication among women. Also, the rate of prior CABG (4.2%) was much lower than in prior TAVI studies, confirming the "protective effect" of CABG against symptomatic coronary ostia obstruction.

With regard to procedural characteristics, most reported patients who suffered coronary obstruction following TAVI had received a balloon-expandable Edwards valve. Data from previous TAVI registries also showed a slightly higher rate of coronary obstruction following balloon-expandable (>0.4%) vs. self-expandable (<0.2%) valve implantation (**Table 8-5**).[144,164,165,186,219,284] While the frame characteristics of the transcatheter valves (straight stainless steel or cobalt chromium vs. nitinol) and the mechanisms for valve implantation (balloon-expandable vs. self-expandable) may partially explain these differences, the criteria regarding minimal sinus of Valsalva diameter and coronary ostia height requirements differ between the 2 transcatheter valves (SAPIEN® and CoreValve® -Medtronic, Minneapolis, MN-), and this may also explain the higher rate of coronary

obstruction observed with the Edwards valve system. Whereas no specific formal recommendation for sinus of Valsalva width and coronary ostia height is provided for the implantation of the Edwards valve, a recommendation of a sinus of Valsalva width ≥27mm (for the 26-mm CoreValve®) or ≥28mm (for the 29-mm CoreValve®) mm, and a coronary height ≥14 mm is provided by the manufacturer for the implantation of the CoreValve® system. These specific recommendations, though probably not followed strictly by all CoreValve implanting centers, might have prevented a significant number of coronary obstructions with the CoreValve® system.

8.6.2 Clinical presentation and management of coronary obstruction following TAVI

The vast majority of patients presented with persistent severe hypotension after valve implantation, and about 50% and 25% of them had also ST-segment changes (about half of them with ST-segment elevation) and procedural ventricular arrhythmias, respectively. This clinical presentation could be explained by the fact that ~90% of the patients had LCA involvement, and thus resulting in significant left ventricular ischemia. It is therefore of major clinical importance in the presence of persistent severe hypotension following valve implantation, even in the absence of ECG changes, that prompt echocardiography be performed to look for new segmental abnormalities and/or coronary angiography to look for coronary obstruction. Interestingly, both in normal postmortem hearts and in a recent study examining the aortic root with multislice CT, the distance from the LCA ostium to the basal attachment point of the aortic valve leaflet was lower as compared to the right coronary ostium, which might explain why coronary obstruction following TAVI is more frequent on the left side.[304,312]

The present study showed that PCI was the preferred strategy for the treatment of coronary obstruction following TAVI. It is noteworthy that PCI was feasible and associated with a 91.3% success rate. Bare metal stents were used more frequently than drug eluting stents, and there were no cases of stent thrombosis or need for repeat revascularization during the hospitalization period. However, 3 patients (13%) needed a second stent due to significant compression of the first implanted stent unresponsive to balloon post-dilation. Hence, one might argue for the use of stents with higher radial force and routinely perform high

pressure post-dilation with a non-compliant balloon. The reasons for these findings are not yet understood, nonetheless the struts from the valve frame and most likely external compression from the calcific native valve cusp, might play an important role.[299,300] Importantly, up to 25% and 8% of the patients required either mechanical hemodynamic support (cardiopulmonary bypass, intra-aortic balloon, and tandem heart support) or conversion to open heart surgery, respectively, highlighting the importance of performing these procedures in highly experienced centers with cardiac surgery facilities.

8.6.3 ***Study limitations***

The present study has the limitations inherent to a systematic review that collects only the information described in the publications. Therefore, there might be relevant information omitted in the publications that could shed some more light on this complication. Indeed, imaging data (especially on CT) was not available in all reported cases, and this prevented an appropriate evaluation of the patient's characteristics determining a higher risk for the occurrence of this complication. In addition, all of the articles found in the literature were either case reports or very small series, precluding comparison with the entire TAVI population at risk. Additionally, the reported patients might have tended to pursue a better outcome than those who were not published ("selection bias").

8.7 CONCLUSION

In conclusion, coronary obstruction remains a rare but potentially life-threatening complication of TAVI. Baseline characteristics from reported cases suggest that this complication occurs more frequently in women with no prior CABG, and in patients receiving a balloon-expandable valve. Future studies will have to confirm these data and elucidate whether the potential lower rate of coronary obstruction observed following self-expandable valve implantation is due to a transcatheter valve class effect or to differences between valve types regarding pre-specified recommendations on coronary ostia height and aortic root dimensions. Also, although the 10-mm "safety cut-off" for coronary ostia height may help to prevent coronary obstruction during TAVI, about half of the patients who had this complication exhibited a coronary ostia height >10 mm, suggesting both that a higher

"safety cut-off" may be required and that factors other than coronary height (dimensions of sinuses of Valsalva and/or severe valve calcification) may probably play an important role in the occurrence of this complication. The results of this study also suggest that the occurrence of persistent severe hypotension, irrespective of the presence or not of ST-segment changes, immediately after valve implantation requires ruling out this complication. Importantly, PCI was a feasible and effective treatment in most cases, though the rates of additional hemodynamic support, conversion to open heart surgery or stent compression requiring the implantation of a second stent remained important. Future prospective studies including consecutive series of TAVI patients with this complication are needed to further evaluate the predictive factors and the most appropriate clinical management of this important complication of TAVI.

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8.9 DISCLOSURE

Dr Robert DeLarochellière is consultant for St. Jude Medical. Dr Eric Dumont is consultant for Edwards Lifesciences. Dr Josep Rodés-Cabau is consultant for Edwards Lifesciences and St. Jude Medical.

CHAPTER 9: ARTICLE 6

Predictive Factors, Management and Clinical Outcomes of Coronary Obstruction Following Transcatheter Aortic Valve Implantation: Insights from a Large Multicenter Registry

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9.1 RÉSUMÉ

FACTEURS PRÉDICTEURS, MANAGEMENT ET RÉSULTATS CLINIQUES DE L'OBSTRUCTION CORONAIRE APRÈS L'IMPLANTATION DE VALVE AORTIQUE PAR CATHÉTER : APERÇUS D'UN GRAND REGISTRE MULTICENTRIQUE

Objectifs : Évaluer les principales caractéristiques initiales et procédurales, la prise en charge et les résultats cliniques d'une large cohorte de patients ayant présenté une obstruction coronarienne (OC) comme complication lors de l'implantation de valve aortique par cathéter (TAVI).

Contexte : Peu de données existent sur les OC en lien avec une procédure TAVI.

Méthodes : Ce registre multicentrique a inclus un total de 44 patients ayant présenté une OC en lien avec une procédure TAVI parmi 6688 patients (0,66 %). Les données de tomodensitométrie initiales étaient disponibles pour 28 patients avec OC et chez 345 patients servant de groupe contrôle (les comparaisons ont été effectuées en incluant tous les patients et avec appariement de la cohorte 1:1 pour l'âge, le sexe, les antécédents de pontage coronarien, le type et la taille de la valve percutanée).

Résultats : Les variables initiales et procédurales associées aux OC étaient l'âge avancé ($p<0,001$), le sexe féminin ($p<0,001$), l'absence d'antécédent de pontage coronarien ($p=0,043$), l'utilisation d'une valve expansible par ballonnet ($p=0,023$) et des antécédents de chirurgie pour l'implantation d'une bioprothèse aortique ($p=0,045$). L'artère coronaire gauche (ACG) était l'artère la plus fréquemment impliquée (88,6 %). La hauteur moyenne de l'ostium de l'ACG et le diamètre du sinus de Valsalva (SV) étaient plus petits chez les patients présentant une obstruction en comparaison avec leurs contrôles appariés (10,7±0,4 mm vs. 13,3±0,3 mm, OR: 2,17, IC de 95 % de 1,62-2,90; et 28,3±0,8 mm vs. 31,3±0,6 mm, OR: 1,37, IC de 95% de 1,13-1,66). La majorité des patients présentait une hypotension sévère persistante (68,2 %) et des changements à l'ECG (56,8 %). L'intervention coronarienne percutanée a été pratiquée dans 75 % des cas et son succès fut de 81,8 %. Le taux de mortalité à 30 jours était de 40,9 %. À la suite d'un suivi médian de 12 (2-18) mois, le taux de mortalité cumulatif était de 45,5 % et il n'y avait aucun cas de thrombose de tuteur ni de réintervention.

Conclusion : L'OC symptomatique à la suite d'une procédure TAVI était rare mais tout de même une complication potentiellement mortelle plus souvent observée chez les femmes, les patients recevant une valve expansible par ballonnet et ceux ayant déjà reçu une bioprothèse chirurgicale. Une base de l'ostium plus basse et un SV peu profond étaient des facteurs anatomiques associés à l'OC. Malgré un traitement réussi, la mortalité immédiate et à moyen terme demeurait très élevée, soulignant l'importance d'anticiper et de prévenir l'occurrence de cette complication.

Mots clés : Implantation de valve aortique par cathéter; Remplacement de valve aortique percutanée; Occlusion coronaire; Obstruction coronaire; Intervention coronaire percutanée.

Ces travaux ont été présentés lors du congrès de la Société Européenne de Cardiologie Interventionnelle (EuroPCR, Paris, France; mai 2013), à la session « Hot Line - Registries and first-in-man for structural heart disease », au congrès de la Société espagnole de cardiologie, où ils ont gagné le prix d'un des meilleurs abstracts présentés aux sessions.

9.2 ABSTRACT

Objectives: To evaluate the main baseline and procedural characteristics, management and clinical outcomes of patients from a large cohort of patients undergoing transcatheter aortic valve implantation (TAVI) who suffered coronary obstruction (CO).

Background: Very few data exist on CO following TAVI.

Methods: This multicenter registry included a total of 44 patients who suffered symptomatic CO following TAVI of 6,688 patients (0.66%). Pre-TAVI computed tomography data was available in 28 CO patients and in a control group of 345 patients (comparisons were performed including all patients and a cohort matched 1:1 by age, gender, prior CABG, transcatheter valve type and size).

Results: Baseline and procedural variables associated with CO were older age ($p<0.001$), female sex ($p<0.001$), no prior CABG ($p=0.043$), the use of a balloon-expandable valve ($p=0.023$), and prior surgical aortic bioprosthesis ($p=0.045$). The left coronary artery (LCA) was the one most commonly involved (88.6%). The mean LCA ostia height and sinus of Valsalva (SOV) diameters were lower in patients with obstruction than in control subjects (10.6 ± 2.1 mm vs. 13.4 ± 2.1 mm, $p<0.001$; 28.1 ± 3.8 mm vs. 31.9 ± 4.1 mm, $p<0.001$). Differences between groups remained significant after the case-matched analysis ($p<0.001$ for coronary height; $p=0.01$ for sinus of Valsalva diameter). Most patients presented with persistent severe hypotension (68.2%) and electrocardiographic changes (56.8%). Percutaneous coronary intervention was attempted in 75% of the cases, being successful in 81.8%. Thirty-day mortality was of 40.9%. After a median follow-up of 12 (2-18) months, the cumulative mortality rate was of 45.5% and there were no cases of stent thrombosis or reintervention.

Conclusions: Symptomatic CO following TAVI was a rare but life-threatening complication that occurred more frequently in women, in patients receiving a balloon-expandable valve, and in those with a prior surgical bioprosthesis. Lower lying coronary ostium and shallow SOV were associated anatomic factors, and despite successful treatment, acute and late mortality remained very high, highlighting the importance of anticipating and preventing the occurrence of this complication.

Key words: Transcatheter aortic valve implantation; Percutaneous aortic valve replacement; Coronary occlusion; Coronary obstruction; Percutaneous coronary intervention.

9.3 INTRODUCTION

Symptomatic coronary obstruction due to the displacement of the calcified native valve leaflets over the coronary ostia is a potential complication of transcatheter aortic valve implantation (TAVI). However, apart from reporting its incidence (usually <1%) in some TAVI studies,[143,144,146,164,186,219,284] data on this life-threatening complication have been limited to case reports and very small case series,[315] and to date there has been no large registry evaluating the baseline characteristics of patients suffering this complication, its management and clinical impact.

We recently conducted a systematic review of the literature on symptomatic coronary obstruction as a complication of TAVI that included a total of 24 cases, all of them reported as case reports or very small case series.[315] In that study, reported cases of coronary obstruction following TAVI occurred more frequently in women and in patients receiving a balloon-expandable valve, and the left coronary artery (LCA) was the one most commonly involved. Percutaneous coronary intervention (PCI) was a feasible and successful treatment in most cases, but hemodynamic support and/or conversion to open heart surgery were frequently needed. This study, however, had the limitations inherent to a review that collects only the information described in publications. In addition to the possible omission of data and the selection bias inherent to published cases (reported cases might tend to have better outcomes than those that are not reported), obtaining data from case reports precluded any comparison with the entire TAVI population at risk and made it difficult to evaluate the baseline and procedural factors associated with this complication. The aim of the present study was therefore to evaluate the main baseline and procedural characteristics, management and clinical outcomes of patients suffering from coronary obstruction following TAVI from a large series of consecutive patients undergoing TAVI.

9.4 METHODS

9.4.1 ***Patient population and data collection***

The present multicenter registry of coronary obstruction following TAVI collected retrospectively all cases with this complication from a total of 81 centers in North America, Europe, South America, and Asia, from January 2007 to January 2013. Gathered data included the main baseline clinical, echocardiographic, computed tomography (CT) and procedural characteristics of the cases. All information on clinical presentation, diagnosis and treatment of the coronary obstruction complication, as well as 30-day and late clinical outcomes were entered. The clinical events were defined according to the VARC-2 criteria (retrospective event assignment).[196] Also, all centers were asked to provide data on the entire population undergoing TAVI with no coronary obstruction in each center; the data included mean age and logistic EuroSCORE (logEuroSCORE), and the percentage of women, and patients with prior coronary artery disease and prior coronary artery bypass graft (CABG). The total number of TAVI cases per center, data on valve type, approach and valve-in-valve procedures (cases with a prior surgical aortic bioprosthesis) were also gathered.

9.4.2 ***Computed tomography***

Data on coronary height, aortic annulus diameter and area, sinus of Valsalva (SOV) diameter, diameter of the sinotubular junction and severity of valve calcification (Agatston units) were also obtained in those patients with CT performed prior to the TAVI procedure. CT exams were evaluated in a central core-lab by 2 investigators (SP; HBR) and all measurements, but valve calcification severity, were performed with the CT images obtained following contrast injection. The techniques used for all these CT measurements have been described in detail in prior reports,[304,316,317] and are summarized in **Figure 9-1**. The CT measurements from patients with coronary obstruction following TAVI were compared to those obtained in a control group (no coronary obstruction) of 345 consecutive patients, obtained from January 2011 to December 2012, in 3 participating centers, with both valve types.

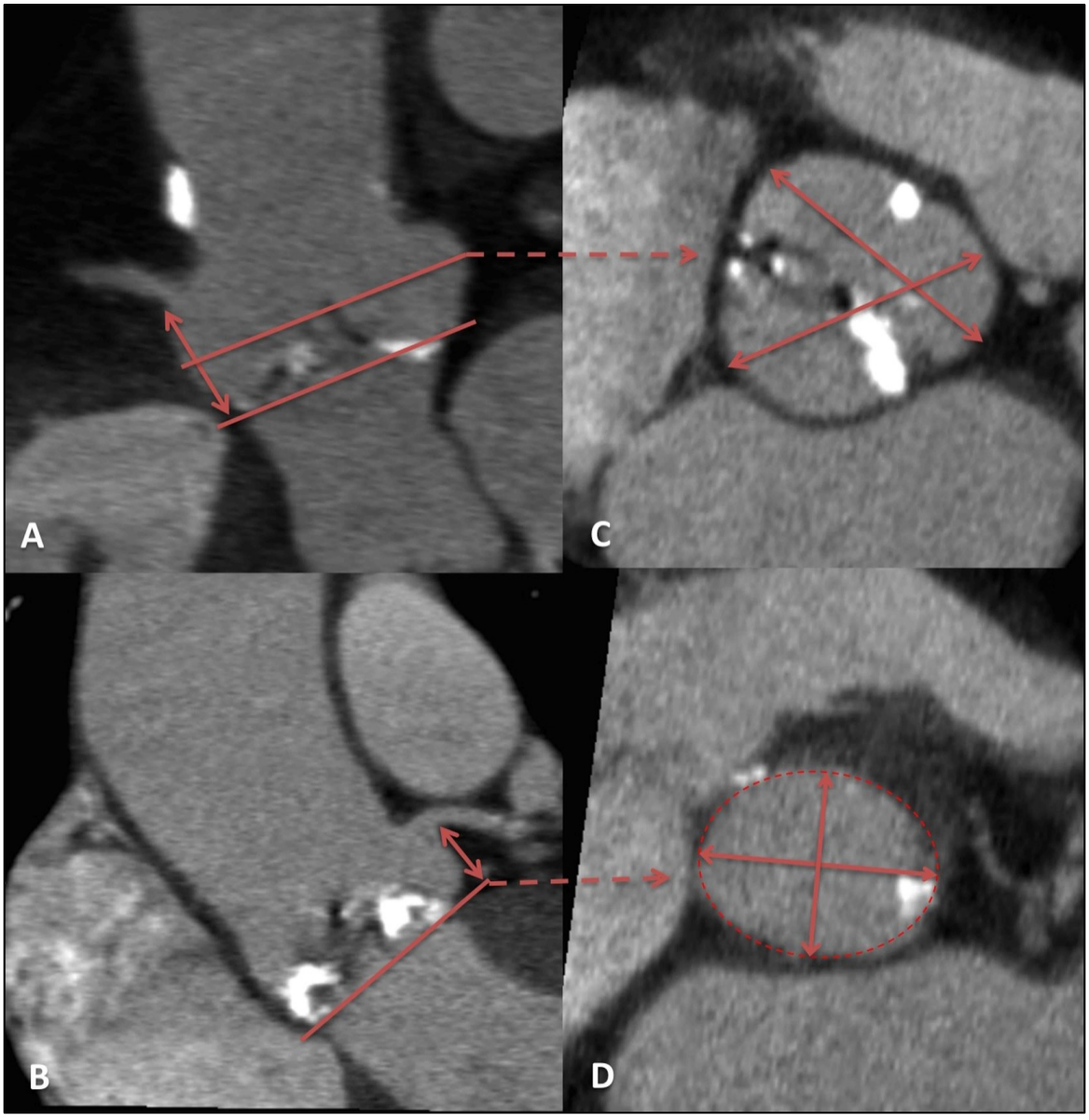

Figure 9-1: Multidetector computed tomography evaluation pre-TAVI

Computed tomography angiographic measurements in the long-axis view for the right (A) and left (B) coronary artery height. The coronary height was measured from the aortic annulus plane to the lower level margin of the right (A) and left (B) coronary ostia. While maintaining the orientation the images are scrolled up to allow for short axis measurement of the sinus of Valsalva (C) and then down to provide measures of the annulus/basal ring (D).

9.4.3 Statistical Analysis

Categorical variables are reported as n (%) and continuous variables are expressed as mean (SD) or median (25th to 75th interquartile range [IQR]) depending on variable distribution. Group comparisons were analyzed using the Student t test or Wilcoxon rank sum test. The chi-square test and the Fisher exact test were performed for categorical variables. In order to further evaluate the CT variables associated with coronary obstruction, patients with this complication and without prior surgical biophostesis were matched 1:1 with controls from a CT cohort of 345 patients using the bootstrap technique (1000 samples with replacement). The clinical variables used for the match were age (±2 years), gender, prior CABG, valve type and size. All analysis were conducted using the statistical package SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

9.5 RESULTS

9.5.1 Baseline characteristics of the study population

Of 6,688 patients who underwent a TAVI procedure in 81 centers worldwide, a total of 44 cases (0.66%) of acute symptomatic coronary obstruction occurred following the procedure. The clinical and procedural characteristics of the study population are shown in **Table 9-1**, and the main clinical and procedural characteristics of the coronary obstruction cases compared to the rest of the study population are shown in **Table 9-2**. Patients who suffered symptomatic coronary obstruction were older and more frequently women ($p<0.001$ for both), had less frequently a history of CABG ($p=0.043$), exhibited a higher risk profile as evaluated by logEuroSCORE ($p<0.001$), more frequently had a prior surgical aortic bioprosthesis ($p=0.045$), and had more frequently received a balloon-expandable valve ($p=0.023$ vs. self-expandable valve). The incidence of coronary obstruction according to valve type and the presence of a prior surgical bioprosthesis ("valve-in-valve procedure") are shown in **Figure 9-2**. The incidence of coronary obstruction according to the approach is shown in **Figure 9-3**.

Table 9-1: Baseline and procedural characteristics of the patients with coronary obstruction following TAVI

	n = 45
Clinical variables	
Age (years)	83.1 ± 8.0
Female sex	37 (84.1)
Body mass index (kg/m^2)	25.3 ± 6.0
NYHA class	
I-II	7 (15.9)
III-IV	37 (84.1)
Diabetes	15 (34.1)
Dyslipidemia	25 (59.5)
Hypertension	41 (93.2)
Coronary artery disease	19 (43.2)
Previous myocardial infarction	6 (13.6)
Prior PCI	9 (20.5)
Prior CABG	4 (9.1)
Patent LIMA/graft to LAD	2 (50)
Complete revascularization prior to TAVI	31 (70.5)
Prior aortic valve surgery	3 (6.8)
Previous pacemaker	8 (18.2)
Cerebrovascular disease	9 (20.5)
Peripheral vascular disease	17 (38.6)
COPD	11 (25.0)
Porcelain aorta	3 (6.8)
eGFR (< 60 mL/min)	23 (52.3)
logEuroSCORE (%)	23.2 ± 16.2
Echocardiographic variables	
Mean aortic gradient (mmHg)	54.5 ± 17.8
Aortic valve area (cm^2)	0.53 ± 0.19
LVEF (%)	53.5 ± 14.7
Annulus size (mm)	20.4 ± 1.5
Procedural variables	
Approach	
Transfemoral	30 (68.2)
Transapical	13 (29.5)
Transaortic	1 (2.3)
Valve-in-valve	3 (6.8)
Prosthesis size (mm)	
23 mm	25 (56.8)
26 mm	15 (34.1)
29 mm	3 (6.8)
31 mm	1 (2.3)

Continued

Conclusion

	n = 45
Prosthesis type	
Balloon-expandable valve (Sapien/Sapien XT)	37 (84.1)
Self-expandable valve (CoreValve)	7 (15.9)
Balloon pre-dilatation	40 (90.9)
Balloon post-dilatation	8 (18.2)

Values are expressed as n (%) or mean (±SD).
NYHA = New York Heart Association; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; LIMA = left internal mammary artery; LAD = left anterior descending artery; TAVI = transcatheter aortic valve implantation; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration ratio; logEuroSCORE = logistic EuroSCORE predicted risk of mortality; LVEF = left ventricular ejection fraction.

Table 9-2: Main Clinical and procedural characteristics, according to the occurrence of coronary obstruction following TAVI

	Coronary Obstruction (n=44)	Controls (n=6,644)	p
Clinical variables			
Age (years)	83.1 ± 8.0	81.0 ± 7.1	<0.001
Female	37 (84.1)	3,408 (51.3)	<0.001
Prior CAD	19 (43.2)	2,270 (55.5)*	0.258
Previous CABG	4 (9.1)	919 (22.5)*	0.043
LogEuroSCORE (%)	23.2 ± 16.2	18.1 ± 13.6	<0.001
Procedural variables			
Valve type			0.023
Sapien/Sapien XT	37 (84.1)	4,533 (68.2)	
CoreValve	7 (15.9)	2,066 (31.1)	
Others	-	45 (0.7)	
Approach			0.442
Transfemoral	30 (68.2)	4,904 (73.8)	
Transapical	13 (29.5)	1,546 (23.3)	
Transaortic/trans-subclavian	1 (2.3)	194 (2.9)	
Valve-in-valve	3 (6.8)	118 (1.8)	0.045

Values are expressed as n (%) or mean (±SD). Dash indicates that there was no case of coronary obstruction with the other valves. CAD: coronary artery disease; CABG: coronary artery bypass graft; logEuroSCORE: logistic EuroSCORE predicted risk of mortality
**Data available for 4,386 patients*

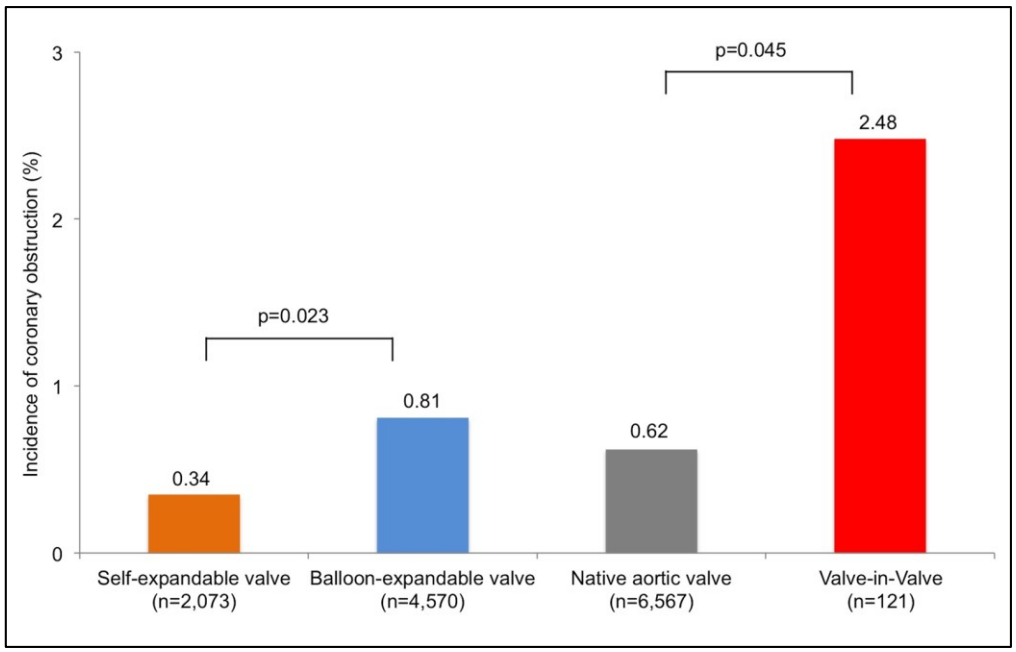

Figure 9-2: Incidence of coronary obstruction according to valve type and valve-in-valve procedures

Incidence of coronary obstruction following transcatheter aortic valve implantation with a self-expandable, balloon-expandable valves, as well as in native or prosthetic aortic valves

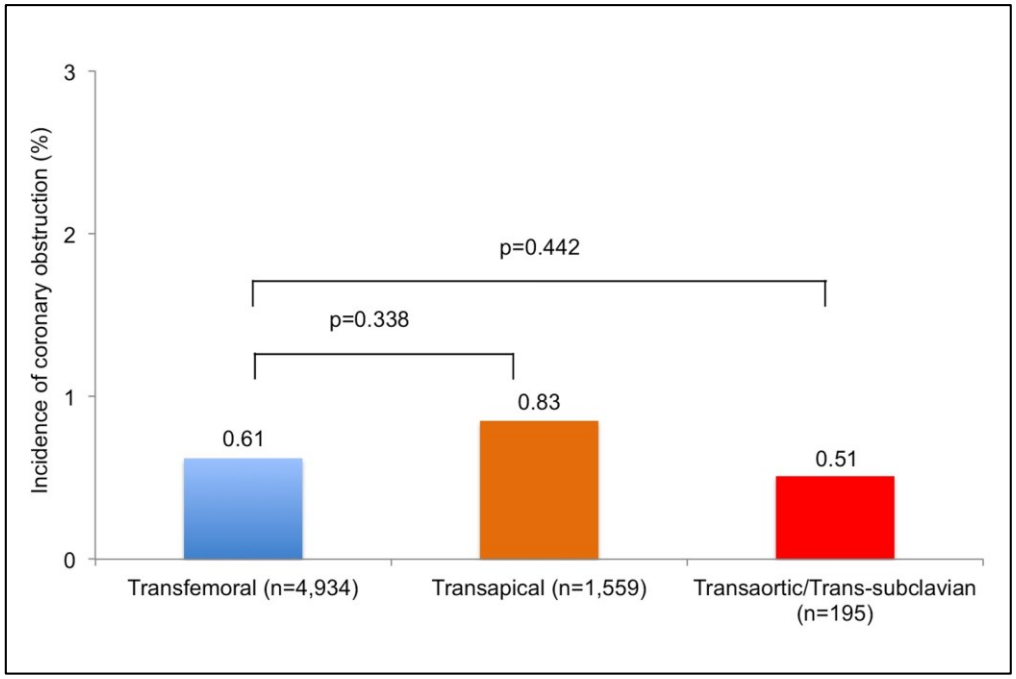

Figure 9-3: Incidence of coronary obstruction according to the different approaches for TAVI

Incidence of coronary obstruction following transcatheter aortic valve implantation through the transfemoral, transapical, and transaortic/trans-subclavian approaches

9.5.2 Clinical presentation, management and outcomes

Data on clinical presentation and management of coronary obstruction, and 30-day outcomes are presented in **Table 9-3**. Coronary obstruction occurred at the ostium of the LCA in most (88.6%) cases and the diagnosis was made by coronary angiography in all patients but one (post-mortem). Coronary obstruction was related to the displacement of a calcified native aortic valve leaflet towards the coronary ostium in all patients but one (97.7%), who had an aortic valve cusp shearing and migration into the LCA. Most cases (68.2%) presented with severe persistent hypotension, and electrocardiographic (ECG) changes, mainly ST-segment elevation and ventricular arrhythmias, occurred in 56.8% of the patients.

Coronary revascularization was not attempted in 7 patients (15.9%). In 2 patients who received a CoreValve system coronary obstruction was resolved by snaring and removing the transcatheter valve towards the ascending aorta. One patient with partial obstruction of the right coronary artery (RCA) ostium was managed with medical treatment and no coronary revascularization was attempted. Another 3 patients died within the few minutes following a complete coronary obstruction of the LCA, with no time for any coronary revascularization attempt. PCI was attempted in 33 patients (75%), and it was successful (residual stenosis <20% and TIMI flow 3) in 81.8% of them.

Procedural death occurred in 7 patients (15.9%), and among those patients who survived the procedure 11 had died at 30 days, leading to a 30-day mortality rate of 40.9%. The causes of death in these patients were sepsis (n=6), cardiogenic shock (n=4) and hypoxic brain injury (n=1). The 30-day mortality rate according to the type and results of coronary revascularization treatment is shown in **Figure 9-4**. Thirty-day survival was of 66.7% among patients who received cardiopulmonary bypass as mechanical support (without CABG). In patients who survived the procedure, the median hospitalization length was of 6 (3-17) days, and echocardiographic data showed a mean residual gradient of 10.9 ± 7.9 mmHg, and a valve area of 1.66 ± 0.36 cm^2. Residual aortic regurgitation was absent/trivial, mild and moderate in 33.4%, 58.3% and 8.3% of the patients, respectively.

At a median follow-up of 12 (2-18) months, a total of 20 patients had died (cumulative mortality rate: 45.5%). Among those patients who survived at 30 days, a total of 2 patients

died during the follow-up period of unknown causes. The vast majority of patients (95%) were in NYHA functional class I-II at follow-up. There were no cases of stent thrombosis or repeat revascularization. The Kaplan-Meier survival curves at 1-year follow-up are shown in **Figure 9-5**.

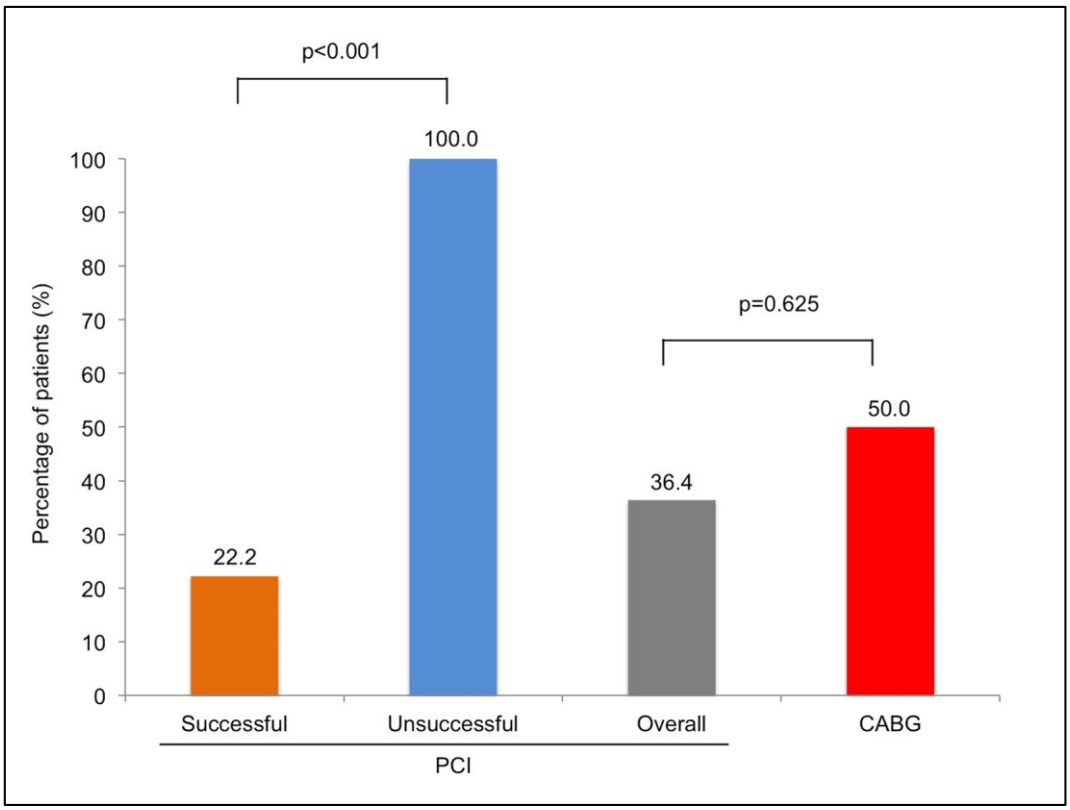

Figure 9-4: Mortality rate at 30 days according to the type and results of the treatment for coronary obstruction

Mortality at 30 days following successful PCI, unsuccessful PCI or CABG after the occurrence of coronary obstruction. PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft

Table 9-3: Clinical presentation and management of coronary obstruction following TAVI

	n = 44
Obstructed coronary artery	
Left coronary artery	39 (88.6)
Right coronary artery	2 (4.5)
Both	3 (6.8)
Timing	
After balloon valvuloplasty	4 (9.1)
After valve implantation	31 (70.5)
After balloon post-dilatation	4 (9.1)
Within 24 hours following TAVI	4 (9.1)
More than 24 hours following TAVI	1 (2.3)
Clinical Presentation	
Severe persistent hypotension	30 (68.2)
ECG changes	25 (56.8)
ST-segment elevation	14 (56.0)
Ventricular fibrillation	7 (28.0)
Ventricular tachycardia	3 (12.0)
Atrial fibrillation	2 (8.0)
Left bundle branch block	2 (8.0)
Stenosis severity	
Partial occlusion	25 (56.8)
Complete occlusion	19 (43.2)
Treatment	
PCI attempted	33 (75.0)
Successful	27 (81.8)
Stent successfully implanted	25 (75.8)
Guide-wire protection only	1 (3.0)
Catheter cannulation only	1 (3.0)
Unsuccessful	6 (18.2)
Coronary cannulation failure	2 (33.3)
Wire crossing failure	2 (33.3)
Stent could not be advanced	1 (16.7)
Stent implanted but no flow	1 (16.7)
Type of stent	
Bare metal stent(s)	6 (24.0)
Drug eluting stent(s)	17 (68.0)
Bare metal and drug eluting stents	2 (8.0)
Urgent CABG	6 (13.6)
Conversion to open heart surgery	2 (6.1)

Continued

Conclusion

	n = 44
Procedural Complications	
Need for cardiopulmonary resuscitation	18 (40.9)
Need for hemodynamic support	16 (36.4)
CPB	7 (43.8)
IABP	4 (25.0)
Fem-Fem CPB	3 (18.8)
ECMO	1 (6.3)
Impella	1 (6.3)
Inotropes	30 (68.2)
Valve embolization	2 (4.5)
Need for a second valve	3 (6.8)
Cardiac tamponade	3 (6.8)
30-day Outcomes	
Myocardial infarction	21 (47.7)
Peak CK-MB (µg/l)	82.4 [24.3-240.6]
New Q waves*	5 (35.7)
New left bundle branch block	4 (9.1)
New Pacemaker	1 (2.3)
Major vascular complications	5 (11.4)
Major or life-threatening bleeding	7 (15.9)
Acute renal failure	9 (20.4)
Dialysis	2 (4.5)
Stroke	4 (9.1)
Death	18 (40.9)
Hospitalization length, days	6 [3-17]

Values are expressed as n (%) or median [IQR]
TAVI: transcatheter aortic valve implantation; ECG: electrocardiographic; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump; Fem-Fem: femoral-femoral bypass; ECMO: extracorporeal membrane oxygenation.
** After excluding the patients with procedural death.*

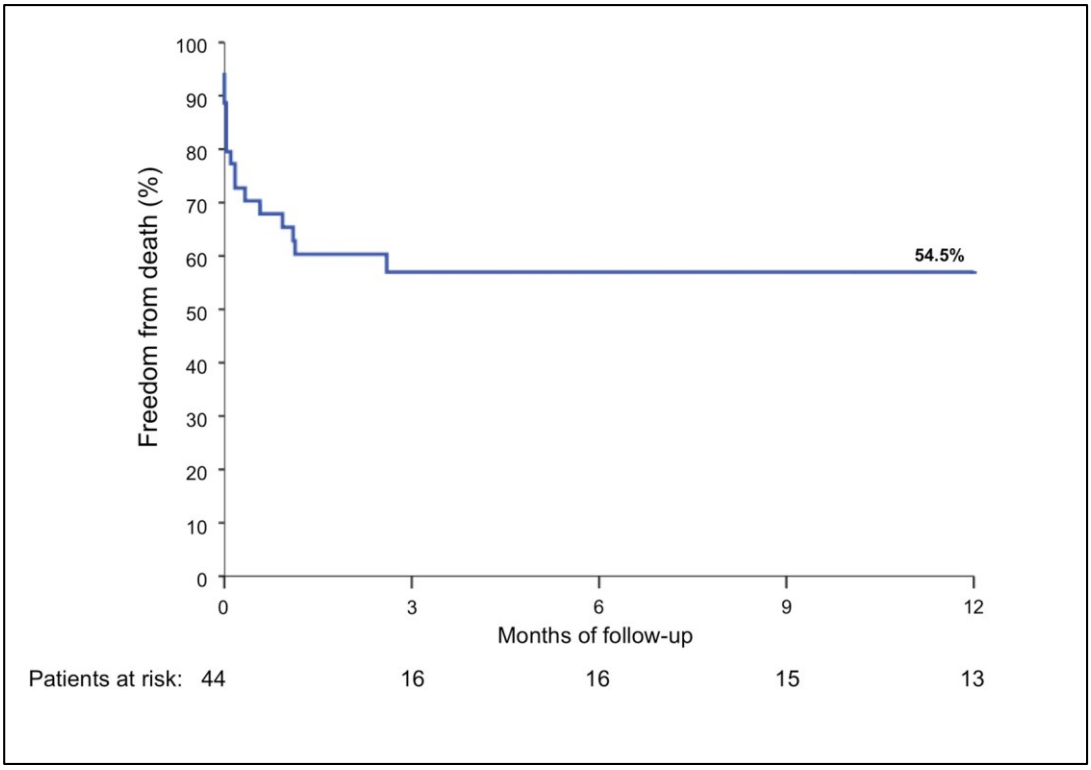

Figure 9-5: Kaplan-Meier survival curves at 1-year follow-up

Survival curve showing a mortality rate of 45.5% at 1-year follow-up after transcatheter aortic valve implantation complicated with coronary obstruction

9.5.3 CT data

Pre-TAVI CT data were available in 28 of the 44 patients with coronary obstruction (63.6%). CT data of the patients with coronary obstruction compared to those of the control group are shown in **Table 9-4**. The main clinical characteristics of the CT control group were similar to the overall study population with no coronary obstruction following TAVI (**Table 9-5**). Patients with coronary obstruction exhibited a smaller aortic annulus area ($p=0.002$), SOV diameter ($p<0.001$), and sinotubular junction diameter ($p=0.003$), as well as a lower LCA height ($p<0.001$). As women represented the vast majority of patients in the coronary obstruction group, a separate analysis of the CT data in women only was also performed (**Table 9-6**).

The results of the case-matched analysis including 27 patients without prior surgical bioprosthesis in both groups are shown in **Table 9-7**. The SOV diameter remained smaller in the coronary obstruction group (OR: 1.37, 95%CI 1.13-1.66) and LCA height lower as

compared to controls (OR: 2.17, 95%CI 1.62-2.90). The individual data for LCA height and SOV diameters are shown in **Figure 9-6**. Up to 86% of the patients who had a coronary obstruction had a LCA height of <12 mm, compared to 26.4% of the patients in the control group (p<0.001). The SOV diameter was <30 mm in 71.4% of the patients who had coronary obstruction compared to 33% of the patients in the control group (p<0.001). Most patients (67.9%) who had coronary obstruction had both a LCA height <12 mm and a SOV diameter <30 mm compared to 13.3% of the patients in the control group (p<0.001).

Table 9-4: Computed tomography data, according to the occurrence of coronary obstruction following TAVI

	Coronary Obstruction (n=28)	Controls (n=345)	p
Annulus diameter (mm)	22.9 ± 3.1	24.4 ± 2.9	0.010
Annulus area (mm^2)	387 [375-424]	476 [405-560]	0.002
Aortic SOV diameter (mm)	28.1 ± 3.8	31.9 ± 4.1	<0.001
Sinotubular junction (mm)	25.2 ± 3.1	28.0 ± 3.9	0.003
Relation prosthesis size/annulus	1.09 ± 0.11	1.05 ± 0.09	0.084
Relation SOV/annulus	1.25 ± 0.17	1.31 ± 0.14	0.054
Left coronary height (mm)	10.6 ± 2.1	13.4 ± 2.1	<0.001
Right coronary height (mm)	12.4 ± 3.2	14.1 ± 2.4	0.003
Left coronary height* (mm)	10.4 ± 2.0	13.5 ± 2.0	<0.001
Right coronary height† (mm)	11.3 ± 2.1	14.0 ± 2.4	0.048
Calcium score (Agatston units)	2,354 ± 1,187	2,872 ± 1,726	0.290

Values are expressed as mean (±SD) or median [IQR]
SOV: sinus of Valsalva.
**Cases of right coronary artery obstruction excluded.*
†Cases of left coronary artery obstruction excluded.

Table 9-5: Main Clinical characteristics between the computed tomography cohort and the overall population

	Computed Tomography Cohort (n=345)	Controls (n=6,298)	p
Clinical variables			
Age (years)	81.1 ± 6.6	81.0 ± 7.1	0.798
Female	161 (46.5)	2.887 (45.8)	0.807
Prior CAD	231 (66.8)	2.039 (50.5)*	<0.001
Prior CABG	98 (28.3)	821 (22.5)*	<0.001
LogEuroSCORE (%)	18.6 ± 14.8	18.0 ± 13.5	0.461

Values are expressed as n (%) or mean (±SD).
CAD: coronary artery disease; CABG: coronary artery bypass graft; LogEuroSCORE: logistic EuroSCORE predicted risk of mortality.
**Data available for 4,040 patients*

Table 9-6: Computed tomography data in women only, according to the occurrence of coronary obstruction following TAVI

	Coronary Obstruction (n=23)	Controls (n=160)	p
Annulus diameter (mm)	22.1 ± 2.0	22.9 ± 2.4	0.113
Annulus area (mm^2)	386 [375-408]	421 [371-480]	0.024
Aortic SOV diameter (mm)	27.3 ± 3.0	28.0 ± 4.0	0.001
Sinotubular junction (mm)	24.5 ± 2.7	27.9 ± 4.0	0.001
Relation prosthesis size/annulus	1.10 ± 0.10	1.06 ± 0.09	0.067
Relation SOV/annulus	1.24 ± 0.16	1.30 ± 0.14	0.093
Left coronary height (mm)*	10.0 ± 1.5	12.7 ± 1.8	<0.001
Right coronary height (mm)†	11.4 ± 3.0	13.3 ± 1.8	0.140
Calcium score (Agatston units)	2,444 ± 1262	2,564 ± 1704	0.824

Values are expressed as n (95% CI) or median [IQR]
SOV: sinus of Valsalva
**Cases of right coronary artery obstruction excluded*
†Cases of left coronary artery obstruction excluded.

Table 9-7: Computed tomography data from the case-matched analysis, according to the occurrence of coronary obstruction following TAVI

	Coronary Obstruction (n=27)	Controls (n=27)	OR (95% CI)	p
Annulus diameter (mm)	23.0 (21.8, 24.3)	23.6 (22.9, 24.3)	1.15 (0.92–1.45)	0.510
Annulus area (mm^2)	410 (374, 445)	458 (426, 490)	1.01 (0.99–1.02)	0.126
Aortic SOV diameter (mm)	28.3 (26.8, 29.9)	31.3 (30.2, 32.4)	1.37 (1.13–1.66)	0.011
Relation prosthesis size/annulus	1.08 (1.04, 1.12)	1.05 (1.01, 1.09)	0.02 (0.01–3.99)	0.315
Relation SOV/annulus	1.26 (1.18, 1.34)	1.34 (1.28, 1.40)	20 (1.28–333)	0.003
Left coronary height (mm)	10.7 (9.8, 11.5)	13.3 (12.7, 13.9)	2.17 (1.62–2.90)	<0.001
Right coronary height (mm)	12.7 (11.1, 14.2)	14.2 (13.3, 15.1)	1.36 (1.10–1.68)	0.047
Calcium score (Agatston units)	2284 (1164, 2904)	2733 (2120, 3346)	1.00 (0.99–1.1)	0.333

Values are expressed as mean (± SE); C: confidence interval; SOV: sinus of Valsalva; OR: odds ratio.

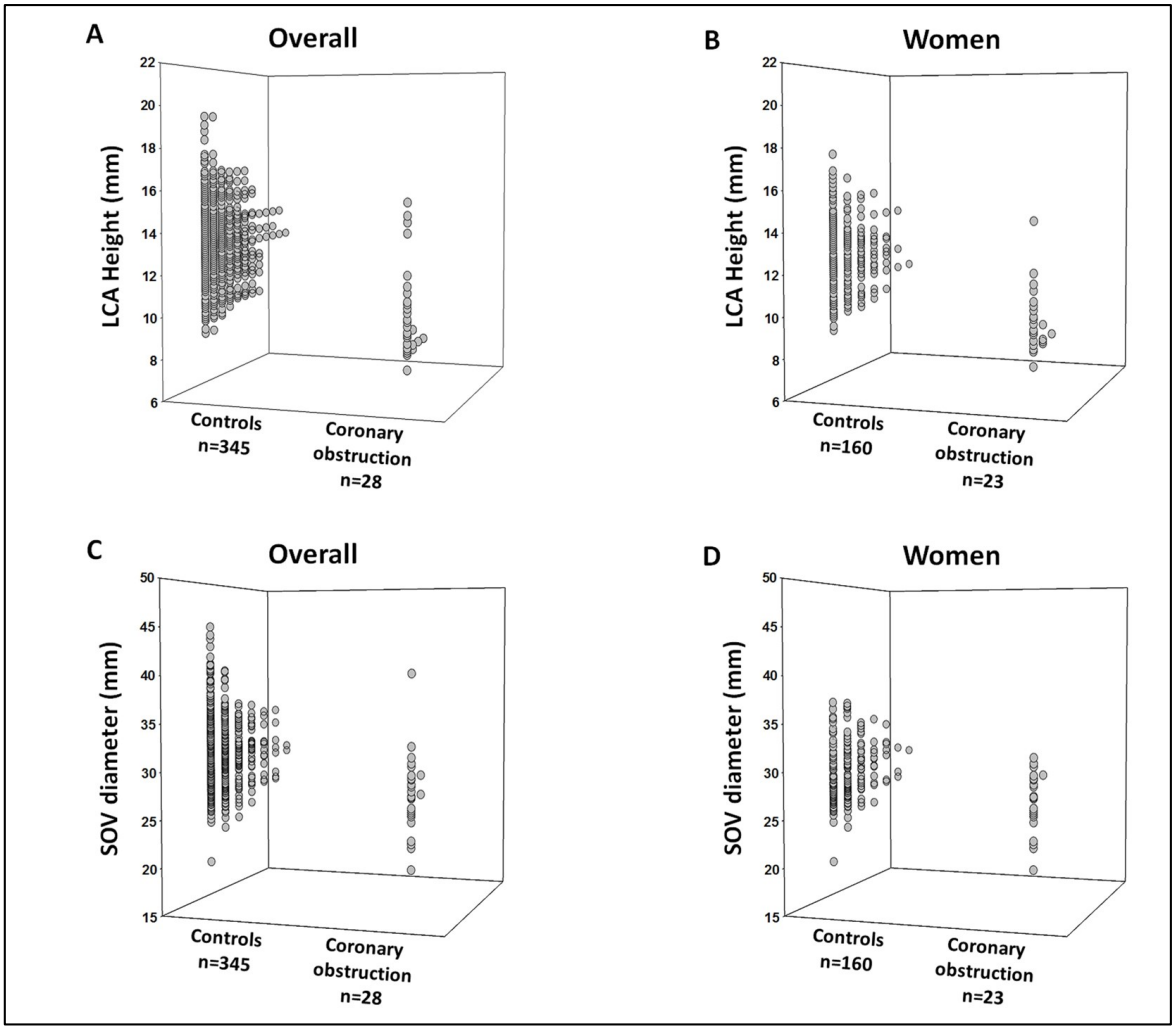

Figure 9-6: Individual data for the left coronary artery height and aortic sinus of Valsalva diameter

Individual data on computed tomography from the patients with coronary obstruction and controls showing that up to 86% of the patients with coronary obstruction had a LCA height of <12 mm (A), compared to 26% of the patients in the control group (A). In women, up to 96% of the coronary obstruction group had a LCA<12mm compared to 36% in the control group (B). The SOV diameter was <30 mm in 71% of the patients who had coronary obstruction versus 33% in the controls (C). In women, up to 78% of the patients in the coronary obstruction group had a SOV<30 mm versus 55% in the controls. LCA: left coronary artery; SOV: sinus of Valsalva.

9.6 DISCUSSION

9.6.1 Coronary obstruction and TAVI: incidence and associated factors

Potential concerns about the occurrence of coronary obstruction had been pointed out in the very first experimental models evaluating the TAVI technique,[134,306] and the occurrence of this complications was also reported in the first human experiences of TAVI.[156] The incidence of this complication in subsequent large TAVI series and registries has been low, and nearly systematically lower than 1%.[143,144,146,164,186,190,219,284] The results of the present study, with a systematic evaluation of this complication in a multicenter cohort including >6,500 TAVI procedures, confirmed an incidence of coronary obstruction of <1% (0.66%).

While the incidence of this complication was low for the 2 transcatheter valve types (balloon-expandable and self-expandable), the coronary obstruction rate was as much as twice as high among patients who received a balloon-expandable valve (0.81% vs. 0.34% among those who received a self-expandable valve). A recent review of TAVI complications including all TAVI studies with ≥100 patients also found a tendency towards a higher incidence of coronary obstruction in patients treated with a balloon-expandable valve (1.1%) compared to those treated with a self-expandable valve (0.4%).[190] This is also consistent with the systematic review of the reported cases of coronary obstruction to date, which involved a balloon-expandable valve in >80% of the cases.[315] Differences in both the frame characteristics of the 2 transcatheter valve systems (straight stainless steel or cobalt chromium vs. nitinol with a concave shape at the level of coronary arteries) and the mechanisms for valve implantation (balloon-expandable vs. self-expandable) might partially explain these differences. However, the specific recommendations on SOV diameter and coronary ostia height for the CoreValve system implantation could also have played a role in these differences. In fact, whereas no specific formal recommendation for SOV width and coronary ostia height was provided for the implantation of the Edwards valve, a recommendation of a SOV width of ≥27mm (for the 26-mm CoreValve) or ≥28mm (for the 29-mm CoreValve) mm, and a coronary height of ≥14 mm was provided by the manufacturer for the implantation of the CoreValve system. While these specific recommendations might not have been followed by all CoreValve implanting centers, it may possibly have prevented a significant number of coronary obstructions with the CoreValve system.

The occurrence of coronary obstruction was also more frequent among patients with prior surgical aortic bioprosthesis ("valve-in-valve" procedures). The incidence of coronary obstruction of 2.4% in such patients was close to the 3.5% rate reported in a recent multicenter registry of "valve-in-valve" TAVI procedures.[318] Some types of surgical aortic bioprosthesis such as stentless valves or stented valves with long leaflets have been associated with this complication, and future studies with a much larger number of patients will be needed to further evaluate the factors associated with coronary obstruction in this specific group of patients.

While women represent about 50% of the patients treated with TAVI, the vast majority (>80%) of patients who had coronary obstruction following TAVI were women. This was consistent with prior data from reported cases of coronary obstruction as a complication of TAVI, mainly single case reports or small case series, which involved women in 83% of the cases.[315] The association between female sex and coronary obstruction may be due to anatomic differences in aortic SOV dimensions and coronary height according to sex. Prior CT studies have already shown the smaller aortic SOV dimensions and lower coronary ostia take-off in women, irrespective of the presence of aortic stenosis,[314,317] and these sex differences in aortic SOV dimensions and coronary height were also observed in the pre-TAVI CT exams of our control group including >300 patients (33.8±3.9 mm vs. 29.7±3.1 mm for SOV dimensions; 14.1±2.1 mm vs. 12.7±1.8 mm for LCA coronary height in men and women, respectively; $p<0.001$ for both). It has been shown that coronary obstruction following TAVI is mainly due to the displacement of the calcified native cusp over the coronary ostia, and this was also the mechanism of coronary obstruction in 98% of the patients in the present study. It is therefore not surprising that aortic SOV dimensions and coronary height were shown to be important factors associated with the occurrence of coronary obstruction following TAVI in this study. Patients with coronary obstruction exhibited a lower coronary ostia take-off of the LCA. The mean LCA height in patients with coronary obstruction was of about 11 mm (10 mm in women), as compared to about 13 mm in those patients without coronary obstruction. Importantly, most patients who suffered coronary obstruction (about 80% overall, 96% of the women) had a LCA height of <12 mm, suggesting that this may be a more accurate cutoff than the 10-mm cutoff suggested by both the ACC/AATS/SCAI/STS and the CT-TAVI expert consensus,[310] and the 14-mm cutoff

suggested by the manufacturer regarding the CoreValve implantation. Morevover, the 12 mm cutoff would be in the upper limit of the 95% CI from the coronary obstruction cases and would not be included in the lower limit for the controls. The RCA ostia take-off is usually higher than that of the LCA,[304,317] and this is probably the reason why RCA obstruction after TAVI is very infrequent (only 11% of the cases in the present series). While the RCA ostia height was also found to be lower in patients who had RCA obstruction after TAVI, the low number of patients with this complication precluded drawing any reliable conclusions about the RCA cutoff height associated with an increased risk.

Although coronary ostia height is an important factor associated with coronary obstruction following TAVI, a significant number of patients in the coronary obstruction group suffered this complication despite a LCA coronary height of >12 mm (21.4%), indicating that factors other than coronary height are also involved in this complication. A narrow aortic root leaving little room to accommodate the native aortic leaflets may also contribute to coronary obstruction after TAVI. In fact coronary obstruction was associated with a certain degree of aortic root effacement as compared to the control group. Most patients (64.3%) who suffered this complication had an aortic SOV diameter of <30 mm, as compared to about one third of the patients in the control group. In fact only a minority of the patients who did not suffer coronary obstruction had both, a coronary height of <12 mm and an aortic SOV diameter of <30 mm (13.3%), meaning that the combination of these 2 anatomic factors has to be taken into account when evaluating the possibility of coronary obstruction due to TAVI. The degree of valve calcification as a global measure was not associated with the occurrence of coronary obstruction in this study, suggesting that this is probably not the main anatomic factor associated with post-TAVI coronary obstruction. However, the presence of bulky calcium nodules was not specifically evaluated and its role in the occurrence of some cases of coronary obstruction cannot be ruled out.

In those patients considered at high-risk for coronary obstruction, we would suggest to implement additional security measures during the TAVI procedure such as simultaneous angiography during balloon valvuloplasty to depict coronary obstruction or coronary protection with a guide wire in the presence of clinical and anatomical parameters of risk. Finally, the use of a transcatheter valve that can be repositioned or retrieved in case of coronary obstruction following valve implantation should probably be recommended in such cases.

9.6.2 Coronary obstruction following TAVI: management and clinical outcomes

Most of the patients with coronary obstruction presented with persistent severe hypotension, about half of them exhibited ECG changes, mainly ST-segment elevation, and more than one third had ventricular arrhythmias. These data suggest that in case of persistent hypotension following valve implantation, coronary obstruction should be included in the differential diagnosis irrespective of ECG changes, and prompt echocardiography to detect new segmental abnormalities and/or coronary angiography to detect coronary obstruction should be performed.

The present study also showed that PCI was the preferred strategy for the treatment of coronary obstruction following TAVI. Importantly, PCI was feasible (attempted in 75% of the patients) and had a success rate of 81.8%. Still, urgent CABG or mechanical hemodynamic support (mainly cardiopulmonary bypass) were needed in 14% and 36% of the patients, respectively, underscoring the importance of performing these procedures in highly experienced centers with cardiac surgery facilities. These results differ from those of a recent systematic review of the literature including small case series and case reports, where PCI was attempted in 96% of the patients and was successful in 91% of them.[315] In fact, the reported patients might have tended to pursue a better outcome than those who were not published ("selection bias"). This is also supported by the fact that our 30-day death rate was as high as 41%, as compared to <10% in the systematic review of reported cases.[315] The mortality rate was high after successful PCI (22%) or CABG (50%) and increased to as much as 100% in case of unsuccessful PCI. While these results suggest that PCI as a first attempt for coronary revascularization is a reasonable strategy, it also highlights the importance of both obtaining coronary flow restoration very rapidly and being ready to change the therapeutic strategy (cardiopulmonary bypass, CABG) if coronary flow is not restored within a few minutes of the attempted PCI.

9.6.3 Study Limitations

Only cases with symptomatic coronary obstruction were gathered; there might have been cases with previous CABG in which coronary obstruction occurred without clinical symptoms ("graft protection"). Available data from baseline clinical characteristics in the global cohort of TAVI patients were limited to a few clinical variables and logEuroSCORE. Reporting of cases of coronary obstruction cases was done on a voluntary basis and there was no external monitoring done to verify the accuracy of the data reported by each center. CT data were available in about 2/3 of the coronary obstruction patients and in a control group of 345 patients. While this was a small control group as compared to the entire TAVI study population, it still represents one the largest series with pre-TAVI CT data to date.[303-305,313,315,317] Also, the main clinical characteristics of the control group were similar to the rest of the study population, and both LCA height and SOV diameter remained as associated factors with coronary obstruction after performing a case-matched comparison. Coronary angiograms leading to the diagnosis of coronary obstruction were analyzed by the investigators of each center, with no centralized analyses. Although the present study represents a large series of coronary obstruction cases following TAVI, the relatively low number of events and CT exams precluded the performance of a multivariate analysis to evaluate the independent predictors of coronary obstruction in this population. Future prospective studies with a very large number of patients with systematic CT measurements will be needed to confirm these results.

9.7 CONCLUSION

In conclusion, the present study including the largest series of patients with coronary obstruction following TAVI to date confirmed that this is a rare but life-threatening complication of TAVI that occurred more frequently in women, in patients receiving a balloon-expandable valve, and in those with a prior surgical bioprosthesis. Lower lying coronary ostium (<12 mm) and shallow SOV (<30 mm) were related anatomic factors, and despite successful treatment (mainly PCI) in most cases periprocedural mortality remained very high, highlighting the importance of anticipating and preventing the occurrence of this complication.

9.8 ACKNOWLEDGMENTS

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9.10 DISCLOSURE

Drs. John G. Webb and Josep Rodés-Cabau are consultants for Edwards Lifesciences and St-Jude Medical. Drs. Mauricio G. Cohen, Alan Zajarias, Stamatios Lerakis, Augusto Pichard and James L. Velianou are consultants for Edwards Lifesciences. Dr. Martin Leon reports a research grants for clinical trials from Edwards Lifesciences. Dr. Ganesh Manoharan is consultant for St-Jude Medical. Drs. Peter de Jaegere, Fabio Sandoli de Brito Jr., Paul T.L. Chiam, Marc Ruel, Marco Perin, Rogerio Sarmento-Leite and Sam Radhakrishnan are consultants for Medtronic. The rest of the authors had no conflict of interest to disclose.

CHAPTER 10: DISCUSSION, PERSPECTIVES AND CONCLUSIONS

10.1 INCIDENCE, LOCALIZATION AND EXTENT OF MYOCARDIAL INJURY AFTER TAVR

The majority of patients undergoing SAVR experience some degree of myocardial injury, as determined by a rise in cardiac biomarkers, mostly related to aortic cross-clamp, cardiopulmonary bypass and cardioplegia.[223,224] Whilst TAVR procedures are less invasive as cardiopulmonary bypass is not required, it has been shown previously that the transcatheter procedures are still related with the systematic increase in cardiac biomarkers denoting some degree of myocardial injury.[167,214,216,217] Of note, this has correlated, in small studies with limited follow-up, to worse short- and long-term prognosis, and impaired LV function.[167,214,216,217]

One of my objectives in this PhD was to first assess the exact incidence of myocardial injury after TAVR, as determined by the serial changes in CK-MB after the procedure. This was evaluated in a Multicenter Registry, including 1,131 patients from 13 centers worldwide, one of the largest studies to date on cardiac biomarkers after TAVR (article 1, chapter 4). We have demonstrated that 66% of the patients presented an increase in CK-MB above the upper normal limit, but this was ~2-fold more prominent in those patients undergoing TAVR by the transapical approach, in whom 97% had an increase in CK-MB levels (Figure 4-1). As a second objective in this PhD, we have also evaluated the incidence of myocardial injury according to the NT-proBNP levels, an important marker of myocardial wall stress. Hence, we have performed serial measurements in a prospective cohort of 333 patients from our center (article 2, chapter 5). NT-proBNP levels were already elevated at baseline in 86% of TAVR candidates, with a median increase as high as 4 times the upper normal limit. After the procedure, in patients treated by the transfemoral approach, the NT-proBNP levels did not change immediately after the procedure and decreased up to 6- to 12-month follow-up (-25%; $p < 0.001$). Nonetheless, in patients treated by transapical approach the NT-proBNP levels increased at hospital discharge (+23%; $p < 0.001$), decreased afterwards until 6- to 12-month follow-up, and then remained stable up to 4 years (Figure 5-3). The subset of patients in this study treated by the transaortic approach was underrepresented and given the really initial experience, we were not able to firmly conclude with regard to myocardial injury after TAVR performed by this

approach. Therefore, we have further extended this population treated by the transaortic approach, an alternative to the transapical approach in those patients that cannot undergo TAVR by the transfemoral access. In addition, we have evaluated 45 consecutive transaortic patients treated at our center, as another objective of the present PhD (article 3, chapter 6). These patients were further matched according to a propensity-match score to 206 transapical patients in order to assess myocardial injury as determined by both troponin T (cTnT) and CK-MB levels. Following TAVR, cTnT increased above the upper normal values in all patients, whereas CK-MB levels increased in 88% of patients (transaortic: 51%, transapical: 96%, $p<0.001$). Compared with transaortic, the transapical approach was associated with a 2- to 3-fold greater increase in cardiac biomarkers of myocardial injury ($p<0.001$ for both). Collectively, the 3 studies evaluating different cardiac biomarkers (CK-MB, troponin and NT-pro-BNP) highlight that although lower than what has classically been described for SAVR patients, [223,224] the TAVR procedures are still related with some degree of myocardial injury. While as determined by CK-MB this increase reached 2/3 of the non-transapical patients and all of those treated by transapical approach, as determined by cTnT almost all of the patients had an increase above the upper normal limit, independently of the approach. Still, either by CK-MB or cTnT the transapical approach was associated with a ~3-fold greater increase in cardiac biomarkers.

In a further step trying to evaluate the mechanisms, and to better determine the localization and extent of TAVR related myocardial injury we have developed another objective of this PhD (article 4, chapter 7). A total of 45 patients undergoing TAVR with a balloon-expandable valve underwent a CMR before TAVR, and 37 patients had a repeat CMR after the procedure. CMR allows the accurate detection and quantification of irreversible myocardial injury, and it can detect even small areas of myocardial necrosis, using the LGE technique.[271,272] CK-MB levels rose above the upper normal limit in 49% of the patients, but this reached 73% of those treated by the transapical approach. Also, cTnT rose above the upper normal limit in all but 1 patient (97% overall). After the TAVR procedure, new focal myocardial necrosis, as determined by LGE, was detected only in the transapical group, and it was restricted to the apical segments in all patients (Figure 7-3). The median extent of LGE after TAVR was of 5 (2.0 to 7.0)% of the myocardium, and with a median of 3.5 (2.3 to 4.6) g of necrosis (Figure 7-4).

Several mechanisms have been implied in the basis of myocardial injury after TAVR (Figure 2-7): mechanical compression of the myocardial septum at the level of the LVOT by the transcatheter valve; several episodes of severe hypotension and global myocardial ischemia (rapid pacing runs, balloon valvuloplasty, valve implantation); coronary emboli; apical perforation during the transapical TAVR. Apart from the necrosis in apex in those patients treated by the transapical approach, we did not find any sign of LGE at the level of the LVOT, nor as multiple defects supporting the embolization mechanism. Nevertheless, this possibility has been recently shown in another study, where 18% of the patients had new LGE with an ischemic pattern, corroborating in part the embolization mechanism.[319] With regard to the several episodes of severe hypotension and global myocardial ischemia, future studies with CMR using T1-mapping will have to determine its potential impact to cause diffuse myocardial injury in line with the increase in cardiac biomarkers.[277] Also, in our study we were not able to correlate the increase in cardiac biomarkers with the presence of necrosis (irreversible myocardial injury) on CMR due to the limited number of patients. Thus we could not determine a cutoff of increase in neither troponin nor CK-MB related with the presence of new focal necrosis on CMR, and this will have to be the scope of future studies.

10.2 PREDICTORS OF MYOCARDIAL INJURY AFTER TAVR

Although TAVR has consistently been associated with mild increases in cardiac biomarkers, indicating some degree of myocardial injury, the factors related with a greater impact in cardiac biomarker elevation have been controversial (Table 2-3). Hence, apart from the transapical approach that has been a major factor associated with myocardial in the studies including patients treated with balloon-expandable valves, various factors have been implied with myocardial injury. One of my objectives in the present PhD was to better establish the factors predicting a greater myocardial injury. In the Multicenter Registry, including 1,131 patients with serial measurements of CK-MB after TAVR (article 1, chapter 4), apart from the transapical approach, the main predictors were procedural complications and the early experience of the center. The procedural complications included valve embolization/need for a second valve, major/life threatening bleeding and

conversion to open heart surgery, while the early experience was defined as those patients treated in the first half of the experience at each center. Likewise, when excluding the patients undergoing TAVR by the transapical approach in this Multicenter Registry, the greater degree of myocardial injury significantly related with a self-expandable valve, apart from the same procedural complications. It has to be pointed out that similarly to the results reported in the CHOICE (Comparison of Balloon-Expandable vs Self-expandable Valves in Patients Undergoing Transcatheter Aortic Valve Replacement) trial,[230] the patients receiving a self-expandable valve in our study exhibited longer procedural times, received a higher volume of contrast agent and had an increased incidence of valve embolization/need for a second valve compared to the balloon-expandable group. This could partially explain the differences in myocardial injury between valve types, but given the non-randomized nature of the study, future studies are warranted to confirm and better understand the mechanisms associated with these results.

Finally, we have also assessed the independent predictors of a higher rise in cTnT levels in the transaortic vs. transapical approaches (article 3, chapter 6). The serial measurements of cTnT in the multivariate analysis have determined the transapical approach, baseline renal function, diabetes, and baseline LVEF as the main predictors of a higher increase in cTnT levels. These factors are similar to prior studies evaluating troponin increase related factors of myocardial injury.[136,214,216,217]

10.3 IMPACT OF MYOCARDIAL INJURY AFTER TAVR

With respect to the impact of myocardial injury related to TAVR, previous small studies with limited follow-up, have shown an increased short- and mid-term mortality associated with a greater rise in biomarkers of myocardial injury following the procedure.[167,196,214,216,232] Still, the limited number of patients/events in these studies precluded a formal validation of the associated worse clinical prognosis, or validation of a threshold of biomarker elevation representing a “clinically relevant” myocardial infarction following TAVR. One of my objectives in this PhD was to further evaluate the clinical impact of CK-MB in a large proportion of patients in the short- and long-term follow-up, and further validate the cutoff proposed by the VARC-2 criteria (%-fold of increase).[196] In

the Multicenter Registry, including 1,131 patients, CK-MB rise post-TAVR was an independent predictor of a greater 30-day mortality (OR: 1.71 [1.25-2.35]; p<0.001). Also, it was confirmed as an independent predictor of 1-year overall mortality, and extends prior observations by showing an increased risk of late (>1-year) overall (HR: 1.32 [1.12-1.54]; p<0.001) and cardiac mortality (HR: 1.39 [1.12-1.74]; p<0.001) (Table 4-4). In accordance with prior studies,[232] any increase in CK-MB values associated with poorer outcomes, with an apparent stepwise increase in late mortality according to the various degrees of CK-MB elevation following TAVR (Figures 4-3 and 4-4). Interestingly, according to the VARC-2 criteria for defining clinically relevant myocardial infarction,[196] a >5-fold CK-MB increase threshold was associated with a higher mortality rate. Of note, this was verified in 9.6% of the patients undergoing TAVR, as compared with nearly 20% of those undergoing SAVR in prior studies.[223,224]

We have also evaluated the impact of myocardial injury in the non-transfemoral cohort including both the transapical and transaortic approaches (article 3, chapter 6). In the multivariate analysis, the cTnT peak post-TAVR was also independently associated with 30-day all-cause mortality (p=0.043), late overall mortality (p =0.005), and late cardiac mortality (p=0.001). Notably, greater increments of post-TAVR cTnT levels were also independently associated with late cardiac death or re-hospitalization due to cardiac causes (p<0.001). A 15-fold increase in post-TAVR cTnT levels, irrespective of procedural approach, best identified patients at greater risk for 30-day mortality (AUC of 0.76 [95%CI: 0.64-0.87], p<0.001), as well as late mortality (AUC of 0.69 [95%CI: 0.61-0.78], p<0.001). This post-TAVR cTnT rise is also consistent with the VARC-2 criteria's proposed threshold for defining peri-procedural TAVR-related myocardial infarction according to troponin elevation,[196] and our study was the first to validate this VARC-2 proposed cutoff.

With respect to the potential impact of myocardial injury on LV function, greater elevations of CK-MB levels in the Multicenter Registry (article 1, chapter 4) were correlated with impaired LV function at mid-term follow-up, although this correlation was modest (Figures 4-5 and 4-6). Additionally, when evaluating the non-transfemoral cohort (article 3, chapter 6), the greater increases in cTnT were also correlated with a negative impact on both the LVEF (Simpson method) and global longitudinal strain (GLS) as assessed in speckle-tracking echocardiography (Figure 6-5). Likewise, the transapical approach was associated with impaired LV systolic

function at mid-term follow-up vs. the transaortic approach, demonstrated by both LVEF and GLS (Figure 6-4). Notably, only those patients undergoing TAVR by the transaortic approach demonstrated significant improvements in LV function over time. Although small, such improvements in LVEF have been associated with improved clinical outcomes after TAVR and SAVR in previous studies.[233,266,267] There however remains controversy as to whether such improvements are predominantly a result of reduced LV afterload post-TAVR[268] or via intrinsic alterations of myocardial structure and function.[255,265,269] Indeed, the transapical approach was significantly associated with LV apical fibrosis involving ~5% of myocardium (article 4, chapter 7), contributing to significant apical wall motion abnormalities as previously demonstrated.[220] This may in turn adversely affect myocardial recovery post-TAVR in these transapical treated patients.

10.4 CORONARY OBSTRUCTION AS A COMPLICATION OF THE TAVR PROCEDURES

Coronary ostia obstruction is a rare but life-threatening complication of TAVR and represents one of the extreme forms of myocardial injury throughout the procedure.[320] Apart from reporting its incidence, there has been very few data in the literature evaluating this complication, and this was mostly related to case reports or small case series. My fifth objective in this PhD was to provide further insights into the exact incidence, baseline characteristics, management, and clinical outcomes of patients suffering from coronary obstruction as a complication of TAVR. This was accomplished through 2 main objectives of this PhD: 1) systematic review of all the studies on TAVR and coronary obstruction published thus far (article 5, chapter 8); 2) multicenter worldwide registry with this complication (article 6, chapter 9).

In the systematic review of the literature, a total of 16 publications describing 24 patients were identified. Most (83%) patients were women, with a mean age of 83 ± 7 years, and a mean logistic EuroSCORE of 25.1 ± 12.0%. Mean left coronary artery (LCA) ostium height and aortic root widths were 10.3 ± 1.6 mm and 28.1 ± 2.8 mm, respectively. Most patients (88%) had received a balloon-expandable Edwards valve, and coronary obstruction

occurred more frequently in the LCA (88%). Percutaneous coronary intervention (PCI) was attempted in 23 cases (95.8%) and was successful in all but 2 patients (91.3%). At 30-day follow-up, there were no cases of stent thrombosis or repeat revascularization, and the mortality rate was of 8.3%. This first study on coronary obstruction provided important insights into this severe complication, however the absence of a control group, the small number of patients and the lack of CT data precluded to better appraise this complication.

Therefore, we developed a large multicenter registry on coronary obstruction during TAVR, with a total of 6,688 included patients, from 81 centers in North America, Europe, South America, and Asia, from January 2007 to January 2013. A total of 44 cases of this complication were identified, with an overall incidence of 0.66%. Although it was more frequent with a balloon-expandable valve (0.81% for the balloon-expandable vs. 0.34% for the self-expandable valves, p=0.02), it is still unclear whether these differences in coronary obstruction rates between valve types are due to differences in the valve stent frame and mechanism of valve implantation or secondary to different recommendation policies according to the manufacturer. Likewise, this complication was also more frequent in patients with a prior surgical bioprosthesis ("valve-in-valve procedure") (2.48% vs. 0.62%; p=0.045), and this is similar to the 2-3.5% rates reported in recent multicenter registries of "valve-in-valve" TAVR procedures.[318,321] Among the valve-in-valve patients, this complication has been even more frequent with some types of surgical aortic bioprostheses, such as stentless valves or stented valves with long aortic leaflets, as well as in prior bioprosthesis with stenosis (3.9%; p=0.02).[318,321] Future studies with a much larger number of patients will be needed to further evaluate the factors associated with coronary obstruction in this specific group of valve-in-valve patients. We have also verified in our multicenter registry that this complication was more frequent in women (84.1% vs. 51.3%; p<0.001), without any differences with respect to the approach used.

To further evaluate the anatomical factors associated with coronary obstruction we have gathered the pre-TAVR computed tomography data in 28 patients with this complication that were compared with 345 consecutive controls from 3 centers (comparisons were performed including all patients and a cohort matched 1:1 by age, gender, prior CABG, transcatheter valve type and size). The mean LCA ostia height and sinus of Valsalva (SOV) diameter were lower in patients with obstruction compared to matched controls (10.7 ± 0.4

mm vs. 13.3 ± 0.3 mm, OR: 2.17, 95%CI 1.62-2.90, and 28.3 ± 0.8 mm vs. 31.3 ± 0.6 mm, OR: 1.37, 95%CI 1.13-1.66, respectively). It has also been shown in the present study that coronary obstruction following TAVR was mainly due to the displacement of the calcified native cusp or prosthetic leaflet over the coronary ostia (98% of the patients). It is therefore not surprising that aortic SOV dimensions and coronary height were shown to be important factors associated with the occurrence of coronary occlusion following TAVR. Similarly, prior CT studies have already shown the smaller aortic SOV dimensions and lower coronary ostia take-off in women, irrespective of the presence of aortic stenosis,[314,317] and these sex differences in aortic SOV dimensions and coronary height were also observed in the pre-TAVR CT exams of our control group including >300 patients (33.8±3.9 mm vs. 29.7±3.1 mm for SOV dimensions; 14.1±2.1 mm vs. 12.7±1.8 mm for LCA coronary height in men and women, respectively; $p<0.001$ for both). This is the reason why women were more prone to this complication as these anatomical factors may facilitate the interaction between the calcified native cusp (or prior leaflet of a bioprosthesis) and the coronary ostia. Of note, most patients who suffered coronary obstruction (about 80% overall, 96% of the women) had a LCA height <12 mm, suggesting that this may be a more accurate cutoff to predict this complication, than the 10-mm cutoff suggested previously by both the ACC/AATS/SCAI/STS and the CT-TAVR expert consensus,[310] and also than the 14-mm cutoff suggested by the manufacturer of the CoreValve. In addition, the 12 mm cutoff would be in the upper limit of the 95% CI from the coronary obstruction cases and would not be included in the lower limit for the controls. Regarding the SOV diameter, most patients (64.3%) who suffered this complication had an aortic SOV diameter <30 mm, as compared to about one third of the patients in the control group. In fact only a minority of the patients who did not suffer coronary obstruction had both a coronary height <12 mm and an aortic SOV diameter <30 mm (13.3%), meaning that the combination of these 2 anatomical factors has to be taken into account when evaluating the possibility of coronary obstruction prior to TAVR procedures (Figure 9-6).

With respect to clinical manifestations most cases (68.2%) presented with severe persistent hypotension, and electrocardiographic (ECG) changes (56.8%), mainly ST-segment elevation and ventricular arrhythmias. These severe clinical findings highlight the fact that the vast majority of coronary obstruction cases occurred at the ostium of the LCA (88.6%), as this coronary is responsible for a greater proportion of myocardium at risk. Regarding

the treatment option when this complication occurs, while PCI was the first revascularization attempt in 75% of patients (successful in ~82%), urgent CABG and/or mechanical hemodynamic support (including cardiopulmonary bypass) were still required in a significant number of patients, underscoring the importance of performing such procedures in highly experienced centers with cardiac surgery facilities. The mortality rate was high after successful PCI (22%) or CABG (50%) and increased to as much as 100% in case of unsuccessful PCI. Notably, while these results suggest that PCI as a first attempt for coronary revascularization is a reasonable strategy, it also emphasizes the importance of both obtaining coronary flow restoration very rapidly and being ready to change the therapeutic strategy (CABG) if coronary flow is not restored within a few minutes of the attempted PCI. The 30-day mortality rate associated with this complication was as high as 41%, but after hospital discharge no patient presented the need for revascularization. Also, at a median follow-up of 12 (2-18) months, a total of 20 patients had died (cumulative mortality rate: 45.5%) (Figure 9-5), and the vast majority of surviving patients (95%) were in NYHA functional class I-II at follow-up.

Finally, in those patients considered at high-risk for coronary obstruction (LCA < 12 mm, SOV < 30 mm, prior bioprosthesis, for instance), we would suggest to implement additional security measures during the TAVR procedure. This could include simultaneous angiography during balloon valvuloplasty to diagnose coronary obstruction, coronary protection with a guide wire for the prompt diagnosis and treatment of the complication, and maybe the use of a transcatheter valve that can be repositioned or retrieved in case coronary occlusion occurs.

10.5 FUTURE PERSPECTIVES IN TAVR

The TAVR procedures have been shown to be an effective alternative to SAVR in high-risk surgical candidates for symptomatic AS, and the treatment of choice in those considered inoperable.[145-148] This procedure has transformed the treatment of AS over the recent years, as up to ~40% of these higher-risk patients had not been treated with SAVR, although highly symptomatic, due to the large burden of comorbidities.[4,322,323] TAVR has opened a new avenue for the treatment of such patients with severe symptomatic AS. While less invasive than

SAVR, because it does not require cardiopulmonary bypass, the TAVR procedures are still related with some degree of myocardial injury as seen in previous studies.[167,214-217] The present PhD research project has confirmed these findings when analyzing cardiac biomarkers determination after TAVR procedures, including CK-MB, cTnT, and NT-proBNP.

In evaluating the potential mechanisms and factors associated with a greater myocardial injury, the present research project has highlighted the major impact of the transapical approach, procedural complications, the use of self-expandable valves and the experience of the centers. Although the TAVR technology has evolved enormously over the recent years, the negative impact of myocardial injury on LV function and clinical outcomes, make future enhancements still advisable. Hence, transcatheter valves iterations, with enhanced valves, smaller profile delivery systems and easier to use devices, will likely help in reducing periprocedural myocardial injury in many ways. First, these advancements should make the non-transfemoral approaches preventable (and especially the transapical approach). Of note, it is expected that the transfemoral approach will expand from the actual 60-70% up to ~90% in the near future with the smaller profile sheaths (≤16F).[137,155] In addition, such advancements may reduce procedural complications and lower ischemic times by easier to use valve delivery systems and shorter rapid-pacing runs (especially with the self-expandable valves).[234] Collectively, these factors and the greater experience of the centers may further reduce myocardial injury during TAVR procedures, what may also favorably impact clinical outcomes.

Poorer outcomes following the transapical approach (vs. transfemoral) TAVR have been demonstrated in a number of large registries, with a 1.5- to 2-fold greater mortality associated with the transapical vs. transfemoral TAVR.[226,270] Some have postulated that the higher-risk profile of patients undergoing non-transfemoral TAVR, despite difficulties in accurately accounting for a number of confounding factors, could partially explain such prognostic differences.[233,270] Nonetheless, we have shown for the first time that the transapical approach was systematically associated with significant irreversible myocardial injury, with the loss of ~5% of the myocardium (>1g of necrotic mass in all cases), what may also partially explain the link of this approach with the poorer clinical outcomes. Of note, prior studies in the context of coronary artery disease have shown that even small amounts of myocardial necrosis (as low as 1 g) were associated with a 5% increase in major cardiac events.[280] While these findings will have to be confirmed in future larger

studies, as we await further data amid patients with low LVEF deemed unsuitable for the transfemoral approach, current data suggest that alternative anatomical approaches to TAVR, such as the transaortic, subclavian or transcarotid approach, may be preferable over the more established transapical approach.[227,233]

Although the transapical approach has been a major factor related with myocardial injury based on the results of this PhD, it is important to underscore that this approach has been key in the overall development of the TAVR field, currently accounting for approximately 20-25% of all balloon-expandable TAVR procedures.[136] Moreover, many novel devices and improved iterations of TAVR-delivery systems, as well as the majority of the current transcatheter mitral valve replacement technologies, are currently in development for performing transapical procedures.[136] Therefore, the importance of improving TA delivery systems and apical closure techniques for minimizing apical trauma and subsequent myocardial injury is paramount. Newer generation devices with lower profile, such as the new 18F Certitude delivery system for the transapical placement of the SAPIEN 3 valve (Edwards Lifesciences Inc., Irvine, CA) may associate with even greater reductions in peri-procedural TAVR-related biomarkers elevation,[154] and this should be the scope of future studies.

Finally, in the present studies including a systematic review of the literature and the largest series of patients with coronary obstruction following TAVR to date we have confirmed that this is a rare but life-threatening complication of TAVR that occurred more frequently in women, in patients receiving a balloon-expandable valve, and in those with a prior surgical bioprosthesis. Lower lying coronary ostium (<12 mm) and shallow SOV (<30 mm) were related anatomic factors, and despite successful treatment (mainly PCI) in most cases periprocedural mortality remained very high, highlighting the importance of anticipating and preventing the occurrence of this complication. Future studies will have to evaluate whether protective measures such as the use of a guidewire protection in those patients with a higher risk for such complication, as well as the use of retrievable valves may further reduce the dismal prognosis of this complication. Other risk factors such as bulky calcifications and the length of the aortic valve leaflet should also be the object of future studies in order to better determine those patients at a higher risk of this important TAVR complication.

10.6 CONCLUSIONS

TAVR has emerged as a less invasive therapeutic alternative to SAVR for patients with severe AS at high or prohibitive surgical risk. Compared to conventional open-heart surgery, TAVR procedures are less invasive, because they are not associated with aortic cross-clamping and cardioplegia. Even so, the procedure is associated with some degree of myocardial injury as determined by different cardiac biomarkers elevation. The present PhD research project has been able to provide novel insights into the incidence, localization, related factors and prognostic significance of myocardial injury following TAVR among the various approaches and transcatheter valve types. This could be summarized as follows:

1) Approximately, 2/3 of the patients may have some increase in CK-MB, reaching all of those treated by the transapical approach. As determined by cTnT all of the patients have some increase after TAVR, but this is 2- to 3 times greater with the transapical approach. More significant increases in cardiac biomarkers (>5-fold in CK-MB) may reach 9.6% of the TAVR patients as opposed to 20% with the SAVR procedures.
2) In terms of the localization, only the transapical patients presented new necrosis as evaluated by CMR, comprising 5% of the apex with a total of ~3.5g of fibrosis by LGE. Although we did not find any sign of mechanical compression of the myocardial septum nor of coronary emboli in CMR, this has been the case in another study that found multiple defects in 18% of the patients, corroborating in part the embolization mechanism.
3) Main predictors of myocardial injury included the transapical approach, procedural complications, the use of a self-expandable valve (non-transapical cohort), and the experience of the center. Likewise some clinical characteristics such as diabetes, baseline renal function and baseline LVEF may also play a role.
4) A greater myocardial injury adversely impacts the short- and long-term overall and cardiac mortality, and may also jeopardize LV recovery after TAVR, especially in the transapical subset of patients. The current VARC-2 cutoff of a >5-fold for CK-MB and >15-fold for troponin seems to be appropriate to determine a greater risk of mortality, although any increase in CK-MB values associated with poorer outcomes, with an apparent stepwise increase in late mortality according to the various degrees of CK-MB increase.

5) Coronary obstruction was a rare but life-threatening complication of TAVR that occurred more frequently in women, in patients receiving a balloon-expandable valve, and in those with a prior surgical bioprosthesis. Lower lying coronary ostium (<12 mm) and shallow SOV (<30 mm) were related anatomical factors, and despite successful treatment (mainly PCI) in most cases periprocedural mortality remained very high, highlighting the importance of anticipating and preventing the occurrence of this complication.

Collectively the negative impact of myocardial injury on clinical outcomes and LV function in the context of TAVR procedures make device enhancements, including smaller profile delivery systems and easier to use valves, the objective of future studies. The TAVR technology is a fast evolving field with innumerous advancements expected within the next few years including the treatment of a large number of patients, with an even lower risk profile. Therefore, the better understanding of the incidence, related mechanism, predictors and potential clinical impact of myocardial injury post-TAVR is paramount in order for this technology to further advance. With the aging of the population it is expected that severe symptomatic AS patients will grow with a significant impact for the health-care systems worldwide. Therefore, such minimally invasive technologies advancements are key factors in order to better treat our patients in the near future.

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