SURVENUE DES ARYTHMIES ET TROUBLES DE CONDUCTION APRÈS UN REMPLACEMENT DE LA VALVE AORTIQUE PAR CATHÉTER: INCIDENCE ET IMPACT

NEW-ONSET RHYTHM AND CONDUCTION DISORDERS AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT: INSIGHT INTO THE INCIDENCE AND IMPACT

Thèse

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RESUME

La sténose aortique est la cardiopathie valvulaire la plus fréquente retrouvée chez les patients agés. Suite à l'apparition des symptômes, la survie des patients diminue de façon drastique en l'absence d'un remplacement valvulaire aortique. Cependant, une proportion considérable de ces patients n'est pas opérée en raison d'un risque chirurgical élevé, l'âge étant l'une des principales raisons de refus d'un remplacement valvulaire aortique chirurgical. Ce défaut dans la prise en charge des ces patients a favorisé le développement du remplacement valvulaire aortique par cathéter où implantation valvulaire aortique par cathèter (TAVR ou TAVI), qui a représenté une révolution dans le traitement de la sténose aortique. Cette intervention est actuellement un traitement de routine chez les patients à haut risque chirurgical atteints d'une sténose aortique, même si la chirurgie cardiaque n'est pas contre-indiquée.

Ces dernières années ont vu un changement de profil des candidats potentiels vers une population à plus faible risque. Cependant, plusieurs préoccupations demeurent. L'une des plus importantes est la survenue des arythmies et de troubles de conduction, notamment le bloc de branche gauche et le bloc auriculo-ventriculaire, qui sont des complications fréquemment associées au TAVR. Malgré l'évolution de la technologie et le développement de nouveaux dispositifs réduisant le taux global de complications, aucune amélioration n'a pas été intégrée pour prévenir l'apparition de telles complications. De plus, l'utilisation de certains dispositifs de nouvelle génération semble être associée à un risque accru de troubles de conduction, et par conséquent, l'incidence de ces complications pourrait augmenter dans le futur. Cependant, L'impact et l'évolution de ces complications sont inconnus.

Ce travail de recherche évalue l'incidence et l'évolution des troubles de conduction suite au TAVR et l'impact des blocs de branche gauche de novo et de l'implantation d'un pacemaker sur les résultats cliniques et échocardiographiques.

ABSTRACT

The aortic stenosis is one of the most frequent valvular heart diseases, which is mostly diagnosed in older patients. With the symptoms onset, the lifespan of such patients dramatically decrease unless an aortic valve replacement is performed. However, a considerable proportion of such patients do not undergo cardiac surgery owing to a perceived high risk, being the advanced age one of main reasons to deny surgical aortic valve replacement. Such deficiency in the care of these patients has favoured the development of transcatheter aortic valve replacement or implantation (TAVR or TAVI), which has revolutionized the treatment of aortic stenosis. This treatment is now a routine therapy in high-risk patients with aortic stenosis, even if cardiac surgery is not contraindicated. Indeed, the last years have witnessed a shift in the use of this technology to lower risk populations.

TAVR technology has experienced a dramatic evolution to integrate enhanced iterations which have allowed, along with the improvement of the technology, a reduction in the risk of complications associated with this therapy. However, several concerns remain. One of them is the occurrence of arrhythmias and conductions disturbances, in particular left bundle branch block and atrioventricular block, which are frequent complications of TAVR. Despite the evolution of the technology and development of new devices leading to a reduction in the overall rate of complications, no new iterations have been integrated to prevent the occurrence of such complications. Moreover, the use of new-generation devices seems to be associated with an increased risk of such complications, and therefore, its incidence is expected to increase in the next future. Nonetheless, little is known about the impact and evolution of these disorders.

This thesis evaluates the incidence and evolution of new-onset arrhythmias and conduction abnormalities after TAVR and the impact of new-onset left bundle branch block and permanent pacemaker implantation on late clinical and echocardiographic outcomes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AF: Atrial fibrillation

AR: aortic regurgitation

AS: aortic stenosis

AT: atrial tachycardia

AVR: aortic valve replacement

AVB: atrioventricular block

BEV: balloon-expandable valve

CAD: coronary artery disease

CK: creatin-kinasa

CI: confidence interval

COPD: chronic obstructive pulmonary disease

CT: computed tomography

CV: CoreValve

CVE: cerebrovascular events

ECG: electrocardiogram

ES: Edwards Sapien

GFR: glomerular filtration rate

HR: hazard ratio

HTA: hypertension

HF: heart failure

HR: hazard ration

IQR: interquartile range

LBBB: left bundle branch block

LV: left ventricle

LVEF: left ventricular ejection fraction

NA: not available

NOP-LBBB: new-onset persistent left bundle branch block

NYHA: New York Heart Association

OR: odds ratio

PPI: permanent pacemaker implantation

PPM: permanent pacemaker

PASP: pulmonary artery systolic pressure

RBBB: right bundle branch block

SAVR: surgical aortic valve replacement

SCD: sudden cardiac death

SEV: self-expandable valve

STS: Society of thoracic surgeons

TEE: transesophageal echocardiography

TA: transpical

TAVI: transcatheter aortic valve implantation

TAVR: transcatheter aortic valve replacement

TF: transfemoral

VARC: valve academic research consensus

VT: ventricular tachycardia

"Science is not only a disciple of reason but, also, one of romance and passion"

Stephen Hawking, PARADE Magazine, 2010

DEDICATIONS AND ACKNOWLEDGMENTS

To my teachers, mentors, all those who shared their knowledge with me, gave their time and energy to help me to improve and those who trusted on me and encouraged me to give it my best. All you made this work possible and I am indebted to you.

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FOREWORD

This research has been carried out at the "Institute de Cardiologie et Pneumologie de Québec" and is part of the line of investigation on transcatheter valve therapies led by Josep Rodés-Cabau.

During her doctoral degree, the student has received a grant from the Spanish society of Cardiology and a grant from the Laval University (Pierre Jacob Durand) for 2 years.

This thesis is composed of 6 articles, which have been already published. Owing to this work, the student was finalist of the prestigious "Linnemeier Young Investigator Award" in 2015.

The first article is entitled: "Arrhythmia Burden in Elderly Patients with Severe Aortic Stenosis as Determined by Continuous ECG Recording: Towards a Better Understanding of Arrhythmic Events Following Transcatheter Aortic Valve Replacement" and has been published in the Circulation Journal. This study assesses the prevalence of silent conduction abnormalities and arrhythmias in candidates for transcatheter aortic valve replacement .The student was the first author of this article and participated, under the supervision of Josep Rodés-Cabau and Dr. Philippe Pibarot in the conception and design of the study, data collection, analyses and interpretation of the data, drafting and revision of the manuscript. The manuscript was approved by all other authors who contributed with their critical review.

The second article is entitled: "Predictive Factors and Long-Term Clinical Consequences of Persistent Left Bundle Branch Block Following Transcatheter Aortic Valve Implantation with a Balloon-Expandable Valve". This study assesses the prevalence, predictive factors, evolution and impact of new-onset left bundle branch block in patients undergoing transcatheter aortic valve replacement. Such results have been published in the Journal of American College of Cardiology and the results were presented in the Congress of American College of Cardiology. The student is the first author of the manuscript. Her role consisted of participating in the study design, analysis and interpretation of the data and drafting of the manuscript. Dr. Josep Rodés-Cabau supervised the student during all these

phases along with Dr. Philippe Pibarot. Other authors approved the manuscript and contributed with their critical review of the manuscript.

The third article, entitled "Impact of New-Onset Persistent Left Bundle Branch Block on Late Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Implantation with a Balloon-Expandable Valve", analyzes the impact of new-onset persistent left bundle branch block in a large cohort of patients. This study was published in the Journal of American College of Cardiology Cardiovascular Interventions. The student participated in the conception and design of the study, analysis and interpretation of the data, drafting and revising the manuscript. The work was supervised by Dr. Josep Rodés-Cabau and Dr. Philippe Pibarot. All other authors approved the manuscript and revised the manuscript for important intellectual content.

The fourth article, entitled "Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Implantation: Impact on Late Clinical Outcomes and Left Ventricular Function", evaluates the impact of permanent pacemaker implantation after transcatheter aortic valve implantation on late outcomes. This study was published in the Circulation Journal and for this article the student was granted with the "Étudiants-Chercheurs Ètoiles Award" by the three "Fonds de recherche du Québec". The student is the first author of the article, and participated in the conception and design of the study, data collection, analysis and interpretation of the data and drafting and revising of the manuscript, always under the supervision of Dr. Josep Rodés Cabau and Dr. Philippe Pibarot. All other authors approved the manuscript and revised the manuscript.

The fifth manuscript, entitled "Late Cardiac Death in Patients Undergoing Transcatheter Aortic Valve Replacement: Insights into the Incidence and Predictors of Advanced Heart Failure and Sudden Cardiac Death", focuses on the causes of late cardiac death after transcatheter aortic valve replacement, and determines the risk of late mortality and sudden cardiac death associated with the occurrence of persistent left bundle branch block. These results were published in the Journal of the American College of Cardiology. The student is the first author and contributed with the conception and design on the study, the data collection, analysis and interpretation of the data and drafting of the manuscript. Drs. Josep Rodés-Cabau and Philippe Pibarot supervised the work. All authors approved the manuscript.

The last and sixth article is entitled "Managing Heart Block after Transcatheter Aortic Valve Implantation – from Monitoring to Device Selection and Pacemaker Indications", which has been published in Eurointervention Journal. This review analyzes the available evidence on conduction disturbances after TAVI and proposes a strategy for the management of such complications. The work was performed under the supervision of Dr. Josep Rodés-Cabau. The student is the first author of the manuscript and participated in the review of the literature, drafting and revision of the manuscript.

INTRODUCTION

The heart is the cornerstone of the cardiovascular system. Composed of four systems - a working myocardial system, the fibrotic skeleton, the valves and the conduction system -, its pumping function requires the perfect function and coordination of all these components. The dysfunctioning of one of these systems leads finally to an impairment of the heart pumping function and a consequently decrease in the cardiac outflow, having in last instance a negative impact on the function of the other ones.

Heart valve diseases are leading causes of morbidity and mortality nowadays, being aortic valve stenosis the most frequent in older people. A new therapeutic arsenal has been developed in the last decades aiming to decrease the invasiveness of the treatment of such diseases. Transcatheter aortic valve replacement (TAVR) is one of such new technologies. It has been widely adopted around the world and has experienced an extraordinary development in the last years. However, the broad use of this therapy has highlighted its limitations, which are its complications. The injury to the conduction system leading to the occurrence of new conduction disturbances, particularly the left bundle branch block and atrioventricular block, and the occurrence of cardiac arrhythmias are frequent findings after TAVR. Nonetheless, its impact has not been determined so far. This thesis evaluates the impact of conduction disturbances and arrhythmias in patients with aortic stenosis undergoing TAVR.

CHAPTER 1. CALCIFIC AORTIC STENOSIS

"The ventricle of the heart was filled with a bloody mass and the whole lung was full of blood, round carbuncles were found like the substance of the lungs, the larger of which resembled a cluster of hazelnuts and filled up the opening of the aorta, which probably caused the failure of pulsations in the arteries. The carbuncles hardened by the heat of the heart and changed their substance."

Lazare Rivière, 1646
Opera Medica Universa

Lazare Rivière described in this way the pathological findings at necropsy of a patient who died with dyspnea and swollen legs. Although it is still discussed if Lazare Rivière refers to valve calcification or vegetation, it seems to be the earliest description of an aortic valve stenosis (AS). However, it was not until 1913, that the first aortic valve replacement (AVR) for AS was performed, establishing the basis of the current treatment of this disease. From this time to now, amazing advances have been made in the knowledge of physiopathology and natural history and therapies of AS.

1.1. EPIDEMIOLOGY OF HEART VALVE DISEASES AND CALCIFIC AORTIC STENOSIS

Valvular heart diseases are a growing concern for health care systems and societies. Two are the most common aetiologies of these diseases: rheumatic and the so-called degenerative diseases. Rheumatic valve disease is the result of chronic inflammation, scarring and thickening of the heart valves with a typical commissural fusion, caused by an abnormal immune response to the infection of group A β-hemolytic Streptococci, responsible for the acute rheumatic fever. The use of antibiotic prophylaxis against recurrent episodes of acute rheumatic fever has led to a marked decrease in the incidence of rheumatic heart diseases in last decades in developed countries. However, this reduction in rheumatic valve diseases burden has been overwhelmed for a sharp rise in the prevalence of degenerative valve diseases, which include a wide spectrum of pathological conditions classically considered as part of a natural aging passive process leading to valve degeneration and dysfunction.[1] Both, the aging of the population and the increased availability of echocardiographic exams to diagnose this pathology may explain the increase of degenerative diseases.[2] The epidemiological change from rheumatic to degenerative observed in developed countries has been accompanied of an increase in the costs associated with these diseases, leading to be considered an important public-health problem.[3, 4]

Overall, the age adjusted prevalence of moderate or greater heart valve disease in USA is 1.8%,[2] with a sharp growth with age: the prevalence is of 4.4 % (95% CI, 3.9%–4.9%) in individuals of 65 to 75 years, and 11.7% (95% CI, 11.0%–12.5%) in individuals of ≥75 years[3]. Adjusted to the entire USA population the estimated prevalence of any valvular heart disease is 2.5% (2.2–2.7),[3] which might be even higher considering that a significant proportion of patients with no symptoms remains undiagnosed.[3]

Importantly, the presence of valvular heart disease is associated with a reduced long-term survival compared to those individuals without valvular heart disease,[2] and valvular heart diseases represent one of the highest costs of health care systems associated with cardiovascular diseases with 106,000 valve interventions performed each year in the USA.[2]

Among valvular heart diseases, calcific aortic valve disease is the most frequent valve disease in the aging population and the most common valvular heart disease referred for therapy in western countries.[4-6] Its estimated prevalence is of 2.9 % in >75 years aged population and 3 to 9% in >80 years patients [3, 5, 7, 8] (Figure 1-1)[8] and it is the third most common cause of cardiovascular disease.[9] Its prevalence is expected to increase in the near future owing to the aging of the population and the lack of strategies to prevent or slow the evolution of this disease.[8] Aortic valve disease might be responsible for more than 15,000 annual deaths in the USA[2] and even aortic valve sclerosis has been associated with increased mortality in the elderly.[10]
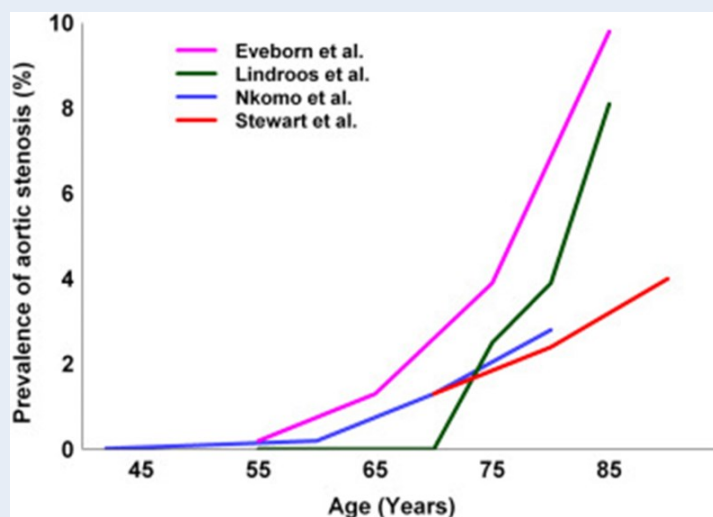
FIGURE 1-1. Prevalence of aortic stenosis according to age

The figure shows the prevalence of aortic stenosis according to age in 4 studies.

From Iung B, Vahanian A. Epidemiology of Acquired Valvular Heart Disease. Can J Cardiol.2014; 30:962-70

1.2. PHYSIOPATHOLOGY OF AORTIC STENOSIS

Calcific aortic valve disease is characterized by thickening, scarring and calcification, often nodular, of the aortic leaflets facing to the aorta. It encompasses a wide spectrum of diseases of the aortic valve from the aortic sclerosis to aortic stenosis, leading to a restriction in the mobility of the leaflets of the valve and a subsequent obstruction of the left ventricular outflow.

1.2.1 Anatomy and Physiology of the Heart –Focus on the Aortic Root

The heart is a fibromuscular organ with 4 chambers, the atria and the ventricles, which serves as a self-adjusted double pump. The atria are located superior and posterior to the same side ventricle and are the receiving chamber for the venous circulation. Bounded by thin muscular walls, atria have an active function in diastolic function, and the loss of its contractility function, as happen in atrial arrhythmias such as AF, leads to a decrease in cardiac output of 15-20%. The ventricles are composed by an inflow separated from atria by the atrioventricular valves (mitral and tricuspid valves) and an outflow which communicates with pulmonary artery and aorta through semilunar valves (aortic and pulmonary valves). They are formed by thicker walls mainly composed by myocardial and fibrous tissue.

The cardiac skeleton is a dense connective tissue composed by four rings-atrioventricular valves and pulmonary and aortic valves- and the contiguous fibrous part of the interatrial and interventricular septa. It provides anchorage for the muscular tissue and valves, interrupt the continuity between atria and ventricles, and hold the heart in its site in the pericardium. The cardiac skeleton is centered in the aortic root and form part of both the aortic valve and conduction system[11] (Figure 1-2).
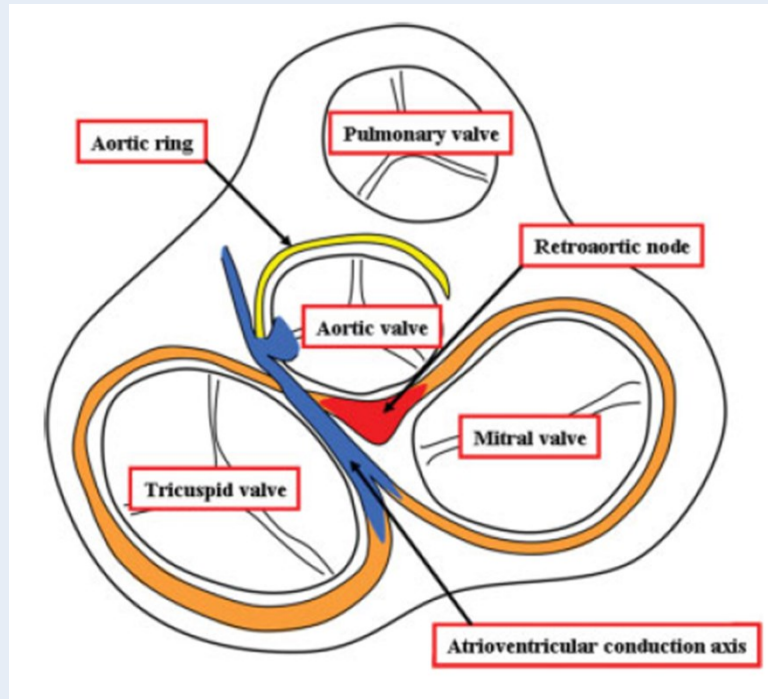
FIGURE 1-2. **The cardiac skeleton**

The diagram shows the rings that compose the cardiac skeleton and the location of the atrioventricular conduction axis (in blue)

From Anderson RH, Yanni J, Boyett MR, Chandler NJ, Dobrzynski H. The anatomy of the cardiac conduction system. Clin Anat. 2009;22:99-113

Heart valves consist of thin, mobile, flexible leaflets which ensure unidirectional circulation of blood without obstruction. Driven by mechanical forces exerted by blood and surrounding structures, heart valves are composed of endothelial and valvular interstitial cells and extracellular matrix, disposed in a layered configuration with regional specializations. This composition allows changes in shape and dimension throughout the cardiac cycle, effective stress transfer to the adjacent structures, and ongoing repair of injury incurred during normal function.[1, 12]

1.2.1.1   The Aortic Root

The aortic root is the junction between the left ventricle (LV) pathway and the ascending aorta (Figure 3A). It is a morphological, anatomical and functional unit formed by the aortic valve, the sinuses of Valsalva, the aorto-ventricular junction with the inter-leaflets triangles located between the basal attachments of the leaflets[13-15] and the sino-tubular junction (Figure 1-3).
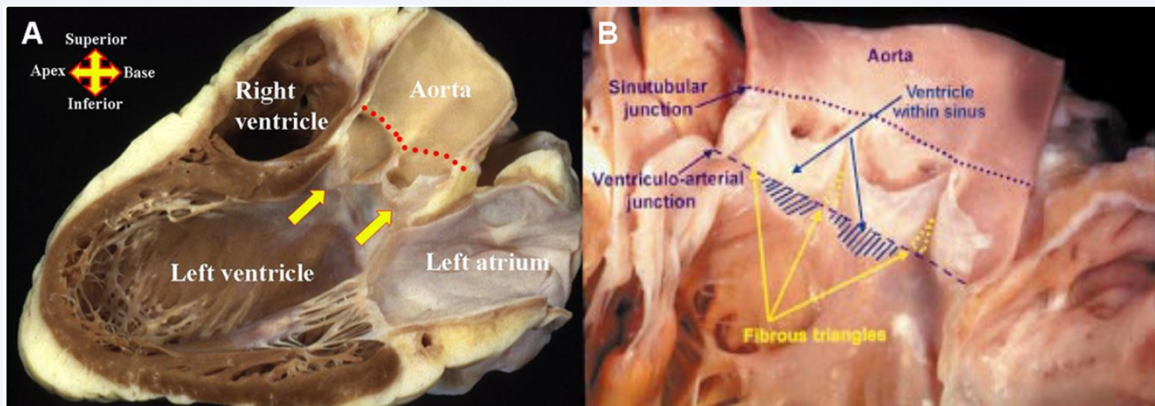
FIGURE 1-3. The aortic root

Picture A shows the placement of the aortic root in the heart, demarcated by the basal attachments of the valvular leaflets within the ventricle (yellow arrows) and the sino-tubular junction (red dotted line). Picture B shows the aortic root opened showing the semilunar attachments of the leaflets, the inter-leaflets triangles.

From Anderson RH. The surgical anatomy of the aortic root. Multimed Man Cardiothorac Surg. 2007;2007:mmcts 2006 002527 and Anderson RH.Clinical anatomy of the aortic root. Heart. 2000;84:670-673 (B)

The aortic valve is composed of three leaflets attached in a semilunar fashion from the sino-tubular junction to a basal ventricular attachment, crossing the aortic sinuses, leading to a crown shape of the aortic annulus. Such configuration allows differentiating 3 anatomical parts of the aortic leaflets: the free margin with a thickened circular node (nodule of Arantius), the belly of the leaflet and the basal attachment.[15] The basal attachment is 1.5-fold longer than the length of its free margins to accommodate to the configuration of the aortic root.[16] The distal parts of leaflet attachments, where run parallels, are called the commissures. Aortic

valve cups are of unequal-size commonly and variations have been observed among individuals, which has been proposed a factor for the development of aortic stenosis.[17, 18] Averaged dimensions of aortic leaflets in normal hearts are shown in Figure 1-4.

FIGURE 1-4. Dimensions of aortic leaflets

Adapted from Silver AM, Roberts WC. Detailed Anatomy of the Normally Functioning Aortic Valve in Hearts of Normal and Increased Weight. Am Heart J 1965;55:454-461
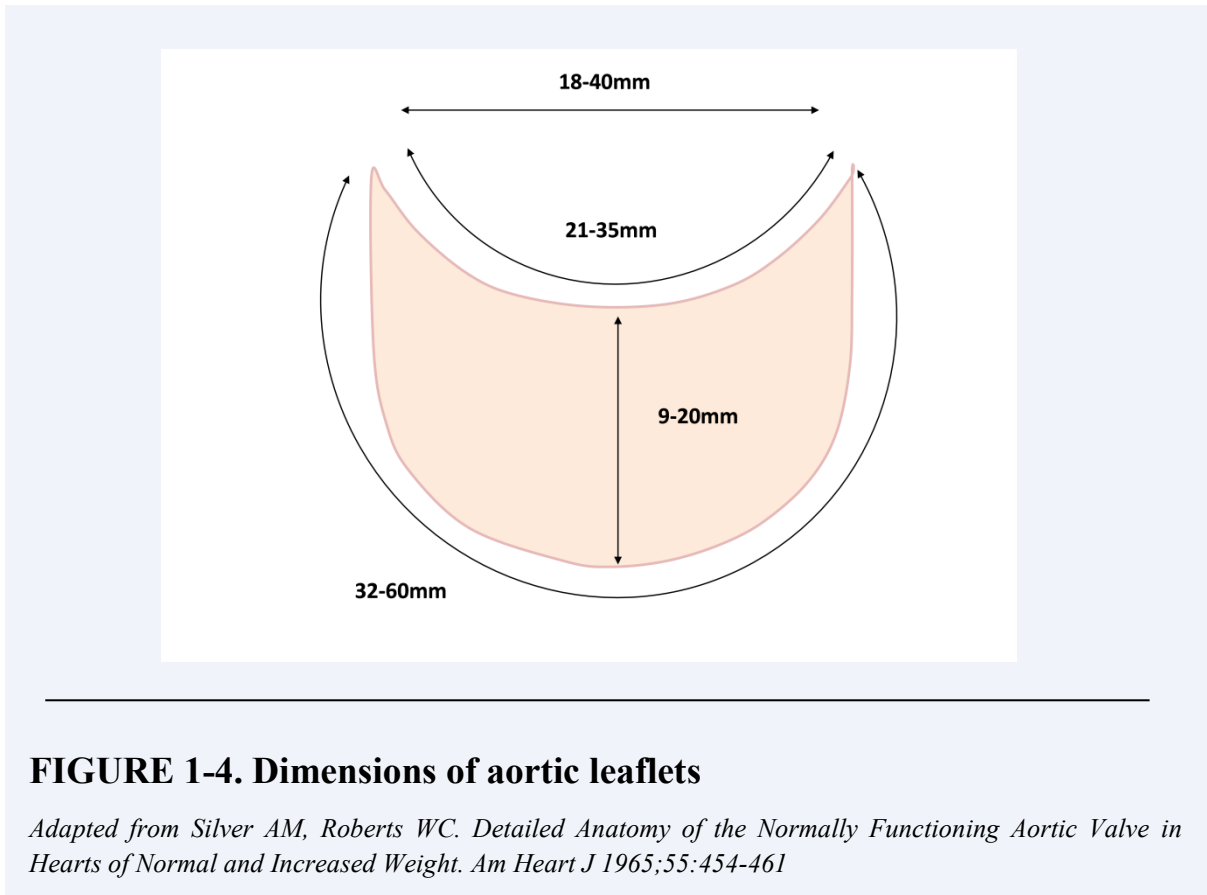
Aortic cusps separate ventricular (proximal) and arterial pressures (distal) and such 3 leaflet configuration allows for the lower resistance to valve opening.

No anatomically or histologically distinct circular structure in the aortic root exist, and therefore, no structure fits with the definition of annulus.[15] However, the term of aortic annulus has been widely used to name two different concepts: while echocardiographers use this term to name a virtual basal ring constructed by joining together the most proximal parts of each leaflet, for most surgeons, aortic annulus is the line formed by the proximal part of the leaflet attachments of the excised leaflets used for the anchoring of sutures in AVR procedures (Figure 1-5).[19, 20]
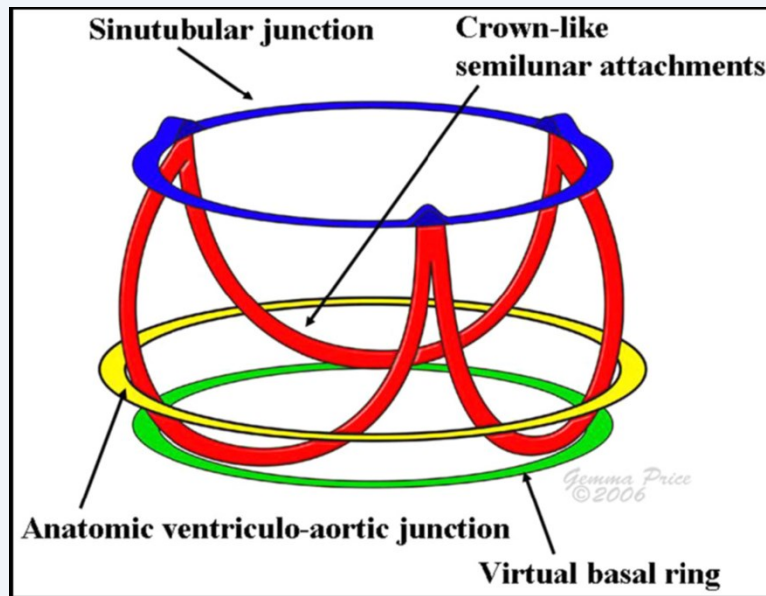
FIGURE 1-5. Aortic annulus

Scheme of the aortic root showing both definitions of aortic annulus: the crown shaped ring in red and the virtual ring formed by joining the basal attachments of the aortic valve leaflets in red.

From Anderson RH. The surgical anatomy of the aortic root. Multimed Man Cardiothorac Surg. 2007;2007:mmcts 2006 002527

According to the first definition, the aortic annulus is the smallest area in the blood path between the LV and the aorta and determines the fitting position of prosthetic valve sizers and echocardiographic dimensions, therefore, the size of the prosthetic valve to be implanted during AVR. In addition it has been used to determine the position of the prosthesis as 'supra' or 'intra-annular', although as mentioned before, prosthetic valves are inserted more proximally, at the level of the crown-shaped proximal attachment of the excised leaflets.[15, 19]

The aorto-ventricular junction (second concept of aortic annulus) is composed of muscular interventricular septum and fibrous tissue formed by the membranous septum and the intervalvular fibrous body (along approximately 45% and 55% of its circumference, respectively). Its crown shape creates the inter-leaflets triangles which are the space beneath each commissure. The inter-leaflet triangle separating the right and left leaflets is composed of muscle and inter-leaflet triangle bordering the posterior leaflet are composed by fibrous

tissue. The inter-leaflet triangle between the right and non-coronary leaflet continues on the membranous septum, where the His bundle and proximal part of the left bundle branch of the conduction system are located (Figure 1-6). [21, 22]

The sinuses of Valsalva are three dilatations of the aortic wall placed between the aortic valve and the sinotubular junction, where coronary arteries originate. The distal part of the sinuses toward the ascending aorta together with the commissures form a tubular structure called the "sinotubular junction" which separates the aortic root from the ascending aorta.
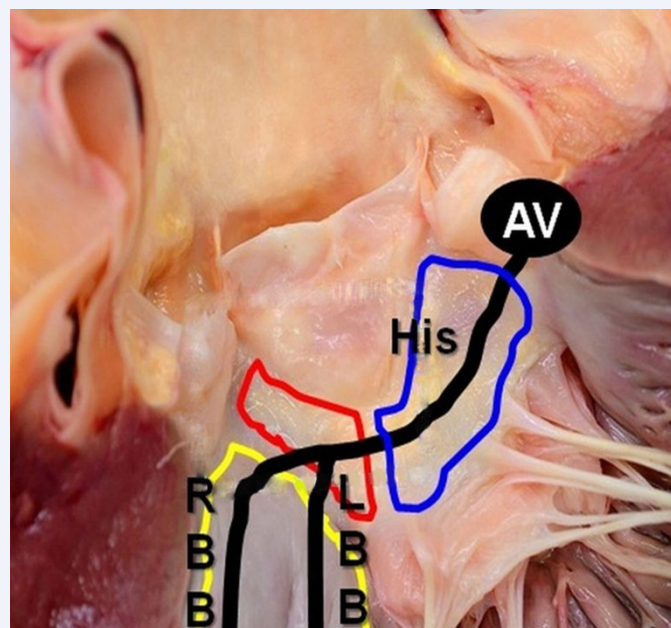
FIGURE 1-6. Anatomical relationship between the aortic valve and the conduction system

Pathological specimen showing the anatomical proximity between the aortic valve and conduction system pathways (black line)
Adapted from Bagur R, Rodes-Cabau J, Gurvitch R,et al. Need for permanent pacemaker as a complication of transcatheter aortic valve implantation and surgical aortic valve replacement in elderly patients with severe aortic stenosis and similar baseline electrocardiographic findings. JACC Cardiovasc Interv. 2012;5:540-551 (B)

The aortic annulus, the aortic cusps, and the sinotubular junction have an important role in maintaining valve competence. A geometric relationship between all these components is necessary to assure unobstructed blood flow across the aortic valve and valve competence.

The aortic sinuses have no effect on valve competence, but it has been suggested that it reduces the mechanical stress on the aortic cusps by creating vortices and currents between the cusps and the sinus walls, which may facilitate the normal leaflet movement and increase valve durability. In addition , aortic sinuses may support coronary flow.[15]

1.2.2. Pathophysiology of Calcific Aortic Stenosis

Although considered a passive age-related degenerative disease for a long-time,[18] recent studies have shown that AS is not only an age-related degeneration of the aortic valve. Two different phases may be differentiated in the evolution of AS: an initiation phase and a progression period. Anatomic, genetic and clinical factors play a role on the initiation and progression of AS which is mediated by cellular and molecular pathways.[23, 24] The presence of bicuspid valves, genetic mutations associated with bicuspid valves and aortic valve calcification, old age, male sex, hypertension, diabetes and metabolic syndrome, smoking and increase serum lipid have been associated with the pathogenesis of AS (Figure 1-7).

The initiation of the disease is caused by endothelial damage due to mechanical stress and reduced shear stress. The lipid and lipoproteins subendothelial accumulation after endothelial damage leads to progressive endothelial injury and lipid oxidization, establishing an inflammatory response characterized by infiltration of macrophages and T-lymphocytes. In this early stage, regions of micro-calcifications in regions of deposits of lipids starting in the fibrosa layer may be observed (Figure 1-7).[23] It has been proposed that aortic valve calcification may result from the activation of signaling pathways that leads to differentiation of valvular interstitial cells into osteoblastic cells.[1]. Also, a process of neovascularization and extracellular matrix remodeling occurs.[25, 26]

The propagation phase of AS consist of a fibrotic process with deposition of matrix collagen mediated by the renin-angiotensin system followed by a subsequently predominant calcification process which mainly depends on osteoblast-like cells.[1, 23] The calcification of the valve further drives calcium formation being the driver of disease progression and the propagation phase of AS.

Similarities of this process with vascular atherosclerosis have led to suggest that calcific AS is a manifestation of atherosclerosis. The presence of lipid infiltration,

inflammation and calcification and the occurrence of calcific AS in animal models of atherosclerosis support this theory. However, up to now, randomized trials have failed to demonstrate a benefit from a lipid-lowering in patients with AS.[27]
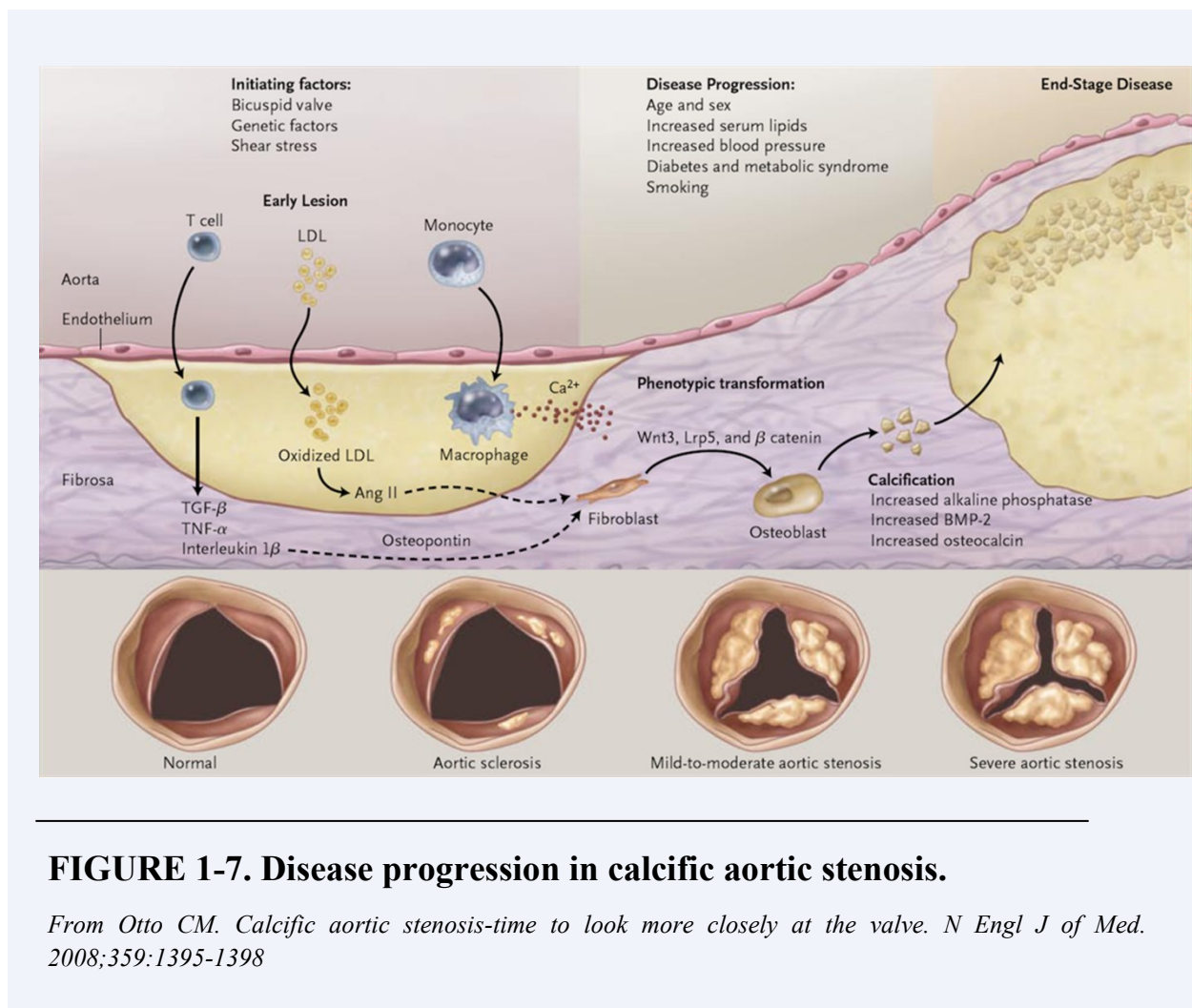
FIGURE 1-7. Disease progression in calcific aortic stenosis.

From Otto CM. Calcific aortic stenosis-time to look more closely at the valve. N Engl J of Med. 2008;359:1395-1398

1.3. NATURAL HISTORY AND MANAGEMENT OF CALCIFIC AORTIC STENOSIS

1.3.1. Natural History and Symptoms

The progressive obstruction to LV outflow caused by the stenotic valve results in a progressively increased LV pressure overload, which translates into a proportional increase in the LV pressure afterload or wall stress and an impaired left ventricular function. The greater LV afterload may be initially compensated by LV hypertrophy which may overcome the LV pressure afterload and maintains the cardiac output and LV performance.[28] However, the occurrence of LV hypertrophy has been considered a maladaptive, rather than adaptive, process for the following reasons: 1) the degree of LV hypertrophy is weakly associated with the severity of LV outflow obstruction and depends on several conditions such as age, sex, comorbidities (hypertension, diabetes and obesity) and genetic factors; 2) some patients with AS do not have LV hypertrophy, but rather a LV remodelling leading to a small cavity. 3) The occurrence of LV hypertrophy does not allow LV afterload to be overcomed in a significant proportion of patients. Furthermore, the presence of LV hypertrophy has been linked to the occurrence of ischemia and diastolic dysfunction, an increased risk of mortality and the development of LV systolic dysfunction.[29-32]

An impaired diastolic function and greater filling pressures have been linked to dyspnea. The occurrence of syncope has been associated with a reduced stroke volume and it has been suggested that angina may be related to ischemia associated with severe hypertrophy.[33 34]

LV afterload itself, the occurrence of ischemia owing to an impairment of coronary blood flow reserve, and neurohormonal factors involving the renin- angiotensin system have been associated with the occurrence of myocytes apoptosis and fibrosis, which have been proposed as the responsible mechanisms for the transition from LV hypertrophy to LV systolic dysfunction[29-32].

The presence of such compensatory mechanisms and the slow progression of AS – (2.5% toward severe AS during a mean follow up of 7 years)[26] results in a long latency period and symptoms usually occur in the sixth, seventh or eighth decades[34]. The onset of symptoms is a landmark event in the natural history of AS (Figure 1-8), with about 50% of mortality within the following 2 years[35] and the symptoms of heart failure (dyspnea) portends the worst prognosis with a survival of 1-2 years.[34]
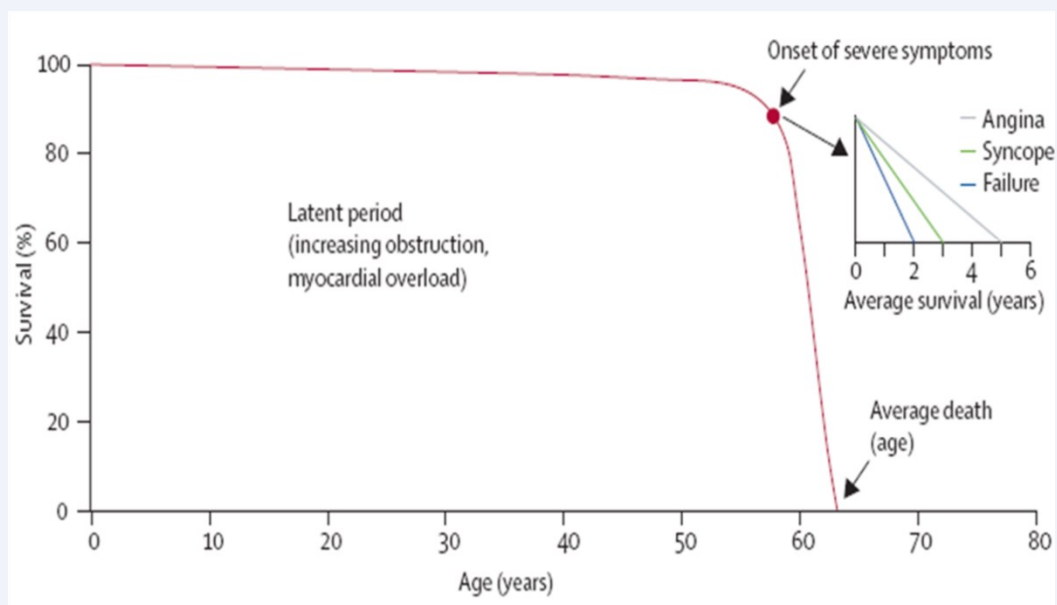
FIGURE 1-8. Natural evolution of aortic stenosis

From Ross J Jr, Braunwald E. Aortic stenosis. Circulation 1968; 38: 61–67.

1.3.2. Diagnosis of Aortic Stenosis

A careful history and physical examination play a crucial role in the diagnosis and indication of therapy for patients with AS. The auscultation might allow the identification of a typical murmur of AS.[34, 36, 37] The chest radiography might also reveal signs of heart failure and the calcification of the aortic valve. Nonetheless, the echocardiography is currently the gold-standard to diagnose valvular heart diseases, to confirm the presence and to determine the severity of AS, and LV function.

According to echocardiographic assessment, severe AS is defined by an aortic valve area (AVA)<1.0 cm^2 (indexed AVA [AVA indexed to body surface area] : 0.6 cm^2/m^2) and a peak aortic velocity > 4 meters per seconde corresponding with a mean pressure gradient of >40 mmHg (Table 1-1). [38, 39] In addition, severe AS might be defined by a velocity ratio (size of the valvular effective area as a proportion of the LVOT area) <0.25.

TABLE 1-1. Echocardiographic Criteria for the Definition of the Severity of Aortic Stenosis

	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	0.60-0.86	<0.6
Velocity ratio (V_{LVOT}/V_{AVA})		>0.50	0.25-0.50	<0.25

According to European Society of Cardiology/American Heart Association/American College of Cardiology guidelines[38, 39]

The occurrence of low-flow in patients with LV dysfunction secondary to severe LV obstruction may lead to a lower mean transaortic gradient despite the presence of a severe AS. It is the so called low-flow low-gradient AS which is defined by an AVA < 1cm^2, a LV ejection fraction <40% and a mean gradient <40mmHg.[39, 41] Low-dose dobutamine stress testing may be useful in such patients in order to both differentiate true stenosis from "pseudo-severe" stenosis and to determine the presence of LV reserve. In patients with severe AS, the increase in cardiac output translates into an increase in transaortic gradients whereas the AVA remains unchanged. In pseudo-severe stenosis, an increase in AVA ≥1.0 cm^2 is observed.

Noteworthy, exercise test may be useful in asymptomatic patients to unmask symptoms,[38] although it is contraindicated in symptomatic patients.

Cardiac catheterization provides an assessment of pressures and cardiac output.[40] However, it should not be done routinely during coronary angiography due to potential risks.[38]

Computed tomography is also valuable to assess the severity of AS. An aortic valve calcification score accurately identifies a severely stenotic aortic valve, independently of flow. In patients with AS, cut-offs of 2065 Agatston Units (AU) in men and 1275 AU in women have been proposed as the most accurate to detect the presence of severe AS.[41]

In addition, cardiac magnetic resonance may give information on the morphology of ascending aorta, LV function and morphology and a direct assessment of the severity of AS by calculating the width of the jet with the use of velocity data.[40]

Brain natriuretic peptides (BNP) and NT-proBNP are cardiac hormones released when LV afterload is increased. In addition, a raise of BNP and NT-pro BNP has been associated with the presence of symptoms in patients with AS with normal LV function [42] and the occurrence of LV impairment.[42] Although its utility in asymptomatic patients remains unclear, in particular in elderly patients who had higher levels of BNP [43], BNP may be useful in patients with heart failure and low-flow low-gradient AS.[44]

In conclusion, the diagnosis of aortic stenosis mostly relies upon echocardiographic measurements. However, measurements of the area are operator-dependent as well as and gradients depent on flow conditions, and therefore, the diagnosis of AS should be based on an integrated evaluation of symptoms, flow rate, pressure gradients, ventricular function, size and wall thickness, degree of valve calcification and blood pressure.[38]

1.3.3. Treatment of Calcific Aortic Stenosis

1.3.3.1. Medical Treatment

No medical treatment is currently effective for AS. The administration of diuretics may relieve symptoms of heart failure. Inhibitors of the renin-angiotensin system have shown a benefit for exercise tolerance in patients with AS by controlling hypertension. In addition, it

has been suggested that inhibitors of the renin-angiotensin system might slow the progression of calcification of the aortic valve, but it has not been confirmed in randomized trials.[45] Finally, as stated above, initial experiences suggested that the administration of statins might retard valve calcification.[45] However, randomized trials failed to demonstrate any significant impact of statins.[27]

1.3.3.2. Percutaneous Balloon Aortic Valvuloplasty

First used in calcific AS by Cribier in 1986,[46] percutaneous balloon aortic valvuloplasty consists in the mechanical dilatation of the aortic valve by inflation of a single or double balloon, which results in an increase in valve opening and a consequent reduction in transaortic valve gradients and increase in AVA.[46-51] Mechanisms leading to the improved leaflets mobility are not completely known, but it has been suggested that the mechanical dilatation of the aortic valve results in fractures of calcified nodules at the leaflet hinge points, leaflet microfractures, cleavage planes along stroma, and separation of fused leaflets.[52, 53] However, these pathological changes after percutaneous balloon aortic valvuloplasty may, in turn, favour valve calcification and fibrosis later on, which might explain the frequent restenosis observed in patients undergoing percutaneous aortic balloon valvuloplasty (more than 50% of patients during the first 6 months after the procedure) and the limited efficacy of a second valvuloplasty.[49,53,54,57]. In addition, a successful procedure defined as a reduction in the mean gradient of at least 50% and a final AVA $\geq$ 1 cm^2,[48] is achieved in less than 50% of patients and most patients have a severe AS at the end of the procedure. Such limited efficacy results in a lack of survival benefit and the failure of this therapy to change the natural evolution of the AS.[55, 56] Indeed, as for patients with AS left untreated, roughly half of patients undergoing percutaneous aortic balloon valvuloplasty die, mostly from cardiac causes during the first year after the procedure,[51] and that even when repeated procedures are performed. Thus, percutaneous balloon aortic valvuloplasty fell into disuse.

Nonetheless, the development of transcatheter aortic valve therapies in the last decade has favoured the resurgence of percutaneous aortic balloon valvuloplasty. Currently, this therapy is used mainly in two scenarios: in 1) the treatment of patients with severe heart failure, cardiogenic shock or those with LV systolic dysfunction[56-58], as a bridge to surgical AVR or transcatheter aortic valve replacement (TAVR) (Class of recommendation IIb, level of evidence C in American guidelines), [39, 48, 56, 59-63] and 2) in patients with symptoms or

decompensated heart failure and/or severe LV systolic dysfunction not clearly caused by aortic valve disease as a diagnostic tool. [48, 63, 64]

1.3.3.3. Aortic Valve Replacement

Relief of mechanical obstruction to LV outflow by AVR is the only effective and definitive therapy for AS and it remarkably increases the survival of patients with symptoms (Figure 1-9).[65] Thus, an early AVR after symptoms onset is strongly recommended.[38, 39] More controversial is the need of AVR in asymptomatic patients. Current guidelines suggest that AVR may be performed in asymptomatic patients if they have an abnormal exercise test showing symptoms on exercise related to AS[38, 39], or a very severe AS defined by a peak transvalve velocity >5-5.5 m/s or a mean gradient >60mmHg[39,39] or a rapid progression of disease with a rate of peak transvalvular velocity progression ≥0.3 m/s per year. [39, 41]
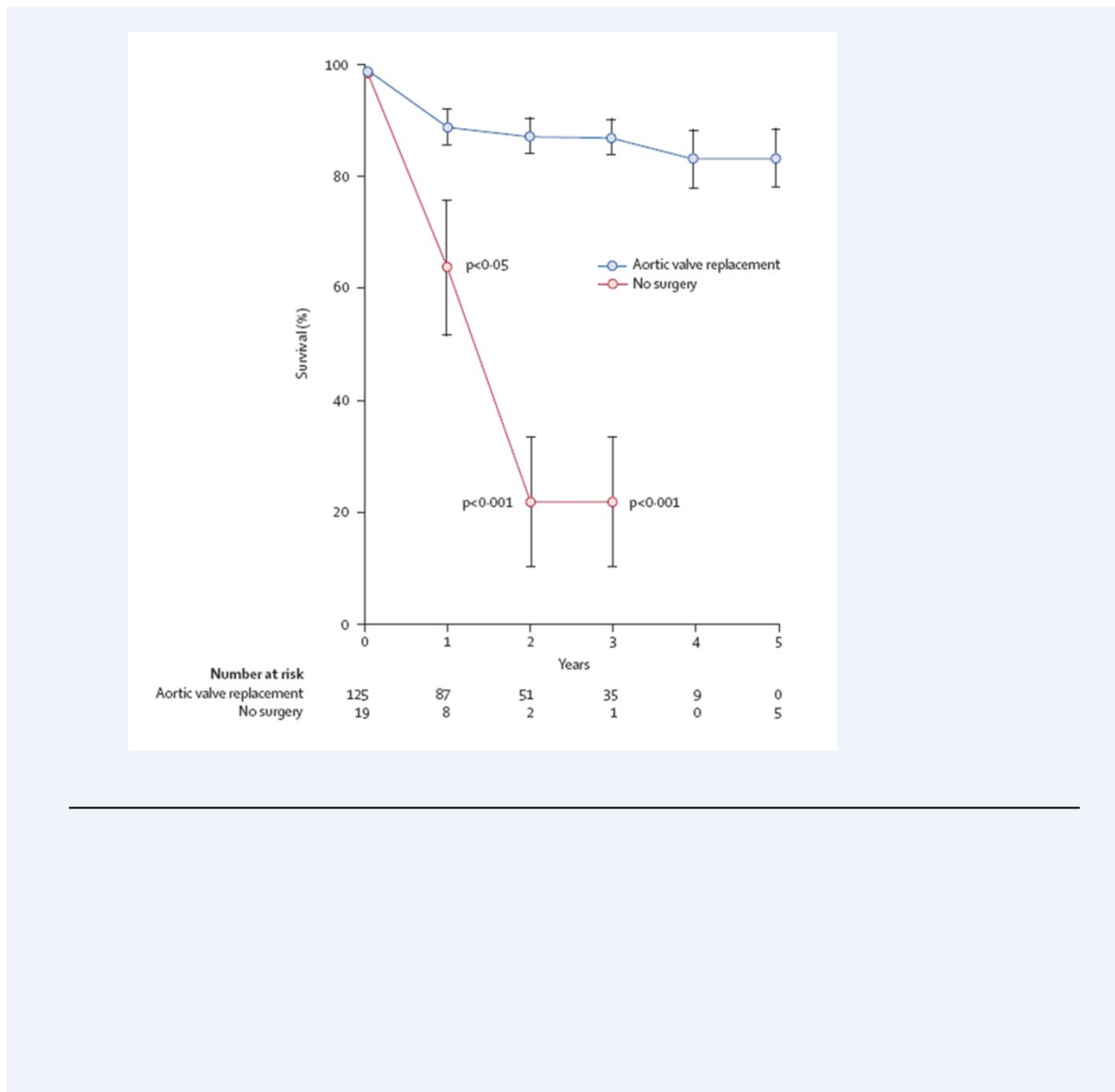
FIGURE 1-9. Mean survival of patients with symptoms of aortic stenosis in a cohort of patients undergoing to aortic valve replacement compared with medical treatment

From Schwartz et al. The Effect of Aortic Valve Replacement on Survival. Circulation 1982; 66: 1105-10

Recommendations for AVR in current European and American guidelines are shown in Table 1-2.

TABLE 1-2. Recommendations for Aortic Valve Replacement in Patients with Aortic Stenosis

	ESC[38]		AHA/ ACC[39]	
AVR is recommended with severe high-gradient AS who have symptoms by history	I†	B‡	I†	B‡
AVR is recommended with severe high-gradient AS who have symptoms on exercise testing	I	C	I	B
AVR is recommended for asymptomatic patients with severe AS and LVEF <50%	I	C	I	B
AVR is indicated for patients with severe AS when undergoing other cardiac surgery	I	C	I	B
AVR is reasonable for asymptomatic patients with very severe AS (aortic velocity ≥5.0 m/s*) and low surgical risk	IIa	C	IIa	B
AVR is reasonable in asymptomatic patients with severe AS and decreased exercise tolerance or an exercise fall in blood pressure	IIa	C	IIa	B
AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF with a low-dose dobutamine stress study that shows an aortic velocity ≥4.0 m/s (or mean pressure gradient ≥40 mm Hg) with a valve area ≤1.0 cm2 at any dobutamine dose	IIa	C	IIa	B
AVR is reasonable in symptomatic patients who have low-flow/low-gradient severe AS who are normotensive and have an LVEF ≥50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms	IIa	C	IIa	C
AVR is reasonable for patients with moderate AS (stage B) (aortic velocity	IIa	C	IIa	C

3.0–3.9 m/s) who are undergoing other cardiac surgery

AVR may be considered for asymptomatic patients with severe AS and rapid disease progression and low surgical risk	IIa	C	IIb	C
AVR may be considered in symptomatic patients with severe AS low flow, low gradient, and LV dysfunction without flow reserve.	IIb	C		
AVR may be considered in asymptomatic patients with severe AS, normal EF and none of the above mentioned exercise test abnormalities, if surgical risk is low, and one or more of the following findings is present: - Markedly elevated natriuretic peptide levels confirmed by repeated measurements and without other explanations - Increase of mean pressure gradient with exercise by >20 mmHg - Excessive LV hypertrophy in the absence of hypertension	IIb	C		

*5.5 in ESC guidelines; † Class of recommendation; ‡ Level of evidence

Two types of prostheses are currently used to replace native aortic valves: biological, composed of biological tissue with a three-leaflet design, and mechanical, which consist of pyrolytic carbon single tilting disc or bi-leaflet valve.[20] The main advantage of mechanical prostheses is the durability of the prosthesis. The biological tissue of bioprostheses may degenerate owing to tissue fatigue and calcification which translate into stenosis, incompetency, or both. Although evidence is limited, it has been shown that durability of bioprosthetic heart valves depends on patients' age and may vary across different bioprosthesis types.[20] In adult patients, the mean durability (expressed as freedom from reoperation) of bioprostheses is of >10 years .[20]

Patients with mechanical prostheses require lifelong anticoagulation therapy, while no anticoagulation therapy is required in patients with bioprostheses unless the presence of another medical condition with an indication for anticoagulation. The selection of the type of prosthesis mainly relies upon the age of patients and the anticipated risks and quality of anticoagulation therapy.[38, 39] Indeed, a survival benefit has been observed in patients >65 years with biological prosthesis,[66] while younger patients seems to benefit from mechanical prosthesis.[67]

The risk of perioperative morbidity and mortality following isolated AVR varies widely depending on operators, clinical presentation and comorbidities of the patients. In contemporary series operative mortality varies between 1-3% in younger patients and 4-8% in older patients.[68-71] Other complications associated with AVR are: cerebrovascular accidents which occur in 1.5% of patients, renal failure in 4.1%, deep sternal infection in 0.3%, prolonged assisted ventilation in 10.9%, reoperation for any reason in 8.4%[70] and conduction disturbances and pacemaker implantation (2%).[72] Approximately 18% of patients undergoing AVR have at least one of these complications.[70]

Despite the marked benefit of AVR, up to 60% of patients with severe AS may not undergo AVR, [71, 73, 74] in 33% of patients aged ≥ 75 years cardiac surgery is denied because of high perioperative risk[74-76]. Moreover, having an age of 80 or more years is an independent predictor for denying cardiac surgery in such patients.[73] This limited access to AVR of an important proportion of patients with AS has favoured the development of a minimally invasive definitive therapy: TAVR.

CHAPTER 2. TRANSCATHETER AORTIC VALVE REPLACEMENT

Since first performed in 2002 by Cribier, [77] transcatheter aortic valve replacement (TAVR) (or transcatheter aortic valve implantation [TAVI], as called in Europe), has expanded around the world[78] with more than 100,000 procedures performed nowadays. The streaking benefit of this new therapy when compared to medical treatment and the progressive reduction in periprocedural complications owing the development of the technology, the evolution of the technique and the improved experience of operators, have made TAVR become a routine therapy for patients with AS. Furthermore, the expected reduction in costs associated with TAVR procedures in the near future owing to a shortening of hospitalization periods and a decrease of costs of TAVR devices, will favour a greater expansion of the use of this therapy even if current recommendations are not changed.[79] In 2013, more than 250,000 patients were candidates for TAVR according to current indications,[79] and such prevalence is expected to increase as the prevalence of AS increases.

2.1. EVIDENCE ON TRANSCATHETER AORTIC VALVE REPLACEMENT

The main evidence on outcomes of TAVR is based on the results of 2 randomized trials, the PARTNER (Placement of Aortic Transcatheter Valve)[80, 81] trial and the US CoreValve Pivotal Trial,[82] and multicenter or national registries.[83-92]

The PARTNER trial is a prospective, randomized, multicenter trial, including 2 arms: a cohort B for comparison of TAVR using the SAPIEN device (Edwards Lifesciences, Irvine, CA, USA) to medical treatment, which included balloon aortic valvuloplasty, in patients considered inoperable, and the cohort A, in which TAVR was compared to AVR in patients considered at high surgical risk. The definition of prohibitive or high surgical risk was based on the assessment of at least 2 cardiac surgeons and interventional cardiologists, and all patients were discussed by conference calls before enrolment was accepted. In addition, for the inclusion in PARTNER A, a minimal Society of Thoracic Surgeons (STS) score (which is used to predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables) of 10% and surgeons' assessment of the risk of death >15% was required, and for PARTNER B, patients were enrolled if at last 2 cardiac surgeons agreed that they were inoperable based on a combined risk of death and severe morbidity >50%.[93] In addition, it was required the presence of a severe AS defined as an AVA <0.8 cm^2, and either a mean transvalvular gradients >40 mmHg or a peak >64 mm Hg, symptoms, a life expectancy >1year and none of the following conditions: recent myocardial infarction or stroke, LV ejection fraction < 20%, chronic kidney disease with a creatinine level >3.0 mg/dL, a bicuspid valve or an aortic regurgitation >3. Of a total of 3,105 patients presented for inclusion in the trial, 1057 were finally enrolled: 358 patients were included in the cohort B and 699 in the cohort A, 12% of total of patients. The overall design of PARTNER trial is shown in Figure 2-1.
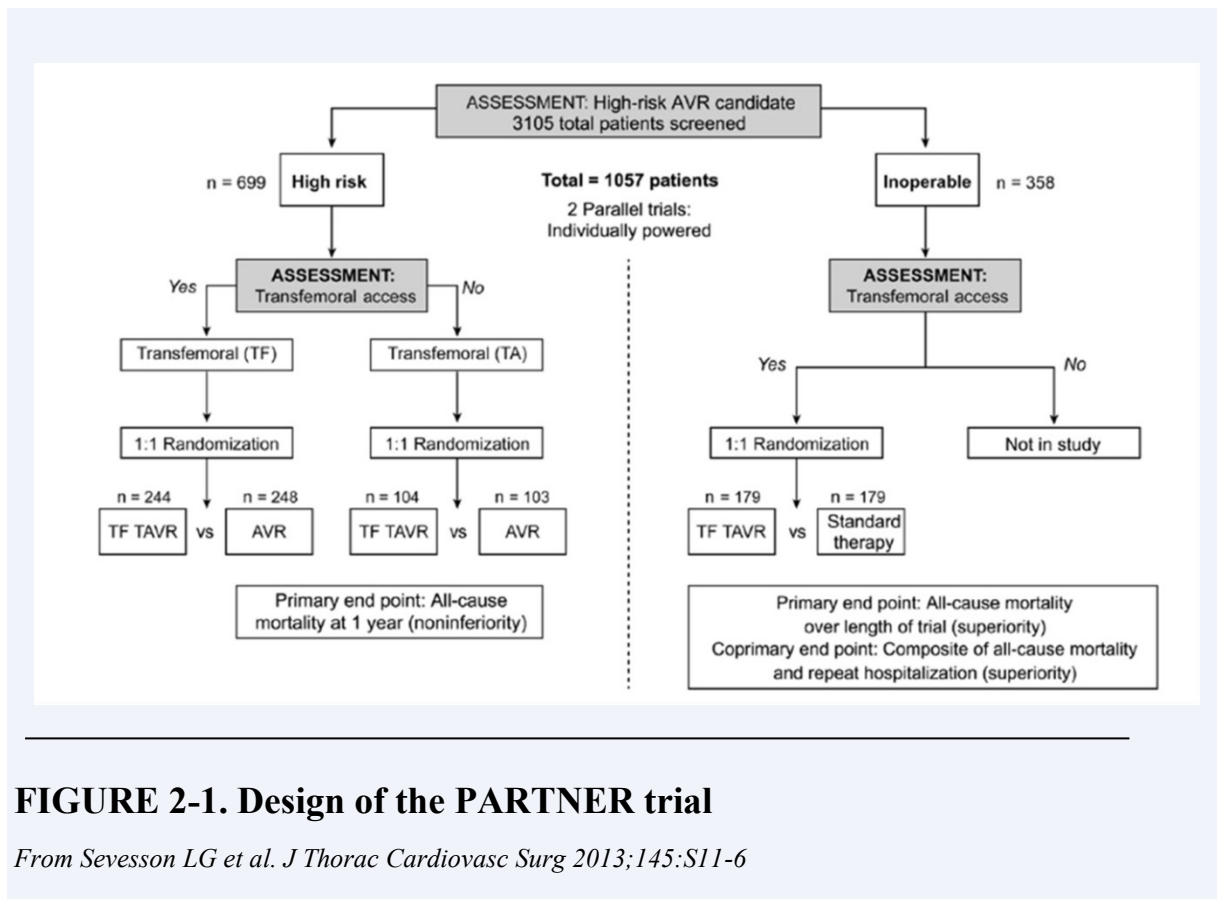
FIGURE 2-1. Design of the PARTNER trial

From Sevesson LG et al. J Thorac Cardiovasc Surg 2013;145:S11-6

The PARTNER B demonstrated a 20% survival benefit of TAVR in inooperable patients compared to medical treatment, with a 1-year mortality of 30.7% in the TAVR group and a 50.7% in the medical therapy group (Figure 2-2A, B). Patients undergoing TAVR had a higher rate of neurologic events at 1-year follow up (10.6 vs. 4.5%, P = 0.04) although such differences were not statistically significant for major stroke (7.8 vs. 3.9%, P = 0.18). [80] In the high-risk surgical cohort, TAVR and surgical valve replacement were equivalent for 30-day mortality (TAVR: 3.4%, surgical AVR 6.7%, P = 0.07), 1-year mortality (TAVR, 24.2%; surgical AVR, 26.8%, P = 0.44) (Figure 2-2 C,D) and 1-year relief of symptoms. A higher incidence in neurologic events was observed in the TAVR cohort compared to surgery (5.1 vs. 2.4%, P=0.04), as well as higher rate of vascular complications (18 vs. 4.8%, P = 0.04) and moderate or severe aortic regurgitation (6.8 vs. 1.9%, P < 0.001). Patients undergoing TAVR had a lower rate of bleeding (14.7 vs. 25.7%, P < 0.001) than surgery[81]. The results led to approval by the Food and Drug Administration of the device for commercial use in inoperable patients, firstly, and in high-risk surgical patients, later. Recently, results of the long-term follow up of the PARTNER trial have been reported, confirming that the TAVR benefit

remains up to to-5 years follow-up, although roughly 60-80% of patients were dead at this point of time.[94, 95]
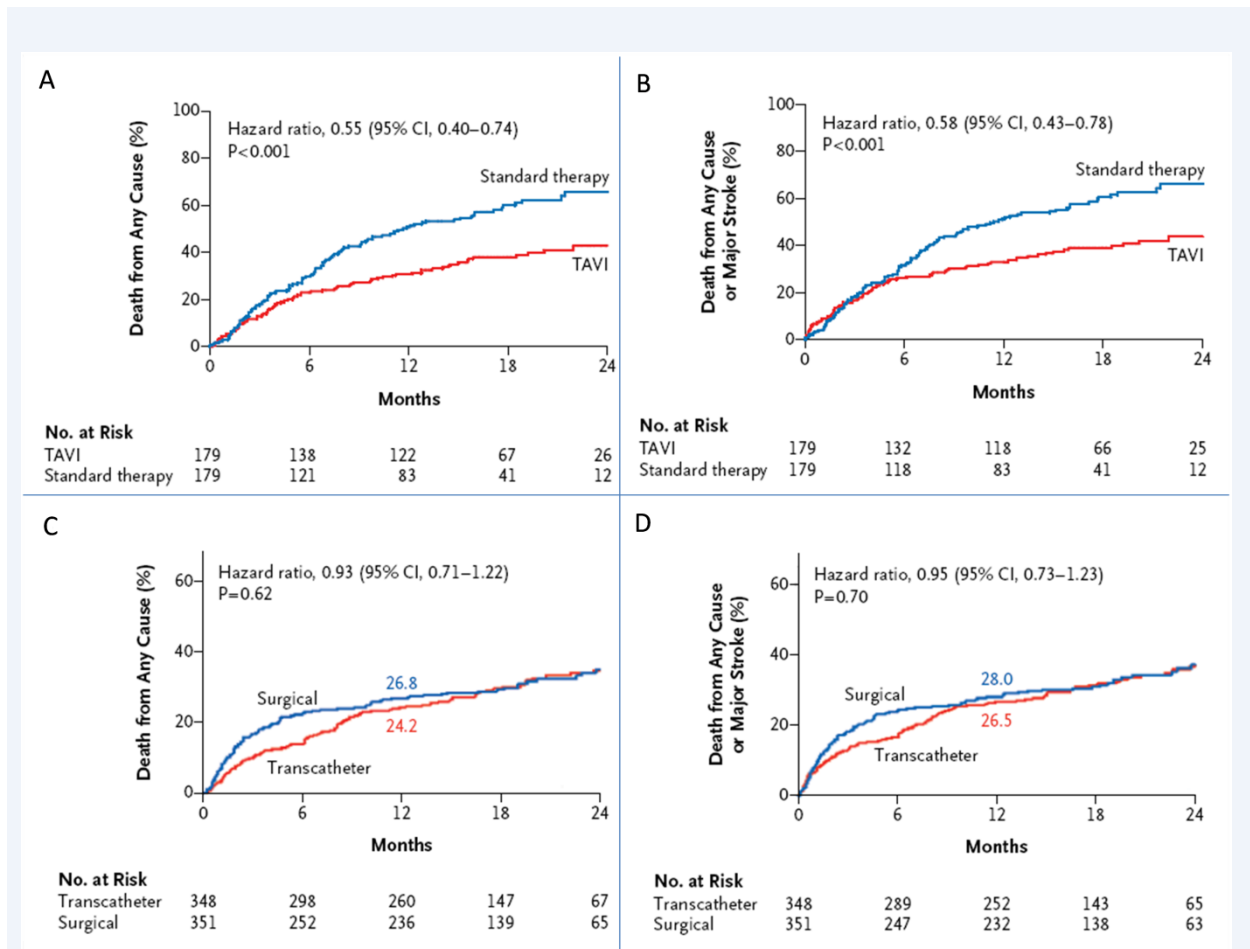
FIGURE 2-2. Main results of PARTNER trial cohort B (A, B) and Cohort A (C,D)

From Leon M et al. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. N Engl J Med 2010;363:1597-1607 (A and B) and Smith CR et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. N Engl J Med 2011;364:2187-98 (C and D)

The CoreValve US pivotal trial included 2 arms: an extreme-risk cohort[96] and a high-risk cohort.[82] The extreme-risk cohort included 489 patients, there was not randomization and the endpoints were compared with a pre-specified performance goal for all-cause mortality or stroke at 1 year of 43% using a non-inferiority with superiority test. In the randomized high-risk cohort, TAVR using the CoreValve system (Medtronic, Minnesota, USA) was compared

to surgical AVR.[82] As for the PARTNER trial, patients were included if they had severe AS and symptoms and a high-surgical risk as judged by cardiac surgeons and interventional cardiologists.

The extreme risk cohort showed that the CoreValve system was safe and effective and led to the FDA approval of the CoreValve system for commercial use. In the high-risk cohort, from 995 patients screened, 795 patients were finally randomized. The primary
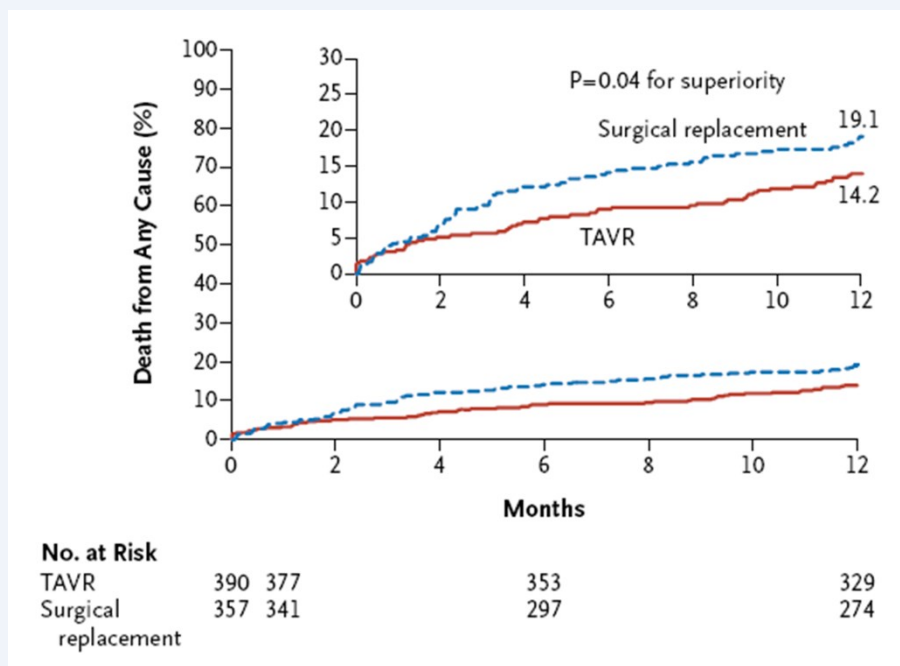
FIGURE 2-3. Primary endpoint of the US CoreValve Trial

From Adams DH et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis. N Engl J Med 2014;370:1790-8

endpoint of all-cause mortality was observed in 14.2% of the TAVR patients and 19.1% of the surgical AVR group, *P* <0.001 for non-inferiority and *P*=0.04 for superiority [97] (Figure 2-3). No differences were observed in major stroke between TAVR and surgical AVR groups at 1 month (8.2 vs. 10.9%, *P* = 0.10). However, the rate of cerebrovascular events at 1-year follow-up was statistically lower in the TAVR group (20.4% vs. 27.3%, *P* = 0.03). The results from this trial led to the approval of the CoreValve system for the Food and Drugs Administration in high surgical risk patients.

In addition to these randomized trials, evidence derived from large multicenter or national registries have confirmed the favourable short-and long-term outcomes of this therapy in "real" populations[83-92], although pooled mortality rates were greater than that observed in the PARTNER trial[98], mainly owing to different profile of populations included. Main results of TAVI in terms of mortality in multicenter registries are displayed in Figure 2-4.
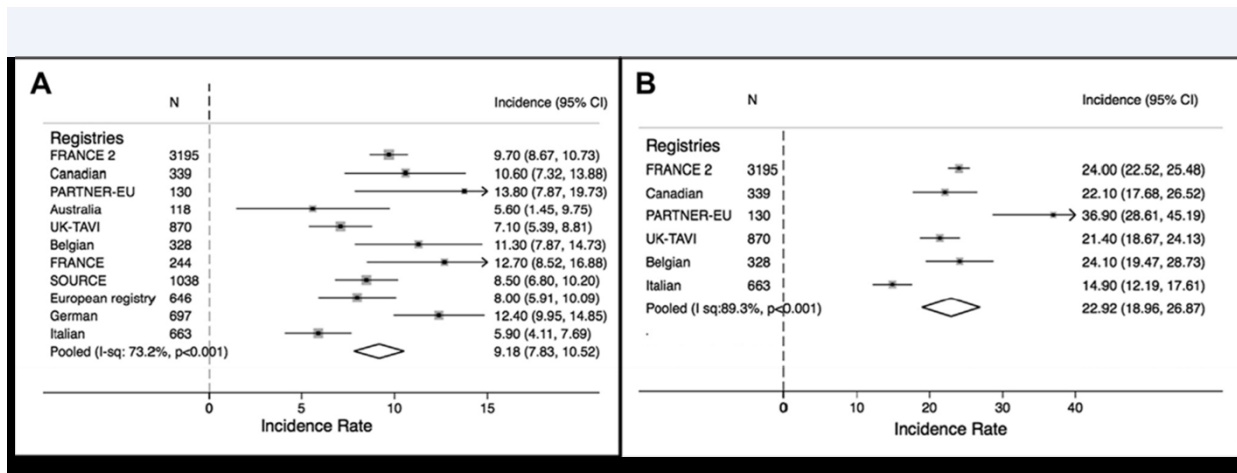
FIGURE 2-4. All-cause mortality and cardiovascular mortality in main multicenter registries of TAVR

Adapted from Agarwal et al. Comparison of multicenter registries and randomized control trials for transcatheter aortic valve replacement (TAVR). Indian heart journal 2013; 65: 400-411

2.2. THE PROCEDURE, DEVICES AND OUTCOMES

2.2.1 The Procedure and Devices

The TAVR procedure consists of deploying a bioprosthesis at the level of the aortic valve in a beating heart without the need of cardio-pulmonary bypass and cardiac arrest by means of a catheter or delivery system.[99] The technique of TAVR depends on the type of device used. Two main types of devices exist: balloon-expandable and self-expanding valves. Among the

balloon-expandable prostheses, the third and fourth generation Edwards heart valve system SAPIEN XT or SAPIEN 3 are the most used. It is composed of a delivery system and atranscatheter heart valve, which consists of a trileaflet bovine pericardial valve sewn into a cobalt chromium stent frame (Figure 2-5).[100] Four different sizes are available: 20-mm, 23-mm, 26-mm and 29-mm, covering aortic annulus diameter from 16 to 28 mm, with the new generation SAPIEN 3 transcatheter heart valve. The size of the prosthesis is selected according the measurements of the native aortic annulus, which mainly rely upon computed tomography images. The height of the stent frame depends on the size and type of the prosthesis (SAPIEN 3 devices is longer than the SAPIEN XT device), being the 29-mm SAPIEN 3 transcatheter heart valves the longest one (22 mm). The SAPIEN 3 incorporates improved features which allow an improved coaxiality and accurate positioning, that along with the sealing properties of its external cuff, reduce the risk of paravalvular leaks.

The prosthesis is crimped into a balloon and deployed by means of balloon inflation. The procedure is performed in catheterization laboratories, operator rooms or hybrid rooms, using general anesthesia or, frequently used in the last years, conscious sedation and local anesthesia. Procedures are performed using fluoroscopy and transesophageal or transthoracic echocardiography guidance. The prosthesis is deployed under rapid pacing, frequently preceded by balloon valvuloplasty.
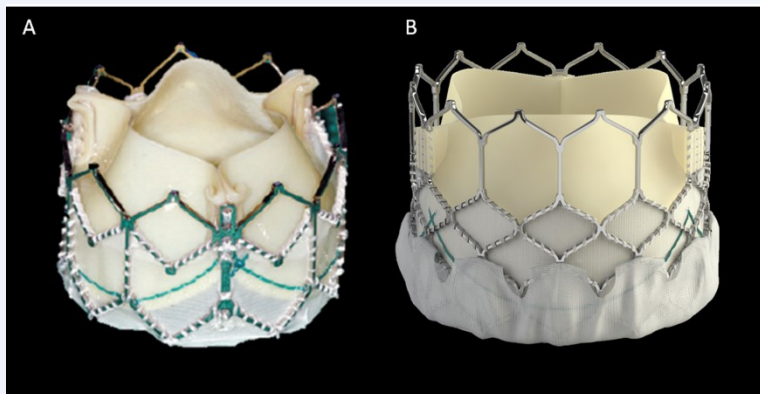
FIGURE 2-5. Edwards SAPIEN XT (A) and SAPIEN 3 (B) transcatheter heart valves

Adapted from Rodés-Cabau et al. Transcatheter aortic valve implantation: current and future approaches. Nat Rev Cardiol 2012; 9: 15-29
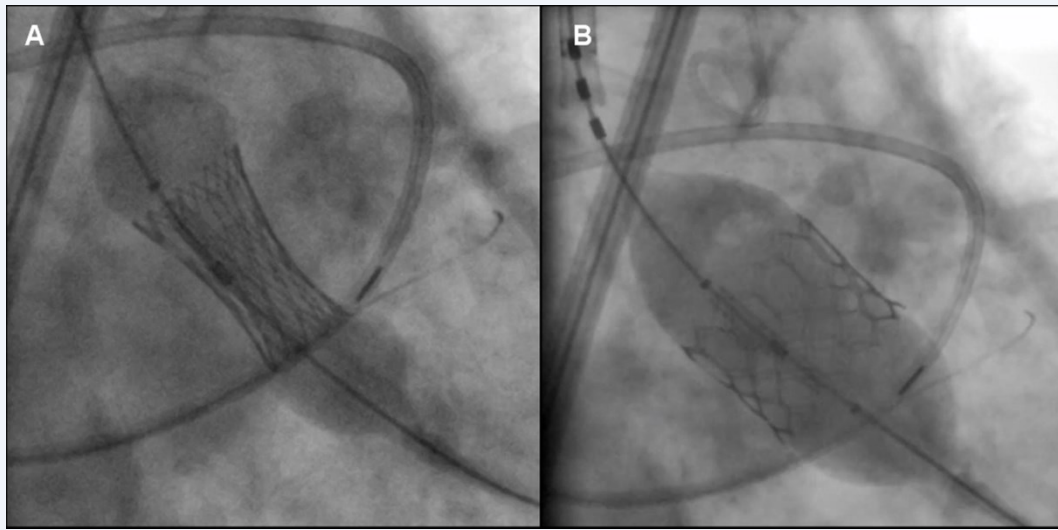
FIGURE 2-6. Sequences of valve implantation using a SAPIEN 3 transcatheter heart valve

The CoreValve transcatheter heart valve is a self-expanding nitinol frame with a porcine trileaflet pericardial valve sewn and a suprannular placement of the leaflets coaptation (Figure 2-7).

The valve has 3 distinct zones: the bottom part or sealing skirt with high radial force to secure the valve radially into the aortic annulus, the middle part with high hoop strength to restrict deformation, and the highest part with low radial force for alignment.[100] Four sizes are available: 23, 26, 29, and 31 mm that cover aortic annular sizes from 18 to 29 mm. The height of the CoreValve transcatheter heart valve varies between 45 and 55 mm.[101] The new-generation CoreValve Evolut R is a recapturable and repositioned prosthesis, shorter than the predecessor and has an extended skirt of the inflow tract, which it is expected to translate into a reduction of paravalvular aortic regurgitation. The prosthesis is deployed by retrieving the delivery system and no rapid pacing is required (Figure 2-8). However, pacing at frequencies ~100-120 beat/min might be used to improve the stability and control of the system.
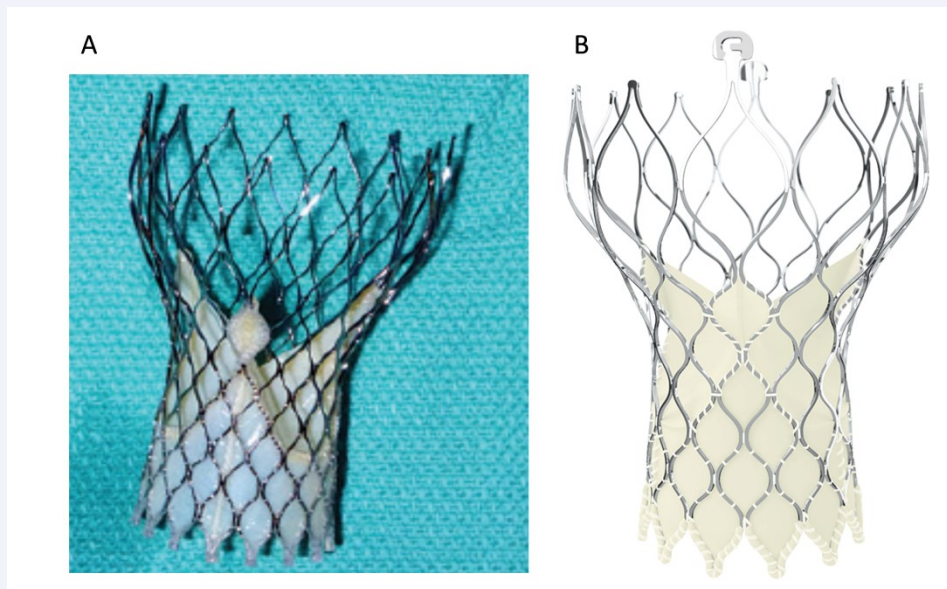
FIGURE 2-7. The CoreValve devices

The CoreValve (A) and CoreValve Evolut R transcatheter heart valve (B)

Adapted from Rodés-Cabau et al. Transcatheter aortic valve implantation: current and future approaches. Nat Rev Cardiol 2012; 9: 15-29

Differences in intrinsic characteristics of both prostheses result in different outcomes. While no differences have been observed between both types of devices in terms of mortality or stroke, the use of self-expandable valves was associated with a higher rate and severity of paravalvular leaks and conduction disturbances (left bundle branch block and atrioventricular block requiring permanent pacemaker implantation).[99] In the contrary, the use of balloon-expandable valves may be associated with a higher (although low) rate of annulus rupture or coronary obstruction.
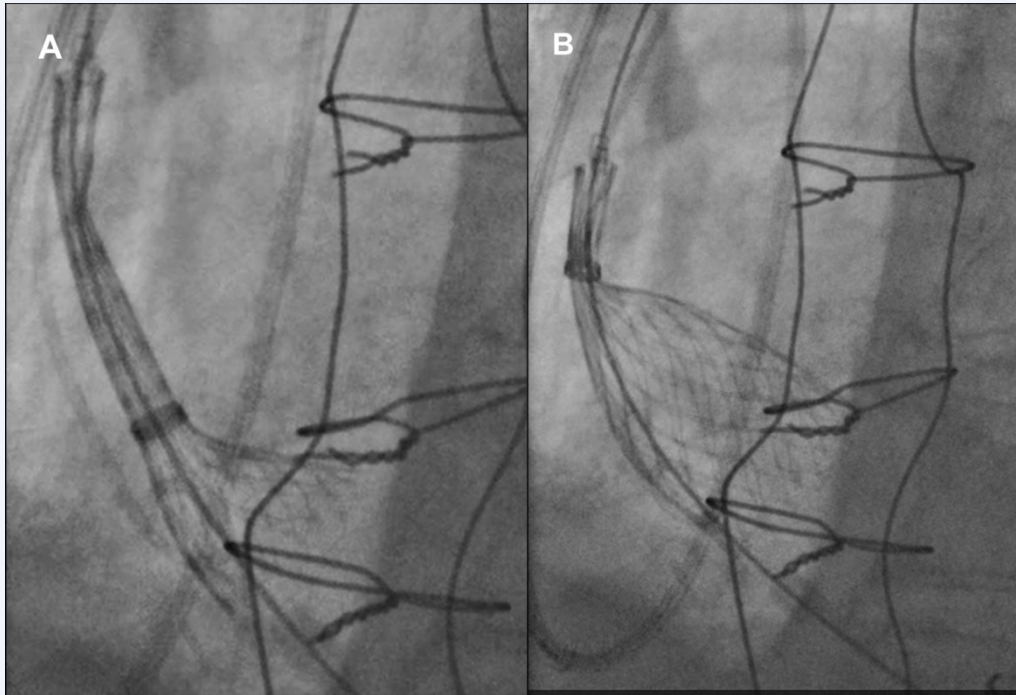
FIGURE 2-8. Sequences of the deployment process of the CoreValve Evolut R device

In addition to the SAPIEN 3 and CoreValve Evolut R, other new-generation devices with enhanced delivery systems have been developed to reduce the risk of periprocedural complications, particularly aortic valve regurgitation and vascular complications. Main characteristics of such new technologies are summarized in Table 2-1. [102]Although promising, evidence on the results of such systems is limited nowadays.

TABLE 2-1. New Generation Devices for TAVR

Device name and valve sizes	Valve structure	CE mark	Delivery system and access routes	Clinical evaluation studies
JenaValve®(JenaValve Technology GmbH, Germany); 23 mm, 25 mm, and 27 mm (for 21–27 mm aortic annuli)	Porcine pericardial tissue valve Self-expanding nitinol stent	September 2011 for aortic stenosis September 2013 for AR	Sheathless 32 Fr Transapical (transfemoral is under clinical evaluation)	**JUPITER registry** (180 patients): 85% overall survival (30 days); 12.5% pacemaker implantation; no major strokes; 1.3% acute MI (30 days); 97.6% mild or absent perivalvular leakage
ACURATE® (Symetis SA, Switzerland); Small (20–23 mm aortic annuli), medium (23–25 mm), and large (25–27 mm)	Porcine pericardial tissue valve Self-expandable nitinol alloy stent	September 2011 for aortic stenosis	Sheathless 28 Fr Transapical (transfemoral is under clinical evaluation)	**ACCURATE TA®** (40 patients): 92.5% device success rate; 82.5% survival (6 months); 7.5% pacemaker implantation; 97.5% ≤mild perivalvular leakage **ACCURATE TF®** (20 patients): 95.6% procedural success; 13% pacemaker implantation; 95% mild or absent perivalvular leakage
Portico® (St Jude Medical, USA); 23 mm (commercial use) and 25 mm (under clinical evaluation)	Bovine pericardial tissue valve Self-expanding nitinol frame Porcine pericardial cuff	November 2012 (23 mm) for aortic stenosis	Transfemoral, transaortic or subclavian: 18 Fr Transapical: sheathless 24 Fr (Only transfemoral is currently approved)	Feasibility and procedural studies23 (50 patients): no major stroke; six patients with new left bundle branch; 0% pacemaker implantation; 95% mild or absent perivalvular leakage (30 days)
Direct Flow Medical® (Direct Flow Medical, USA) 25 mm and 27 mm	Bovine pericardial tissue valve Two polyester rings filled with polymer solution	January 2013 for aortic stenosis	18 Fr outer diameter Transfemoral	**DISCOVER trial** (75 patients): 99% overall survival (30 days); 2.7% major strokes; 4% life-threatening bleeding; 16% pacemaker implantation; 99% mild or absent perivalvular leakage (30 days)
Engager® (Medtronic, USA) 23 mm and 26 mm (for 21.0–26.5 mm aortic annuli)	Bovine pericardial tissue valve Self-expanding nitinol frame and a polyester skirt	February 2013 for aortic stenosis	29 Fr inner diameter Transapical, transaortic	**Engager® CE pivotal trial**(125 patients): 95% device success rate; 13.1 mmHg mean aortic gradient (30 days); 8.1% mortality; 6.5% life-threatening bleeding (30 days); 1.7% strokes; 28% pacemaker implantation; 100% mild or absent perivalvular leakage (30 days)

CoreValve Evolut® (Medtronic) 23 mm	Porcine pericardial tissue valve Self-expanding nitinol frame	May 2013 for valve-in-valve	AccuTrak® stability layer (18 Fr outer diameter) Transfemoral, transaortic, and subclavian	**Valve-in-valve study** (126 patients): 100% procedural success rate; no deaths or adverse events related to the procedure or the device (30 days); 0% pacemaker implantation
Lotus® valve (Boston Scientific, USA) 23 mm and 27 mm	Bovine pericardial tissue valve Self-expanding, braided nitinol frame	October 2013 for aortic stenosis	18 Fr Transfemoral (minimum vascular access diameter 6.0 mm [23 mm valve] or 6.5 mm [27 mm valve])	**REPRISE II trial** (60 patients): 100% procedural success rate; 11.2 ± 5.2 mmHg mean aortic gradient (30 days); 1.7% cardiovascular mortality; 8.7% ischaemic stroke; 100% mild or absent perivalvular leakage (30 days)
SAPIEN® 3 (Edwards Lifesciences, USA) 26 mm (20 mm, 23 mm, and 29 mm sizes are anticipated)	Bovine pericardial tissue valve Balloon-expandable cobalt chromium frame	Under evaluation	Edwards eSheath® 14 Fr with dynamic expansion mechanism Transfemoral (transapical and transaortic are under clinical evaluation)	**First-in-human feasibility SAPIEN 3 study** (15 patients): 100% procedural success rate; 11.9 ± 5.3 mmHg mean transaortic gradient after procedure; 6.7% pacemaker implantation; no deaths, strokes, or cardiovascular complications (30 days); 100% mild or absent perivalvular leakage (30 days) Transapical implantation (two patients): 100% procedural success rate; no neurological events or major vascular complications
CENTERA® (Edwards Lifesciences) 23 mm, 26 mm, and 29 mm	Bovine pericardial tissue valve Self-expanding nitinol frame with polyethylene terephthalate skirt	Under evaluation	Edwards eSheath® 14 Fr with dynamic expansion mechanism and motorized handle Transfemoral and subclavian	**First device** (15 patients): 100% procedural success rate; 10.8 ± 4.1 mmHg mean transaortic gradient (1 year); 27% pacemaker implantation; no neurological or major vascular complications; 92% mild or absent perivalvular leakage (30 days) New configuration device42 (14 patients): 100% implantation success; 0% pacemaker implantation; 100% mild or absent perivalvular leakage
Helio® transcatheter aortic dock (Edwards Lifesciences) 25 mm (for 29 mm Sapien® XT)	Self-expanding nitinol stent encased in polyethylene terephthalate	Under evaluation	Edwards eSheath® 16 Fr Transfemoral	**Helio feasibility trial** (four patients, combined transfemoral and transapical approach): 100% implantation success; 100% freedom from all-cause mortality (30 days); two patients reached 12 month follow-up with no residual AR

AR: aortic regurgitation, Fr, French; MI, myocardial infarction.
From Taramasso, M. et al. New devices for TAVI: technologies and initial clinical experiences Nat. Rev. Cardiol. 2014; 11: 157–167

2.2.2. Approaches

TAVI is mainly performed using the transfemoral (TF) approach, the preferred route nowadays owing to its less invasive nature. Indeed, the TF route is the only one allowing for a fully percutaneous procedure and, therefore, the performance of procedures without general anesthesia. The second most used route is the transapical approach.[99] Both approaches were used in the PARTNER trial. Evidence suggests an increased risk of mortality, heart failure and a significant impairment of LV function associated with the use of the transapical (TA) approach compared to the TF route, which is not completely explained by a higher risk profile of patients. [85, 103-105] In addition, the transubclavian, transaortic, transcarotid are also used nowadays,[99] although results of these approaches are still limited to small case series (Figure 2-9).
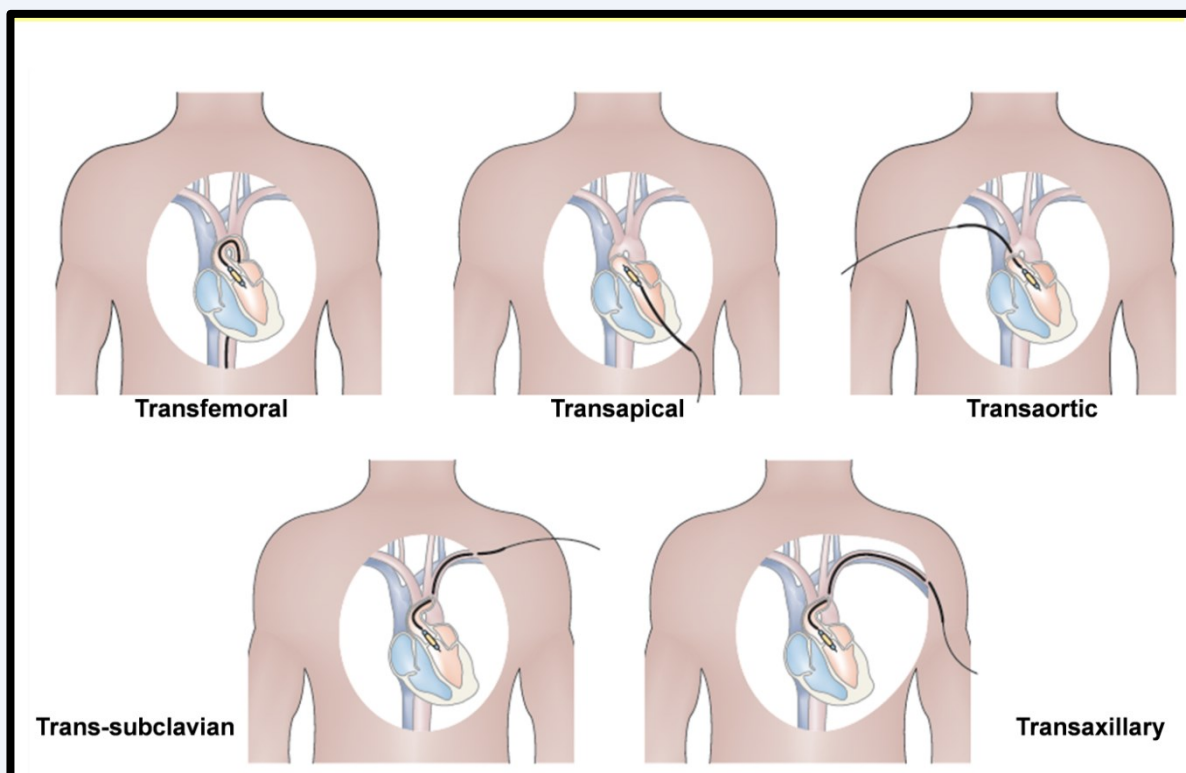
FIGURE 2-9. Approaches used for TAVR

Adapted from Rodés-Cabau et al. Transcatheter aortic valve implantation: current and future approaches. Nat Rev Cardiol 2012; 9: 15-29

2.2.3. Patients Selection.

Based on the available evidence, current American and European guidelines recommend the use of this therapy in patients with symptomatic AS considered inoperable or at high risk of perioperative mortality according to the judgement of the heart team (Table 2-2). [38, 39]

TABLE 2-2. Recommendations for the Use of Transcatheter Aortic Valve Implantation or Remplacement

ESC[38] Guidelines	Recommendation	Evidence
TAVI should only be undertaken with a multidisciplinary 'heart team' including cardiologists and cardiac surgeons and other specialists if necessary	I†	C‡
TAVI should only be performed in hospitals with cardiac surgery on-site	I	C
TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a 'heart team' and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities	I	C
TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favoured by a 'heart team' based on the individual risk profile and anatomic suitability	IIa	B
AHA/ACC[39] Guidelines		
For patients in whom TAVR or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care	I	C
TAVR is recommended in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival >12 months	I	B
TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR and who have high surgical risk	IIa	B
TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS	III	B

AVR: aortic valve replacement; AHA/ACC: American Heart Association, American College of Cardiology; ESC: European Society of Cardiology; TAVI: transcatheter aortic valve implantation; TAVR: transcatheter aortic valve replacement

The definition of a high or prohibitive surgical risk has mainly relied upon surgical risk scores, in particular the STS score and the EuroSCORE. A STS score of 8 or a Logistic EuroSCORE> 20 were used to define high surgical risk in the PARTNER trials and most of multicenter registries. However, current surgical risk scores have a low predictive value for both 30-day and medium-term mortality and morbidity in TAVR patients. [106] A new TAVR risk score to predict early mortality has been proposed developed from the results of FRANCE-2.[107] Nonetheless, no functional outcomes, which may be of great importance in TAVR populations, were evaluated and only events occurring during the first 30 days were considered.[108] Thus, an integrative approach of risk assessment considering clinical, anatomical, and social factors have been recommended, and should rely on the judgement of a multidisciplinary heart team.[39]

Clinical factors associated with increased risk of mortality after TAVR are: a severely reduced LV function, a very low transvalvular gradient (mean gradient <20 mm Hg), a low-flow (low stroke volume index, <35 ml/m^2), the presence of severe myocardial fibrosis, severe concomitant mitral and/or tricuspid valve disease, severe pulmonary hypertension (pulmonary artery systolic pressure: [PASP] >60 mmHg), oxygen-dependency, advanced renal impairment, liver disease or a very high STS score (predicted risk of mortality >15 %). In addition, geriatric index associated with increased risk are: advanced frailty, disability in activities of daily living, malnutrition, mobility impairment, low muscle mass and strength, cognitive impairment, and mood disorders.[109]

Of note, 30% of patients undergoing TAVR in the aforementioned cohort B of the PARTNER trial have died 1 year after the procedure and 50% were dead or had less than a moderate improvement in their quality of life or New York Heart Association (NYHA) functional class. This confirms that other factors than surgical risk scores have to be considered in the assessment of procedure risks in TAVR patients. The treatment of AS was futile in such patients since did not alter their poor prognosis. It is the so called "Cohort C".[109]

Although evidence on results of TAVR in lower risk populations is scarce, nowadays, a progressive reduction in overall risk profile of patients has been observed in last case series, including patients at intermediate risk. Indeed, this therapy is currently evaluated in intermediate and low surgical risk patients. Thus, a future expansion to lower risk populations is expected.

2.2.4. Complications of TAVR

Main complications of TAVR are death (~7%), stroke (~3%), major vascular complications and bleeding (5-10%), coronary obstruction (<1%), annulus rupture (<1%), paravalvular leaks (>60%), new onset atrial fibrillation (AF) (15-30%) and conduction abnormalities (mainly atrioventricular block [AVB] ~15% and left bundle branch block (LBBB) (~25%). [99, 110] Overall, it has been estimated that ~33% of patients may have at least one major event (all-cause mortality, major stroke, life-threatening bleeding, stage 3 acute kidney injury, periprocedural myocardial infarction, major vascular complications, and repeat procedure for valve-related dysfunction)[111] defining according to the Valve Academic Research Consortium (VARC)[112].

A progressive reduction in the risk of complications has been observed with new generation devices which incorporate iterations leading to a reduction in the risk mainly of vascular complications with a reduction in profile of delivery system and aortic regurgitation with the addition of a skirt, increased radial force or improvement in the oversizing of prosthesis. In addition, the improvement in the screening of patients, the reduction in the degree of oversizing and the use of retrievable valves have led to a reduction in the risk of annulus rupture or coronary obstruction. Finally, the use of new embolic protection devices, optimisation of anticoagulation therapy and lower profile of new devices allowing a reduced manipulation of the native valve might contributed to this reduction in the occurrence of periprocedural complications.[110] However, a significant increase in the risk of conduction disturbances has been observed with these new generation devices, confirming that such complications are not solved and highlighting the importance of determining the impact of conduction and rhythm abnormalities. This thesis focuses on the impact of arrhythmias and new conduction disturbances and, therefore, this issue will be discussed later on.

CHAPTER 3. CONDUCTION DISORDERS, ARRHYTHMIAS AND AORTIC VALVE DISEASE

3.1. PHYSIOPATHOLOGY OF ATRIAL FIBRILLATION AND CONDUCTION DISTURBANCES

3.1.1. The Anatomy of the Conduction System

The cardiac conduction system consists of myocytes specialized in generation and transmission of the cardiac stimulus from the atria to the ventricles. It is composed of the sinus node, the atrio-ventricular node, the His bundle, the bundle branches and Purkinje fibers. The sinus node is located at the junction of the superior cava vein with the right atrium and has a pacemaking function. The atrio-ventricular node originates in the inferior wall of the right atrial within the so called triangle of Koch, demarcated by the ostium of the coronary sinus, a fibrous structure denominated tendon of Todaro and the hinge of the septal leaflet of the tricuspid valve. The apex of this triangle consisted of the atrio-ventricular component of the membranous septum. In the membranous septum, the atrio-ventricular node continues into the bundle of His, which penetrates the surrounding fibrous tissue and emerges at the crest of muscular septum. After a variable distance, it gives off the left bundle branch which further divides into 2 fascicles, and continues into the right bundle branch[113, 114]. While the right bundle branch becomes subendocardial in the distal half of the ventricular septum, anterior and posterior fascicles of the left bundle branch run in the surface of left ventricular septum. Both bundles branches end in the fibers of Purkinje at the cardiac apex[115, 116] (Figure 3-1).

In the course of the membranous septum and crest of the muscular septum, the His bundle and left bundle branch have a close anatomical proximity to the aortic valve and, in fact, the origin of the left branch lies below the commissure between the right and non-coronary cusps, 2-3 mm below the attachment of the aortic valve leaflets [114, 115, 117-119] (Figure 1-6). In this region the left brunch is superficial, just under the endocardium.
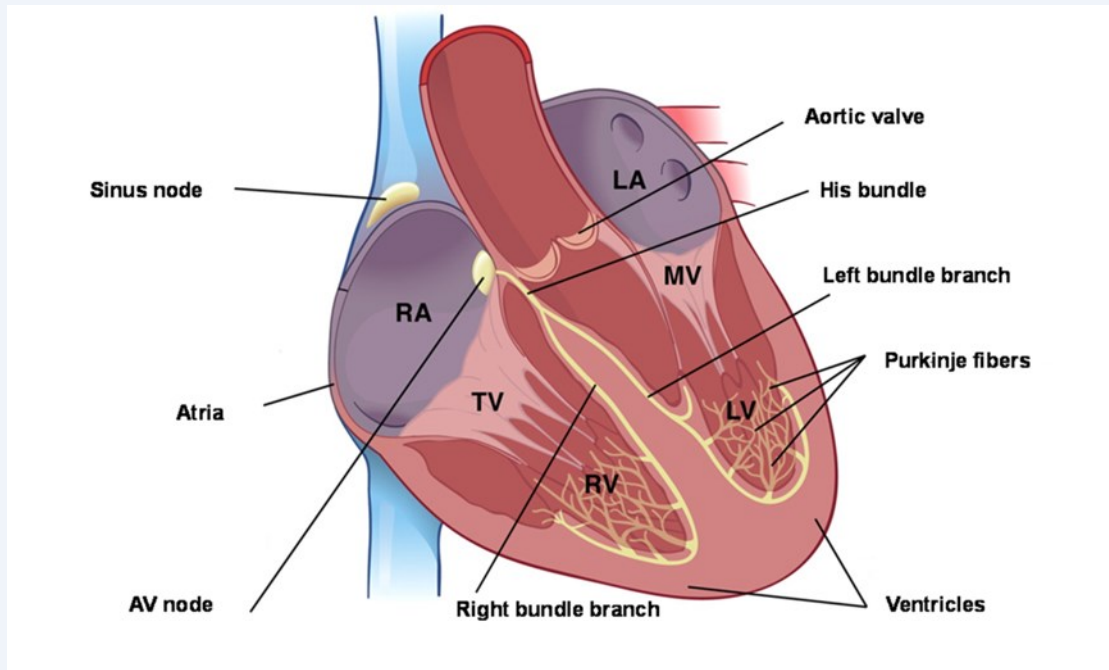
Figure 3-1. **Anatomy of the conduction system**

From Munshi NV. Gene regulatory networks in cardiac conduction system development. Circ Res. 2012;110:1525-1537.

The normal cardiac stimulus originates in the sinus node, and is conducted through atrial fibers, the atrio-ventricular node, His, right and left branches to the apex of the both ventricles allowing the simultaneous contraction of both ventricles. In normal conditions, the atrioventricular node is the sole connection between the atria and the ventricles and its main function is to delay and to limit the number of atrial impulses reaching the ventricle. In addition, the atrioventricular node may act as pacemaker in cases of blocks above in the conduction system. AF results from the uncoordinated electrical activity of atria. An interruption or a delay of conduction in one of such components leads to the occurrence of conduction disturbances, which can be detected on electrocardiographic registries.

3.1.2. Atrial Fibrillation

AF is the most common arrhythmia and its incidence is increasing with the aging of the population. AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation and consequently ineffective atrial contraction.[120] Its prevalence increases with age, and more than third of patients with AF are 80 years or older.[120, 121] In addition, factors increasing the risk of AF are: structural heart disease, in particular heart failure, coronary artery disease and valve heart disease, and comorbidities such as hypertension, diabetes, anemia, chronic kidney disease or chronic obstructive pulmonary artery disease.[122]

AF might be classified as paroxysmal, persistent, long-standing persistent and permanent according to the duration of episodes, and valvular or non-valvular according to the presence of rheumatic mitral stenosis, biological or mechanical bioprosthesis and mitral valve repair.[122]

AF has been associated with increased mortality,[123] congestive heart failure[124] and cerebrovascular events.[125] Overall, AF increases the stroke risk of 5-fold. The attributable risk of ischemic stroke related to AF increases with age, and compared with non-AF–related strokes, strokes related to AF are associated with higher mortality and greater disability.[125] Beyond age, several comorbidities increase the risk of stroke in patient with AF. It has led to the development of scores of risk for the prediction of stroke. The most common used are the $CHADS_2$ (1 point for congestive heart failure, hypertension, age >75 years, diabetes mellitus and 2 points for stroke)[126] and the CHA_2DS_2-VASC scores (1 point for age $\geq$65 years, female sex, congestive heart failure, diabetes mellitus and vascular disease and 2 points for age>75 and stroke/thromboembolism).[127]

In patients with AF, anticoagulation therapy dramatically reduces the risk of cerebrovascular events.[128]

3.1.3. Atrio-ventricular Block and Cardiac Pacing

AVB is a disorder in which atrial impulses are conducted with a delay or are not at all conducted to the ventricles at a time when the AV conduction pathway is not physiologically refractory.[129] The incidence of AVB incidence increases with age.

AVB are classified according to electrocardiographic criteria as first degree, second degree or third degree, and according to anatomical criteria as supra, intra or infrahisian blocks.[130] A first degree AVB is defined as a prolongation of PR interval > 200 ms and each P wave is followed by a QRS complex. A second-degree AVB is characterized by prolongation of PR with a single intermittent P wave non-conducted, which may be preceded and followed from variable PR interval type I or constant PR, type II. Advanced second-degree AV block refers to the blocking of 2 or more consecutive P waves with some conducted beats, which indicates some preservation of AV conduction. The third degree or complete AVB is characterized for the failure of each P-wave or each atrial impulse to conduct resulting in complete atrioventricular dissociation with atrial rates higher than ventricular ones and frequently bradycardia.
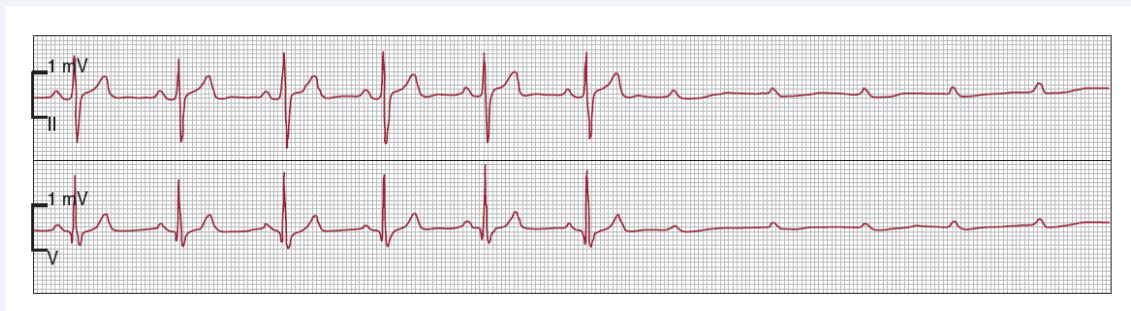
FIGURE 3-2. Paroxysmal third-degree atrioventricular block

From Vogler J et al. Rev Esp Cardiol. 2012;65(7):656–667

The anatomical location of the block may be at the level of the AV node, the His, and the right and left bundles branches. Such arrhythmias might be permanent or paroxysmal, and patients may be asymptomatic or have severe symptoms.

The diagnosis mostly relay upon electrocardiographic findings. However in patients with paroxysmal events, prolonged ECG monitoring might be necessary.

Strong evidence suggests that cardiac pacing improves survival in patients with advanced degree AV or complete permanent AVB. The indication of a permanent pacemaker relies on the presence of symptoms, the anatomical location of the block, and the occurrence

of potentially reversible causes. In the contrary, most patients with first degree AVB do not require treatment beyond treating potentially reversible causes.[130]

More than 700,000 permanent pacemakers (PPM) are implanted annually worldwide.[131] Three types of PPM are currently used: dual-chamber with atrial and ventricular pacing and sensing, single-chamber pacemakers with ventricular or atrial pacing, and biventricular pacing with right and left ventricular pacing. In patients with AVB, dual-chamber pacing is more frequently used because these devices maintain atrio-ventricular synchrony, which translate into a reduction in the incidence of AF and heart failure and an improvement in quality of life.[132] However, this physiological pacing has not proven to be superior over non-physiological pacing in terms on mortality.

Strong evidence supports a deleterious effect of long-term apical pacing on ventricular function which has been associated with an increased risk of mortality or heart failure[2-4] or the occurrence of pacing-induced cardiomyopathy.[133] The myocardial activation from the apex to the base may induce an electrical and mechanical dyssynchrony which results in an increased sympathetic activation, abnormalities in myocardial perfusion and impaired cardiac output and endothelial function.[133] The clinical impact of such changes seems to depend on the pre-existing myocardial condition and reserve.

3.1.4. Left Bundle Branch Block

Current recommendations define left bundle branch block (LBBB) as a prolongation of the QRS > 0.12 seconds with the following electrocardiographic criteria (Figure 3-2).[134]
- Broad notched or slurred R wave in leads I, aVL, V5, and V6 and an occasional RS pattern in V5 and V6 attributed to displaced transition of QRS complex.
- Absent q waves in leads I, V5, and V6, but in the lead aVL, a narrow q wave may be present in the absence of myocardial pathology.
- R peak time greater than 60 ms in leads V5 and V6 but normal in leads V1, V2, and V3, when small initial r waves can be discerned in the above leads.
- ST and T waves usually opposite in direction to QRS.
- Positive T wave in leads with upright QRS may be normal (positive concordance).

FIGURE 3-3. Electrocardiographic record showing a left bundle branch block

The electrical and mechanical activation of LV in patients with LBBB is similar to that observed in patients with cardiac pacing and, thus, similar hemodynamic changes and structural alterations are expected.[135] Furthermore, the induction of LBBB by radiofrequency in experimental models was associated with an immediate redistribution of myocardial blood flow and systolic circumferential shortening which translated into a reduction in LV ejection fraction and an increased volume of the LV cavity.[136]

This intraventricular asynchrony associated with LBBB is an independent predictor of severe cardiac events in patients with heart failure. Indeed, in the Framingham study the onset of LBBB was associated with heart failure symptoms[137] and several studies have shown an increased mortality in patients with LBBB.[138, 139] Moreover, a progression to complete AVB has been reported, although the risk is low.

3.2. RHYTHM AND CONDUCTION DISORDERS AND CALCIFIC AORTIC STENOSIS

3.2.1. Aortic Stenosis and Rhythm and Conduction Disorders

The close anatomical relationship between AS and the conduction system translates into a frequent association between aortic valve disease itself and conduction abnormalities.[140-147] The occurrence of conduction disorders has been observed in up to 30% of patients with AS, most of them involving the His bundle and left bundle branch[142] and it has been associated with the extension of calcium from the aortic valve into the conduction system.[148]

Although predictors of conduction disorders in patients with severe AS remain to be elucidated, it has been suggested that an older age,[141] a greater severity of AS,[147] extensive calcification of the aortic valve and left ventricular septum,[141, 142, 147] left ventricular dysfunction,[141, 146] and severe calcification of the mitral annulus might be associated with the occurrence of conduction abnormalities.[144]

The clinical relevance of such disorders remains unknown. However, some studies have suggested that the occurrence of conduction disturbances, specifically AVB, might explain some of the symptoms observed in these patients, such as syncope,[147] or even being asymptomatic due to the high rate of paroxysmal events.[145] This might might lead to overlook these conduction disorders unless continuous electrocardiogram (ECG) monitoring is performed,[149] which frequently occurs after cardiac interventions.

AF occurs in ~5% of patients[150, 151] with AS, with an annual incidence of 1.2% and it has been associated with an increased risk of stroke and heart failure.[151]

3.2.2. Surgical Aortic Valve Replacement and Conduction Disorders

The calcium accumulated on the aortic valve may reach the bundle of His and the left bundle branch, leading to a conduction delay and a higher vulnerability to trauma, such as that occurring during cardiac surgery.[142] Indeed, pathological studies have demonstrated the presence of both acute traumatic and acute no traumatic lesions on the conduction system,

specifically on the His bundle and left bundle branch, after surgical AVR. Acute traumatic lesions are more frequently associated with the occurrence of new conduction abnormalities and are due to laceration by sutures, residual calcific material of the aortic annulus and compression by the seat of the prosthesis.[152]

The incidence of new conduction disturbances, new-onset LBBB and the need of PPM, following surgical AVR has been reported in up to 16-33% and 2-11% of patients respectively. [142, 153-160] Nonetheless, new conduction defects may occur later during the follow-up period[72, 142, 161, 162] and up to 50% of these conduction abnormalities may resolve days after the cardiac surgery. [153, 162, 163] Indeed, current guidelines recommend a PPM implantation in patients with postoperative AVB, which persists at least 7 days after cardiac surgery and/or is not expected to recover.[164]

Given that the presence of LBBB has been classically considered a marker of poorer long-term survival in patients with pre-existing cardiac disease[135, 137] and even in apparently healthy individuals,[135] the impact of new conduction abnormalities after surgical AVR has been matter of concern. Several studies have suggested that the development of new conduction disorder, particularly new-onset LBBB might be associated with increased risk of late sudden cardiac death [155, 160, 165, 166] mainly owing to the progression to complete AVB[155]. Nonetheless, other studies have failed to show any impact of perioperative new-onset LBBB on mortality.[153, 167] The relatively limited sample size of all these studies, differences between studies regarding inclusion criteria (transient versus persistent new-onset LBBB) and study design, and the considerable variability in the length of follow-up may partially explain these discrepancies. Main characteristics of studies assessing the impact of new-onset LBBB after cardiac surgery are shown in Table 3-1.

Although evidence is scarce, the need of PPI has not been found to have a negative impact on overall mortality of patients undergoing surgical AVR (Table 3-2)[158, 168] in opposition to the overall population. Reasons for such discordances are unknown. However, the late-term pacing and the limited follow-up (maximal of 7 years) might explain these discordances. In a study including 6,268 patients undergoing AVR replacement, only 40% of patients requiring PPM had long-term pacing.[157]

TABLE 3-1. Main Characteristics of Studies Assessing the Impact of New-Onset LBBB after Cardiac Surgery

Studies n	Conduction disturbances	Media/Mean follow-up (years)	Impact
Fournial et al. (1979)[153] N=200	Any new conduction disturbances of the left bundle branch	4	None
Santinga et al. (1980)[167] n=16 sudden death and 49 controls	Any new conduction defect at the postoperative ECG	-	None
Thomas et al. (1982)[160] n=133	Any new conduction disturbances of the left bundle branch	2.6	Overall mortality Sudden death
Penta et al. (1984)[166] n=140	Any new conduction disturbances of the left bundle branch	10	Overall mortality
Foppl et al. (1989)[165] n=599	Prior or post LBBB	4.7	Sudden death
El-Khally et al. (2004)[155] n=262	Any persistent new-onset BBB Persistent new onset-LBBB	4.2	Combined endpoint of Sudden death, AVB and Syncope

AVB: atrioventricular block, BBB: bundle branch block, LBBB: left bundle branch block.

TABLE 3-2. Studies Assessing the Impact of Pacemaker Implantation on Mortality after Cardiac Surgery

Author, year (Ref. #)	n	Intervention	Age (years)	LVEF (%)	Incidence PPM (%)	Mean/ median follow-up (years)	Results
Bagur et al, 2011[158]	780	SAVR	77 ± 4	60 ± 13	3.2	3.3	4 vs. 26%, $P = 0.12$
Razza et al, 2011[168]	6,268	Any cardiac surgery	66 ± 10	50 ± 10	2.2	7.2 ± 5	Adjusted HR: 1.30, $P = 0.17$

HR: hazard ratio; LVEF: left ventricular ejection fraction; SAVR: surgical aortic valve replacement

3.2.3. Transcatheter Aortic Valve Replacement and Rhythm and Conduction Disorders

Advanced age and comorbidities such as hypertension, diabetes, obesity, heart failure or AS are associated with an increased risk of AF,[169] conduction defects[144] or need of PPM implantation.[21, 140, 170] Nowadays, patients undergoing TAVR are old, have severe AS and heart failure, and frequently present severe comorbidities such those aforementioned. Although arrhythmic events occur frequently after TAVR (approximately in 1/3 of patients),[171, 172] both AF and conduction defects may be paroxysmal and asymptomatic or lead to identical symptoms that those of AS, being detected for the first time during ECG monitoring after TAVR procedures. This might have led to overestimate the rate of arrhythmic complications after TAVR.

3.2.3.1. AF and TAVR

Pre-existing AF is a frequent finding in candidates for TAVR with a mean prevalence of ~30%. [173, 174] It has been associated with the occurrence of late cardiovascular events (CVE) after TAVR. The incidence of new-onset AF following TAVI is ~10-15%. Larger atrial size and transapical approach are associated with a higher risk of new-onset AF after TAVR. As for pre-existing AF, the occurrence of new-onset AF has been associated with increased rate of stroke.[173, 174]

3.2.3.2. New-onset LBBB after TAVR

Main studies reporting the incidence and predictors of new-onset LBBB are displayed in Table 3-3. New-onset LBBB has been reported in 29% to 72% of the patients following TAVR with a CV device,[175-190] and in 12% to 18% with ESV implantation.[149, 177, 178, 185, 189, 191, 192] This wide difference between both valves might be explained by the characteristics of the bioprosthesis. Despite no differences exists in radial force for the recommended ratio annulus/size of prosthesis between both devices,[193] the longer skirt of self-expandable valves penetrates deeper into the LV outflow tract which might lead to a mechanical trauma to the conduction system. In fact, the depth of device implantation has been the only reported independent predictor of new-onset LBBB,[189] regardless of the device used and a distance of 6 mm from the aortic annulus to the ventricular end of the prosthesis has been proposed as a

cut-off for the development of LBBB and the need of PPM.[186] Others predictors are: the use of CoreValve system, male sex, prior myocardial infarction, annulus/prosthesis ratio, preprocedural right bundle branch blockand valve expansion.[180, 181, 186, 188, 189, 191]

It has been described that a considerable proportion of new-onset LBBB resolves days after TAVR, although with differences between bioprosthesis: while in up to 60% of patients undergoing Edwards SAPIEN/SAPIEN XT devices[191, 192] new-onset LBBB may resolve within the first month following the procedure, only up to 30% of new-onset LBBB induced by CoreValve devices resolves over time.[175, 181, 182] Nuis et al. showed that about 50% of new conduction abnormalities observed in patients undergoing TAVR occur before valve implantation secondary to wire manipulation or balloon valvuloplasty,[175] which might explain the transitory nature of these conduction abnormalities when the frame of the valve does not exert a compression force on the conduction system.

TABLE 3-3. Incidence and Predictors of New-Onset LBBB

Studies n	Approach	Valve Type	Baseline conduction disturbances (n)	Incidence* n (%)	Predictors of LBBB
Sinhal et al. (2008)[149] n=106	TF	ESV	LBBB: 12 RBBB: 9 PPM: 0	7 (6.6)	NA
Gutierrez et al. (2009)[191] n=33	TA	ESV	LBBB: 3 RBBB: 2 PPM: 4	6 (18.2)	Depth of implantation
Godin et al. (2010)[192] n=69	TF in 54 TA in 15	ESV	LBBB: 10 RBBB: 7 PPM: 0	9 (13.1)	NA
Erkapic et al. (2010)[177] n=50	TA in 14 TF in 36	ESV in 14 CV in 36	LBBB: 5 RBBB: 7 PPM: 0	15 (30)	NA
Koos et al. (2011)[178] n=80	TA in 22 TF in 58	ESV in 22 CV in 58	LBBB: 8 RBBB: 6 PPM: 0	20 (25)	NA
Aktug et al. (2011)[189] n=154	TA in 82 TF in 72	EVS in 82 CV in 72	LBBB: 15 RBBB: NA PPM: 10	13 (16) in ES 27 (38) in CV	Depth of implantation Use of CoreValve Annulus ratio
Roten et al. (2011)[185] n=67	TA in 26 TF in 41	ESV in 26 CV in 41	LBBB: 13 RBBB: 11 PPM: 0	3 (12) in ES 12 (29) in CV	NA
Berry et al. (2007)[176] n=11	TF	CV	NA	4 (36)	NA
Piazza et al. (2008)[119] n=39	TF	CV	LBBB: 6 RBBB: 2 PPM: 1	16 (41)	Depth of implantation
Calvi et al. (2009)[179] n=24	TF	CV	LBBB: 0 RBBB: 0 PPM: 0	11 (45.8)	NA
Baan et al. (2010)[180] n=25	TF	CV	LBBB: 0 RBBB: 0 PPM: 0	18 (72)	Depth of implantation

Continued

Study	Approach	Valve	Conduction abnormalities	New PPM or conduction abnormalities n (%)*	Predictors
Ferreira et al. (2010)[182] n=18	TF	CV	LBBB: 0 RBBB: 0 PPM: 0	11 (61.1)	NA
Haworth et al. (2010)[183] n=33	TF	CV	LBBB: 3 RBBB: 13 PPM: 1	16 (48.5)	NA
Piazza et al. (2010)[181] n=44	TF	CV	LBBB: 7 RBBB: 2 PPM: 1	14 (31.8)	Male sex Previous myocardial infarction Pre-procedural RBBB Frame expansion Depth of implantation
Ussia et al. (2010)[194] n=108	TF	CV	LBBB: NA RBBB: NA PPM: 10	43 (39.0)	NA
Fraccaro et al. (2011)[187] n=64	TF	CV	LBBB: 9 RBBB: 8 PPM: 0	28 (43.7)	Male sex, Pre-procedural RBBB Depth of implantation
Guetta et al. (2011)[184] N=70	TF	CV	LBBB: 17 RBBB: 11 PPM: 0	33 (47.1)	NA
Khawaja et al. (2011)[188] n=185	TF	CV	LBBB: 0 RBBB: 0 PPM: 0	105 (56.8)	Aortic stenosis Absence of RBBB Native valve
Nuis et al. (2011)[175] N=65	TF in 64 SC in 1	CV	LBBB:6 RBBB: 1 PPM:6	40 (61.5)	NA
Rubín et al. (2011)[190] n=18	TF	CV	LBBB:2 RBBB: 1 PPM: 0	9 (50)	NA

*Including patients with prior conduction abnormalities

CV: CoreValve, ESV: Edwards SAPIEN valve, LBBB: left bundle branch block, NA: not available, PPM: permanent pacemaker implantation, RBBB: right bundle branch block, SC: subclavian, TF: transfemoral, TA: transapical.

Nonetheless, most studies included patients with preexisting bundle branch block and sometimes prior pacemaker (Table 3-3), which might have led to underestimate the real incidence of postoperative conduction disturbances. In addition, little is known about the temporary changes in conduction disturbances in patients undergoing a balloon-expandable valve implantation. Also, it is unknown whether predictors of persistent new-onset LBBB might be different from ones of transient LBBB and no evidence exists on the clinical impact of new-onset LBBB after TAVR. This might be of utmost importance since it has been described that up to 17% of deaths within the first 30 days and 10% deaths between 30-days and 1 year following TAVR are classified as sudden cardiac or unknown death.[195, 196]

A small study showed a lack of improvement in LV ejection fraction in patients undergoing CoreValve device implantation developing new conduction disturbances (including new-onset LBBB and PPM) vs. a marked improvement in patients without new conduction abnormalities.[197] However whether this different evolution on LV ejection fraction might be translated into progression or development of clinical heart failure or mortality after TAVR remains unknown.

3.2.3.3. Permanent Pacemaker Implantation after TAVR

Incidence and predictors of PPI have been widely reported. Up to 10% of patients undergoing TAVR using an Edwards SAPIEN/SAPIEN XT and 49% of patients with a CoreValve device implantation require in-hospital or 30-day PPM.[80, 81, 86, 88, 119, 149, 175, 177-185, 187, 188, 190-192, 194, 198-209] Main studies reporting incidence and predictors of PPI in patients without prior PPI are showed in Table 3-4.

The most frequent clinical indications for PPM are complete or high degree of AVB in up to 70% of cases, followed by prophylactic indication due to trifascicular block or LBBB and 1st degree AVB in up to 21% of patients and slow AF and disease of the sinus node in ~ 4% and 2%,[185, 187, 206] respectively.

Although the mechanistic basis of new onset complete AVB after TAVR has not been demonstrated, pathological findings have suggested that a mechanical trauma might be an important factor.[210] As for the occurrence of new-onset LBBB, the depth of implantation is a recognized factor associated with the need of PPM. Other independent predictors are: age, preexisting RBBB, the use of the CV, intraprocedural AVB, LBBB with left-axis deviation,

interventricular-septum thickness (>17 mm), noncoronary cusp thickness (>8 mm), female sex, LV ejection fraction, landing-zone calcification, peri-implantation AVB, balloon predilatation, peri-implantation QRS duration, the use of a 29 mm and prosthesis septal-wall thickness (Table 3-4). [177, 178, 184, 187, 188, 202, 204, 206, 211]

Whether the need of PPM might be associated with a clinical impact is unknown, and it is of utmost importance since outside the field of cardiac surgery, strong evidence supports the potential negative impact of right ventricular apical pacing, which has been associated with an increased rate of the combined endpoint of mortality and rehospitalization due to heart failure in patients with LV dysfunction,[212-214] ventricular tachyarrhythmias[215, 216] and pacing-induced cardiomyopathy in patients without overt structural heart disease.[133]

TABLE 3-4. Incidence and Predictors of Permanent Pacemaker Implantation in Patients without Prior to Pacemaker Implantation from Studies Reporting the Rate of Permanent Pacemaker at Baseline

Studies n	Approach	Valve Type	In-hospital/ 30-day Incidence n (%)	Predictors of PPI
Sinhal et al. (2008)[149] n=106	TF	ESV	7 (6.6)	NA
Gutierrez et al. (2009)[191] n=29	TA	ESV	0	NA
Webb et al. (2009)[198] n=143	TA in 45 TF in 98	ESV	5 (11.1) in TA 5 (5.1) in TF	NA
Dworakowski et al. (2010)[199] n=140	TA in 77 TF in 63	ESV	5 (6.4) in TA 3(4.7) in TF	NA
Godin et al. (2010)[192] n=69	TF in 54 TA in 15	ESV	3 (4.3)	NA
Leon et al. (2010)[80] n=118	TF	ESV	6 (5.0)	NA
Rodés-Cabau et al. (2010)[86] n=332	TA (NA) TF (NA)	ESV	17 (5.1)	NA
Walter et al. (2010)[200]	TA	ESV	9 (10.1)	NA

N=89				
Ye et al. (2010)[201] n=71	TA	ESV	6 (8.5)	NA
D'Ancona et al. (2011)[202] n=322	TA	ESV	20 (6.2)	Age Absence of coronary disease
Smith et al. (2011)[81] n=276	TF (NA) TA (NA)	ESV	13 (4.7)	NA
Bleiziffer et al. (2010)[203] n=159	ESV in 36 CV in 123	44 (27.7)	NA	NA
Erkapic et al. (2010)[177] n=50	TA in 14 TF in 36	ESV in 14 CV in 36	1 (7.1) in ESV 16 (44.4) in CV	RBBB CoreValve device
Koos et al. (2011)[178] n=80	TA in 22 TF in 58	ESV in 22 CV in 58	0 in ESV 17 (21.3) in CV	CoreValve device RBBB
Roten et al. (2010)[185] n=67	TA in 26 TF in 41	ESV in 26 CV in 41	3 (11.5) in ESV 20 (48.7) in CV	RBBB CoreValve Amiodarone use Betablocker use Valvuloplasty balloon size HTA
Etchaninoff et al. (2011)[209] n=209	TA in 71 TF in 160 SC in 12	ESV in 145 CV in 64	9 (6.2) 20 (31.3)	NA
Piazza et al. (2008)[186] n=38	TF	CV	7 (18.4)	NA
Calvi et al. (2009)[179] n=25	TF	CV	6 (24)	NA
Jilahiawi et al. (2009)[204] n=34	TF	CV	10 (33.3)	Left-axis deviation LBBB with left-axis deviation Interventricular septum >17mm Non coronary cusp thickness> 8mm Heart-rate limiting medication

Baan et al. (2010)[180] n=34	TF	CV	7 (20.6)	Left ventricular outflow tract diameter Left-axis deviation Mitral annular calcification Postimplantation effective-orifice area
Bekeredjian et al. (2010)[205] n=59	TF	CV	28 (47.5)	NA
Latsios et al. (2010)[206] n=67	TF	CV	32 (47.8)	Left ventricular ejection fraction QRS duration Agatston score
Piazza et al. (2010)[181] n=43	TF	CV	7 (16.3)	QRS duration Interventricular septum thikness
Ferreira et al. (2010)[182] n=27	TF	CV	8 (29.6)	Depth of implantation
Haworth et al. (2010)[183] n=29	TF	CV	8 (27.5)	RBBB Annulus diameter
Munoz-Garcia et al. (2010)[207] n=61	TF	CV	21 (34.4)	HTA RBB Dilatation of ascending aorta Depth of implantation
Ussia et al. (2010)[194] n=98	TF	CV	21 (21.4)	NA
Fraccaro et al. (2011)[187] n=64	TF	CV	25 (39.1)	Male sex RBBB Depth of implantation
Guetta et al. (2011)[184] N=70	TF	CV	28 (40)	RBBB Pulmonary hypertension Depth of implantation
Khawaja et al. (2011)[188] n=243	TF	CV	82 (33.7)	Male sex Interventricular septum diameter Left-axis deviation RBBB Prolonged QRS duration

				Peri-implantation AVB Calcification below the aortic valve
Nuis et al. (2011)[175] N=65	TF in 64 SC in 1	CV	14 (21.5)	NA
Rubín et al. (2011)[190] n=18	TF	CV	4 (22.2)	NA
Tamburino et al (2011)[88] n=621	TF	CV	108 (17.4)	NA

CV: CoreValve, ESV: Edwards SAPIEN/SAPIEN XT valve, LBBB: left bundle branch block, NA: not available, PPI: permanent pacemaker implantation, RBBB: right bundle branch block, SC: subclavian, TF: transfemoral, TA: transapical.

Adapted from Bax JJ et al. Open issues in transcatheter aortic valve implantation.Part1: patient selection and treatment strategy for transcatheter aortic valve implantation. E Heart J 2014; 35: 2627–2638

CHAPTER 4. HYPOTHESES AND OBJECTIVES

4.1. HYPOTHESIS

4.1.1. General hypothesis

The general hypothesis of this study is that the occurrence of new conduction abnormalities after TAVR, mainly new-onset LBBB and PPM requirements are associated with increased risk of late mortality.

4.1.2. Specific hypotheses

1. A significant proportion of bradyarrhythmic, and tachyarrhythmic events or conduction disorders detected after TAVR are not related to the procedure per se but already existed before the TAVR procedure.
2. The inclusion of patients with pre-existing conduction abnormalities (especially LBBB and PPM implantation) in prior studies has led to underestimate the real risk of new conduction disorders after TAVR.
3. The evolution of conduction disturbances after TAVR using balloon-expandable valves is different to that reported for self-expandable devices.
4. New-onset persistent LBBB after TAVR is a predictive factor of PPM implantation during long-term follow-up and is associated with an increased risk of overall mortality.
5. PPM implantation following TAVR is not associated with late mortality, but it may be associated with hospitalizations due to heart failure.
6. Both, the need of PPM and the occurrence of new-onset LBBB have a deleterious effect on LV ejection fraction.

4.2. OBJECTIVES

General objective

The primary objective of these studies series was to determine the impact of new-onset persistent- LBBB (NOP-LBBB) and PPM implantation after TAVR on late mortality.

4.2.1. .Specific objectives

1. To investigate the prevalence of pre-existing conduction abnormalities and AF in TAVR candidates.
2. To study the real incidence and evolution of new conduction disturbances after TAVR.
3. To determine causes of late cardiac death in patients undergoing TAVR and to determine the impact of new conduction disorders on mortality after TAVR.
4. To assess the impact of NOP-LBBB on pacing requirements after TAVR.
5. To evaluate the impact of these new conduction abnormalities after TAVR on the evolution of LV function over time.

CHAPTER 5- Article 1

Arrhythmia Burden in Elderly Patients with Severe Aortic Stenosis as Determined by Continuous ECG Recording: Towards a Better Understanding of Arrhythmic Events Following Transcatheter Aortic Valve Replacement

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5.1. RESUME

Contexte: Le but de cette étude était d'évaluer la prévalence des arythmies non diagnostiquées chez les candidats à un TAVR et de déterminer leur impact sur le traitement et les événements rythmiques au décours de la procédure.

Méthodes et Résultats: Un total de 435 candidats à un TAVR ont subi 24 heures de surveillance électrocardiographique (ECG) continue la veille de la procédure. Des arythmies diagnostiqués de novo ont été observées chez 70 patients (16,1%) avant le TAVR: fibrillation auriculaire paroxystique (FA)/tachycardie auriculaire (TA) chez 28, bloc auriculo-ventriculaire (BAV) de haut degré ou bradycardie sévère chez 24, tachycardie ventriculaire non soutenue chez 26 et bloc de branche gauche (BBG) intermittent chez 3 patients. Tous les événements rythmiques sauf un étaient asymptomatiques et ont conduit à une modification thérapeutique chez 43% des patients. Chez les patients sans FA/TA connue, l'apparition d'FA/TA pendant la surveillance ECG de 24 heures a été associée à un taux plus élevé d'événements vasculaires cérébraux à 30 jours (7.1% vs. 0.4%, $P = 0.030$). Parmi les 53 patients atteints d'une nouvelle FA/TA après TAVR, 30.2% avaient une FA paroxystique/TA diagnostiquée avant la procédure. Chez les patients qui ont eu besoin d'un pacemaker permanent après la procédure (n = 35), 31.4% avaient un BAV de haut degré ou une bradycardie sévère avant le TAVR. Un BBG de novo persistant à la suite du TAVR est survenu chez 37 patients et 8.1% d'entre eux avaient un BBG intermittent avant la procédure.

Conclusions: Des arythmies diagnostiquées de novo ont été observées chez environ un cinquième des candidats au TAVR, ont conduit à un taux accru d'événements vasculaires cérébraux et représentaient un tiers des événements rythmiques suivant la procédure. Cette charge élevée d'arythmie souligne l'importance d'un diagnostic précoce des événements rythmiques chez ces patients afin de débuter les mesures thérapeutiques appropriées sans retard.

5.2. ABSTRACT

Background: This study aimed to evaluate the prevalence of previously undiagnosed arrhythmias in candidates for TAVR and to determine its impact on therapy changes and arrhythmic events following the procedure.

Methods and Results: A total of 435 candidates for TAVR underwent 24-hour continuous electrocardiographic (ECG) monitoring the day before the procedure. Newly diagnosed arrhythmias were observed in 70 patients (16.1%) before TAVR: paroxysmal AF/atrial tachycardia (AT) in 28, advanced atrio-ventricular block (AVB) or severe bradycardia in 24, non-sustained ventricular tachycardia in 26, and intermittent left bundle branch block (LBBB) in 3 patients. All arrhythmic events but one were asymptomatic, and led to a therapy change in 43% of patients. In patients without known AF/AT, the occurrence of AF/AT during 24-hour ECG recording was associated with a higher rate of 30-day cerebrovascular events (7.1% vs. 0.4%, P=0.030). Among the 53 patients with new-onset AF/AT after TAVR, 30.2% had newly diagnosed paroxysmal AF/AT before the procedure. In patients who needed permanent pacemaker implantation following the procedure (n=35), 31.4% had newly diagnosed advanced AVB or severe bradycardia before TAVR. New-onset persistent LBBB following TAVR occurred in 37 patients, 8.1% of whom had intermittent LBBB before the procedure.

Conclusions: Newly diagnosed arrhythmias were observed in about a fifth of TAVR candidates, led to a higher rate of cerebrovascular events and accounted for a third of arrhythmic events following the procedure. This high arrhythmia burden highlights the importance of an early diagnosis of arrhythmic events in such patients in order to implement the appropriate therapeutic measures earlier on.

5.3. INTRODUCTION

The occurrence of new conduction abnormalities and the need for permanent pacemaker implantation (PPI) are frequent complications of transcatheter aortic valve replacement (TAVR), and may potentially jeopardize the use of this technology in a lower risk and younger population.[217, 218] In addition to the aortic stenosis itself, it has been shown that advanced age and comorbidities such as heart failure, hypertension and diabetes, all of them very frequent in candidates for TAVR, are associated with a high prevalence of left bundle branch block (LBBB) and severe bradyarrhythmias, irrespective of TAVR.[143, 219-223] Furthermore, it is well known that these conduction disorders may be paroxysmal and asymptomatic[224] or lead to symptoms similar to those of aortic stenosis, and the occurrence of these abnormalities may therefore be overlooked unless electrocardiographic (ECG) monitoring is undertaken. However, most candidates for TAVR undergo ECG monitoring for the first time only during and immediately after the TAVR procedure.

The occurrence of new-onset AF following TAVR has been reported in 10% to 30% of patients.[225] It is widely known that AF is frequently paroxysmal and subclinical, and the occurrence of an embolic event might be its first manifestation.[226] As for the occurrence of conduction disorders, the high prevalence of risk factors for AF in the TAVR population may lead to a high prevalence of subclinical AF[227] which may go undiagnosed in the absence of ECG continuous monitoring. The objectives of this study were therefore i) to evaluate the prevalence and predictors of previously unknown paroxysmal arrhythmias (bradyarrhythmias and tachyarrhythmias) or transient conduction disorders in patients with severe aortic stenosis who are candidates for TAVR, and ii) to determine the influence of detecting silent arrhythmias before TAVR on both therapy changes and the real incidence of arrhythmic events attributable to the TAVR procedure.

5.4. METHODS

5.4.1.   Study population

A total 435 patients with symptomatic aortic stenosis candidates for TAVR in 6 different centers were included. All centers but one enrolled consecutive patients into the study. Patients were eligible for TAVR if they were considered to be at high or prohibitive surgical risk as evaluated by the heart team composed of interventional cardiologists and cardiac surgeons. TAVR procedures were performed using both balloon- and self-expanding valves as previously reported.[99] The approach was selected according to the suitability of iliofemoral access, calcification and disease of ascending aorta, and proximity of previous left internal mammary artery graft to the sternum and operators' expertise. Echocardiographic and/or fluoroscopy guidance was used in all procedures. Unfractionated heparin was used during all procedures, with an initial dose of 100 U/Kg, subsequently adjusted to maintain an activated clotting time ≥300 ms. After the procedure, anticoagulation was partially or totally reversed (protamine) and anti-vitamin K agents were started within the 24-48 hours following the procedure in patients with an indication for chronic anticoagulation therapy. All studies were performed in accordance with the local Ethics Committee of each center, and all patients signed informed consent forms before the procedures. Data were prospectively entered in a dedicated database at each center.

5.4.2. 24-Hour Continuous ECG Monitoring

Patients were admitted to the hospital the day before the TAVR procedure. A 12-lead ECG was obtained at hospital admission and 24-hour continuous ECG monitoring was carried-out thereafter. ECG monitoring was performed by means of telemetry systems with constant surveillance by trained nurses or Holter monitors[228] in 407 (93.4%) and 28 (6.4%) patients, respectively. The occurrence of symptoms during arrhythmic events was assessed. All events were recorded and telemetry strips were further analyzed by a cardiologist at each center.

All TAVR procedures were performed with ECG monitoring and arrhythmic events were prospectively collected. Patients were on continuous ECG monitoring at least 72 hours after TAVR[229] and an ECG was performed daily until hospital discharge. Physicians in charge

of patients were aware of the ECG monitoring findings and were responsible for the changes in treatment if warranted. PPI was indicated if third-degree or advanced second-degree atrio-ventricular block (AVB) at any anatomical level occurred and was not expected to resolve, or in the presence of sinus node dysfunction and documented symptomatic bradycardia, according to current recommendations.[230] The indication and duration of anticoagulation therapy in newly detected AF was left at the discretion of the physician responsible for the patient.

5.4.3. Definitions

Paroxysmal AF was defined as any irregular atrial rhythm with absence of consistent p waves and atrial tachycardia (AT) as a period of sudden rapid and regular atrial rhythm with identifiable p waves.[231] Non-sustained ventricular tachycardia (VT) was defined as runs of ≥ 3 ventricular beats at a heart rate of >100 beats per minute lasting < 30 seconds.[232] When ventricular runs lasted ≥ 30 seconds it was classified as sustained VT.[232] Advanced atrio-ventricular block (AVB) was defined as 2:1 second-degree or higher AVB.[228] Severe bradycardia was defined as heart rate<40 bpm.[130] New-onset persistent left bundle branch block (NOP-LBBB) was defined as a new-onset LBBB which persisted at hospital discharge in patients. Thirty-day clinical events were defined according to the Valve Academic Research Consortium-2 (VARC-2).[112]

5.4.4. Statistical Analysis

Qualitative variables were expressed as absolute values (percentage) and compared using Fisher exact test when comparisons involved more than 2 groups or Chi-Square or Fisher exact test as appropriate otherwise. Quantitative variables are displayed as mean ± standard deviation or median (25-75 percentile) according to variable distribution and were analyzed by means of two-sample t-test or Wilcoxon rank sum test as appropriate for comparisons between two groups and 1-way analysis of variance or Kruskal-Wallis 1-way analysis of variance if comparisons involved >2 groups. The Tukey test for multiple comparisons was used if statistical significance was achieved. A multivariate logistic regression model was used for the analysis of independent predictors of newly diagnosed events. Variables with *P* value<0.10 in the univariate analysis were included in the model. Variables included were

male, CHADS2 score, CHA2DS2-VASc score, Logistic EuroSCORE, left ventricular ejection fraction [LVEF] and mean transaortic gradient. The results were considered significant with two-sided p-values <0.05. Analyses were conducted using the statistical package SAS, version 9.2 (SAS Institute Inc., Cary, NC)

5.5. RESULTS

5.5.1. Baseline Characteristics

Baseline clinical and echocardiographic characteristics of the study population are shown in Table 5-1.

TABLE 5-1. Baseline clinical and echocardiographic characteristics of the study population

	N=435
Clinical Characteristics	
Age (years)	81 ± 8
Male	218 (50.1)
Hypertension	379 (87.1)
Diabetes mellitus	144 (33.1)
COPD	111 (25.5)
eGFR <60 ml/min	248 (57.0)
Coronary artery disease	267 (61.4)
CHADS$_2$	2 (2-3)
CHA$_2$DS$_2$-VASc score	4 ± 1
Logistic EuroSCORE (%)	21.7 ± 15.0
STS-PROM score (%)	7.3 ± 5.4
Echocardiography	
LVEF (%)	57 (45-60)
Mean gradient (mmHg)	45 ± 18

Values are expressed as n (%), mean (±SD) or median (25-75th percentile).
CHADS2: stroke risk index which assigns 1 point each for any of the following: recent CHF, hypertension, age 75 years or older, and DM and 2 points for a history of stroke or TIA; CHA$_2$DS$_2$-VASc score: cardiac failure or dysfunction (1), hypertension (1), age ≥75 (2), age 65–74 (1), diabetes (1), stroke (2), vascular disease (1), and female(1); COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular

Overall, 62 patients (14.3%) had permanent pacemaker before TAVR and 169 patients (38.9%) a history of paroxysmal/chronic AF/AT. Both, permanent pacemaker and history of AF/AT were encountered in 36 (8.3%) of such patients.

5.5.2. Prevalence and Predictors of Previously Unknown Arrhythmias before TAVR

During the 24-hour ECG monitoring before TAVR, paroxysmal arrhythmias or transient conduction disorders were encountered in 102 patients (23.4%) and were classified as follows: paroxysmal AF/AT in 59 patients (13.6%), advanced-AVB or severe bradycardia in 24 patients (5.5%), sustained or non‑sustained ventricular tachycardia in 27 patients (6.2%). Of these, the arrhythmic events had been previously diagnosed in 32 patients (31.3%), and newly diagnosed arrhythmias were detected in 70 patients (68.7%, 16.1% of the study population). The newly diagnosed arrhythmic events encountered during ECG monitoring before TAVR are shown in Table 5-2.

TABLE 5-2. Previously unknown arrhythmic events observed during 24-hour ECG monitoring before transcatheter aortic valve replacement (n=435)

	N (%)
Overall	70 (16.1)
Tachyarrhythmias	
Paroxysmal AF/AT	28 (6.4)
Non-sustained ventricular tachycardia	26 (6.0)
Sustained ventricular tachycardia	0
Bradyarrhythmias	24 (5.5)
Advanced AVB	12 (2.8)
Sinus node dysfunction/severe bradycardia	12 (2.8)
Intermittent LBBB	3 (0.7)

Values are expressed as n (%), mean (±SD) or median (25-75th percentile). AF: AF, AT: atrial tachycardia, AVB: atrio-ventricular block, LBBB: left bundle branch block

Previously unknown paroxysmal AF/AT was encountered in 28 patients (10.5% of patients without known AF/AT), advanced AVB in 12 patients (3.2% of patients without prior PPI), sinus node dysfunction/severe bradycardia in 12 patients (3.2% of patients without prior PPI), non-sustained VT in 26 patients (6.0%), and intermittent LBBB in 3 patients (0.9% of patients without pre-existing LBBB or pacing). A total of 8 patients (11.4% of patients with previously unknown events) had more than one type of arrhythmia diagnosed during the 24-hour ECG monitoring. The mean duration of AF/AT episodes was of 2.6 ± 5.8 hours. When considering only AF, the mean duration of episodes was of 1.9 ± 4.2 hours. No symptoms were reported in all but 1 patient, who had shortness of breath related to paroxysmal AF episodes. A change in therapy was indicated in 30 patients (42.9%; 56.6% of patients with newly diagnosed paroxysmal AF/AT or advanced-AVB or severe bradycardia): a change in medical therapy in 25 patients (35.7%) and PPI in 5 patients (7.1%) (Figure 5-1). Individual characteristics of patients with newly diagnosed arrhythmias and the therapy recommended following its diagnosis are shown in Supplemental Table 5-1.

Baseline clinical and echocardiographic characteristics of the study population grouped according to the occurrence of newly diagnosed arrhythmias or transient conduction disorders, previously known arrhythmias and no arrhythmias are shown in Table 5-3. Patients with newly diagnosed arrhythmias (vs. known or no arrhythmias) were more frequently male (65.7% vs. 46.8%, P=0.004), had a higher $CHADS_2$ score (3 [2-3] vs. 2 [2-3], P <0.001) and a trend towards a higher CHA_2DS_2-VASc score (4 ± 2 vs. 4 ± 1, $P = 0.095$) and Logistic EuroSCORE ($25.0 \pm 15.8\%$ vs. $21.2 \pm 14.8\%$, $P = 0.093$). They also had a lower LVEF (50 [37-55]% vs. 60 [49-60]%, $P < 0.001$) and a lower mean transaortic gradient (38 ± 15 mmHg vs. 46 ± 18 mmHg, $P = 0.003$). In the multivariate logistic regression analysis, a higher $CHADS_2$ score ([odds ratio: 2.42 [1.35-4.34], $P = 0.003$ for each unit increase), and a lower LVEF (odds ratio: 1.23 [1.09-1.40], P< 0.001 for each decrease of 5%) were independent predictors of the occurrence of newly diagnosed arrhythmias.

Also, a trend towards a lower transvalvular mean gradient (OR: 1.22 [1.00-1.52], $P = 0.051$ for each decrease of 10 mmHg) was observed in patients with newly diagnosed arrhythmias.
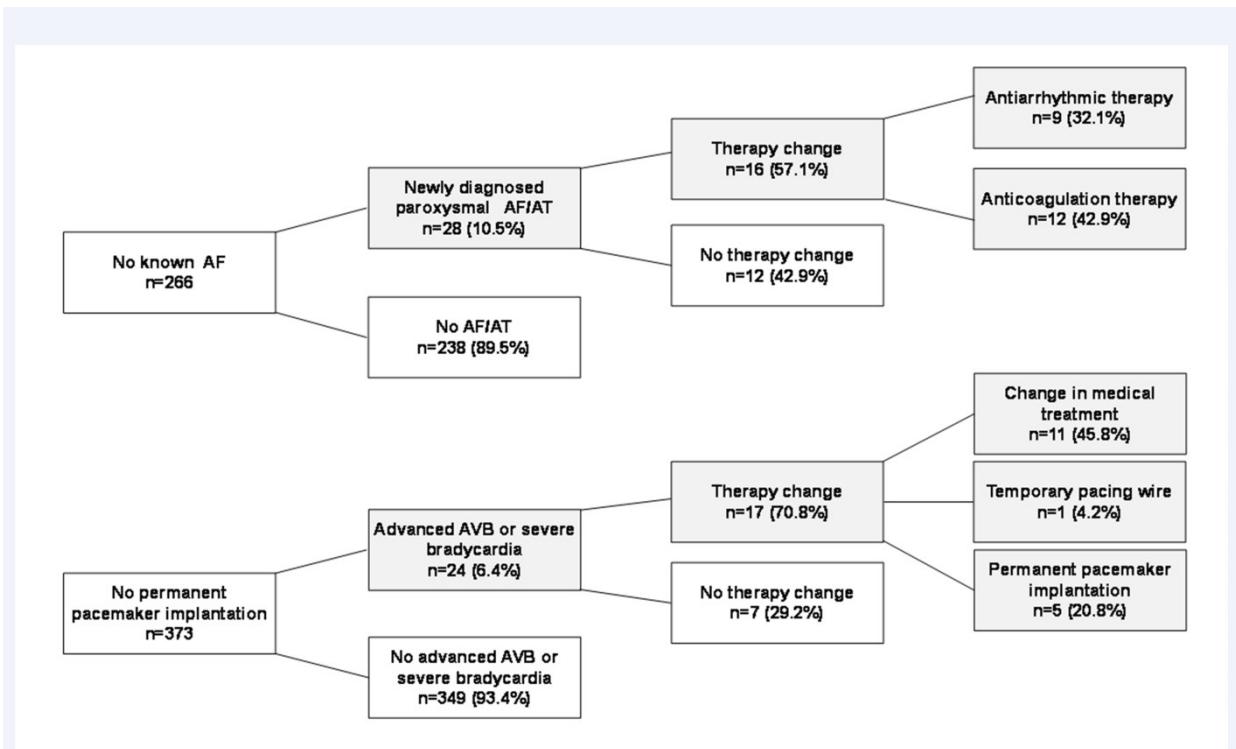
FIGURE 5-1. Newly diagnosed events and therapy changes

Patients with newly diagnosed AF/AT and advanced AVB or severe bradycardia during 24-hour ECG monitoring leading to a change in medical therapy or an indication of PPI

AF: AF, AT: atrial tachycardia, AVB: atrio-ventricular block, PPI: permanent pacemaker implantation

5.5.3. Arrhythmic Events Following TAVR

Procedural findings and 30‑day clinical outcomes for the study population overall, and according to the diagnosis of previously unknown arrhythmias during ECG monitoring pre-TAVR are shown in Table 5-4. Most patients (>90%) in both groups received a balloon-expanding valve. No significant differences were observed in procedural characteristics between groups ($P > 0.4$ for all). There were no differences between groups regarding 30-day mortality. A higher rate of cerebrovascular events was observed among patients with newly

TABLE 5-3. Baseline Clinical and Echocardiographic Characteristics of the Study Population, According to Newly Diagnosed Arrhythmias, Known Arrhythmias and No Arrhythmias Groups

	Newly Diagnosed Arrhythmias (n=70)	Previously Known Arrhythmias (n=179)	No Arrhythmias (n=186)	*P* value
Clinical Characteristics				
Age (years)	81 ± 8	82± 7	80 ± 10	0.101
Male	46 (65.7)	85 (47.5)	86 (46.2)*	0.015
Hypertension	60 (85.7)	163 (91.1)	156 (83.9)	0.169
Diabetes mellitus	24 (34.3)	54(30.2)	66 (35.5)	0.530
COPD	16 (22.9)	47 (26.3)	48 (25.8)	0.892
eGFR <60 ml/min	39 (55.7)	105 (58.7)	104 (55.9)	0.839
Coronary artery disease	49 (70.0)	108 (60.3)	110 (59.2)	0.288
$CHADS_2$ (%)	3 (2-4)	2 (2-3) ‡	2 (2-3)*	<0.001
CHA_2DS_2-VASc score (%)	4 ± 2	4 ± 1	4 ±1	0.080
Logistic EuroSCORE (%)	25.0 ± 15.8	23.0 ± 15.1	19.0 ± 14.0*	0.028
STS-PROM score (%)	7.6 ± 5.0	7.8 ± 6.1	6.6 ± 4.8	0.220
Echocardiography				
LVEF (%)	50 (37-55)	60 (45-60) ‡	60 (50-60)*	<0.001
Mean gradient (mmHg)	38 ± 15	46 ± 18	46 ± 19*	0.004

*P<0.05 vs. newly diagnosed arrhythmias; †P<0.05 vs. known arrhythmias; ‡P <0.05 vs. newly diagnosed arrhythmias.
Values are expressed as n (%), mean (±SD) or median (25-75th percentile). Abbreviations as in table5-1

diagnosed arrhythmias before TAVR, although this differences were non-significant (5.7% vs. 1.6% in the group without newly diagnosed arrhythmias, *P* = 0.062; Figure 5-2A). Among the

266 the patients without known AF/AT, the rate of stroke or transient ischemic attack at 30 days was 7.1% in patients with newly diagnosed AF/AT before TAVR compared to 0.4% among patients without new episodes of AF/AT (P = 0.030; Figure 5-2B). The 2 patients with newly diagnosed AF/AT during the 24-hour ECG monitoring who had a stroke post-TAVR had not received anticoagulation therapy upon the diagnosis of the arrhythmia. After the

TABLE 5-4. Procedural and 30‑Day Outcomes, According to Newly Diagnosed Arrhythmias during the 24-Hour ECG Monitoring Before TAVR

	Newly Diagnosed Arrhythmias (n=70)	Known Arrhythmias (n=179)	No Arrhythmias (n=186)	*P* value
Procedural findings and 30-day outcomes				
Device success*	55 (78.6)	143 (79.9)	144 (77.4)	0.948
Approach				
Transapical/Transaortic	22 (31.4)	63(35.2)	65 (34.9)	0.866
Transfemoral/Subclavian	48 (68.6)	116 (64.8)	121 (65.1)	
Prosthesis type				
Self-expanding	6 (8.6)	11 (6.1)	16 (8.6)	0.632
Balloon-expandable	64 (91.4)	168 (93.9)	170 (91.4)	
≥Moderate AR	12 (17.1)	24 (13.4)	29 (15.6)	0.832
30-day death	4 (5.7)	10 (5.7)	8 (4.3)	0.801

*According to VARC-2: Absence of procedural mortality, correct positioning of a single prosthetic heart valve into the proper anatomical location and intended performance of the prosthetic heart valve (no prosthesis–patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, and no moderate or severe prosthetic valve regurgitation. Values are expressed as n (%), mean (±SD) or median (25-75th percentile). AR: aortic regurgitation

detection of AF, antiarrhythmic therapy had been started in both patients and normal sinus rhythm was observed on ECG at the time of the cerebrovascular event, which
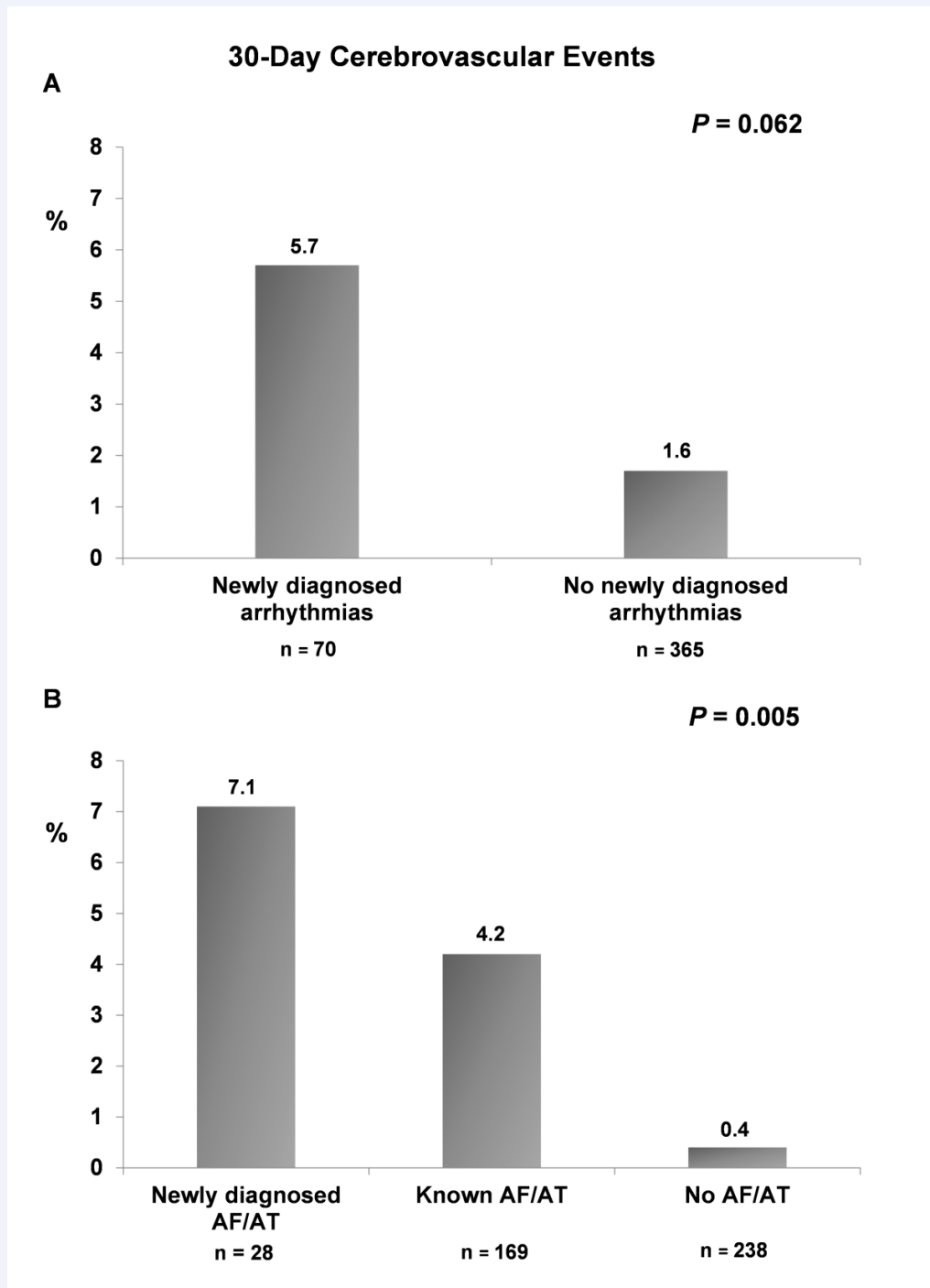
FIGURE 5-2. Cerebrovascular events within the 30 days following TAVR

(A) Thirty-day cerebrovascular events according to the occurrence of newly diagnosed arrhythmias during the 24-hour ECG monitoring

(B) Thirty-day cerebrovascular events according to the occurrence of newly diagnosed AF/AT during the 24-hour ECG monitoring

occurred 8 and 9 days after the TAVR procedures. The timing of stroke within 30 day following TAVR is shown in Figure 5-3A. In patients with newly diagnosed arrhythmias during ECG monitoring, 75% of strokes occurred $\geq$ 72 hours after TAVR, whereas in those patients with no newly previously known AF/AT and no AF/AT 33% of strokes occurred $\geq$ 72 hours after the procedure ($P = 0.197$) (Figure 5-3B). The rate of sub-acute stroke ($\geq$ 72 hours after TAVR) was of 4.3% and 0.6% in patients with diagnosed arrhythmias and without newly diagnosed arrhythmia ($P = 0.032$). No differences were observed in the rate of strokes occurring during the first 24 hours after TAVR between the 2 groups (1.4 vs. 1.1%, $P = 0.589$).

A total of 125 arrhythmic events or conduction disturbances were diagnosed following TAVR, and of these, 26 events (20.8%) had already been diagnosed during the 24-hour ECG monitoring before TAVR. New-onset AF/AT following TAVR was observed in 53 patients after TAVR (12.2%, 19.9% of patients with no history of AF/AT). Previously unknown AF/AT had been encountered in 16 of these patients (30.2%) during the 24-hour ECG monitoring pre-TAVR. Patients with newly diagnosed episodes of AF/AT before TAVR had a much higher rate of AF/AT episodes following TAVR (57.1% vs. 10.4%, OR: 11.50, 95% CI: 5.05-26.16, $P < 0.001$; Figure 5-4). Thirty five patients required a PPI following TAVR (8.0%, 9.5% of patients with no PPI pre-TAVR), and of these, 11 patients (31.4%) had silent episodes of advanced AVB or severe bradycardia during 24-hour ECG monitoring before the procedure. In addition, PPI occurred more frequently in patients with episodes of advanced AVB/severe bradycardia during 24-hour ECG monitoring pre-TAVR (45.8% vs. 5.8%, OR: 12.64, 95% CI: 5.19-30.80, P < 0.001) (Figure 5-4). NOP-LBBB was encountered in 37 patients after TAVR (8.5%, 10.6% of patients at risk). Of these, 3 patients (8.1%) had episodes of intermittent LBBB during 24-hour ECG monitoring, and all of them developed NOP-LBBB following TAVR (100% vs. 8%, $P = 0.001$) (Figure 5-4).
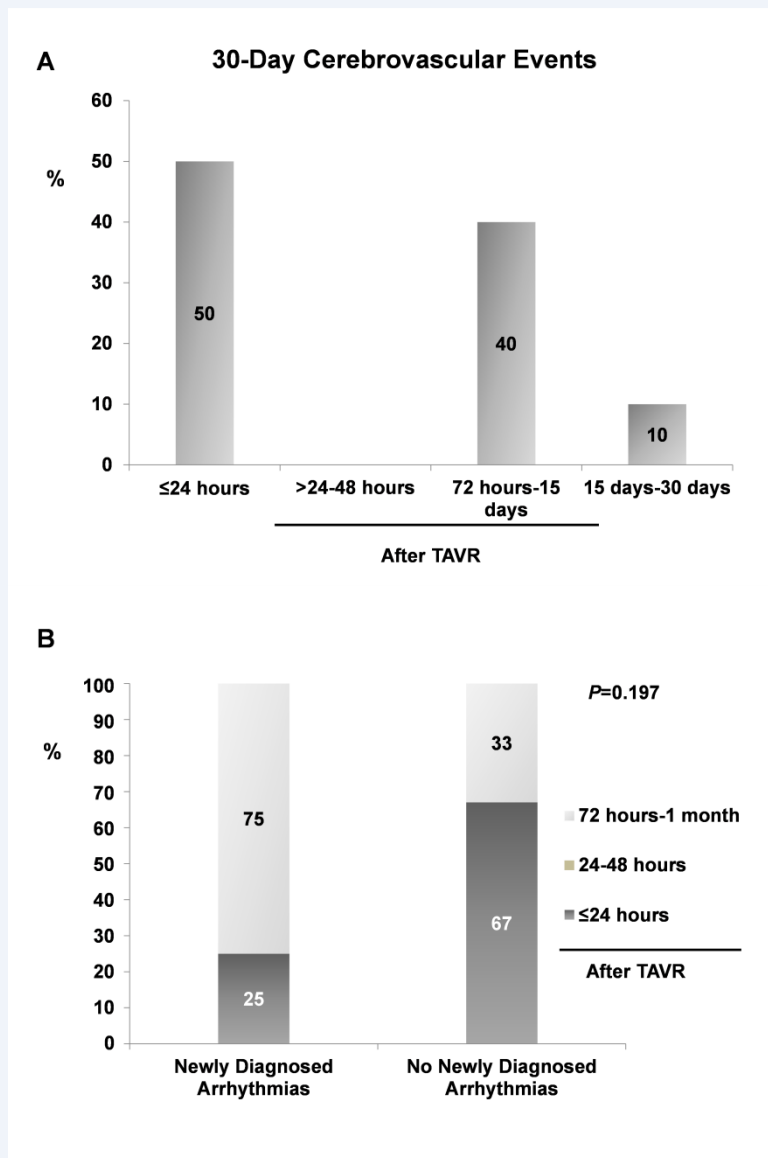
FIGURE 5-3. Timing of cerebrovascular events within the 30 Days following TAVR

(A) Timing of 30-day cerebrovascular events in the study population

(B) Percent 30-day cerebrovascular events occurring ≤24 hours, 24-48 hours and ≥72 hours in patients with newly diagnosed AF/AT and those without

A. Patients with Arrhythmic Events post-TAVR
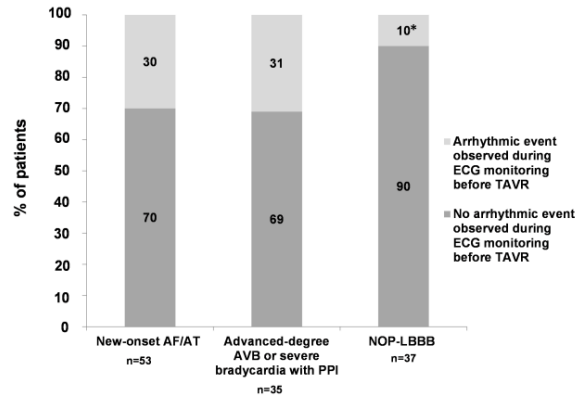
B. Overall Population (n=435)
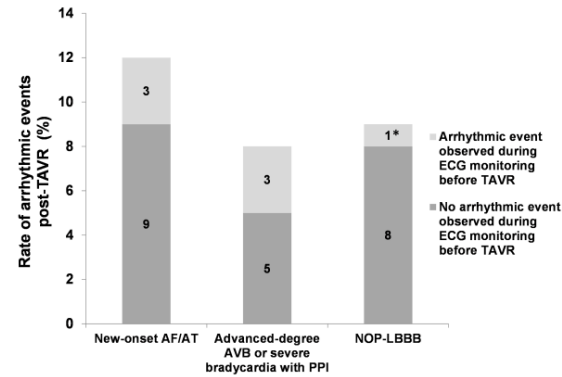
C. Patients Without Known Arrhythmia before TAVR
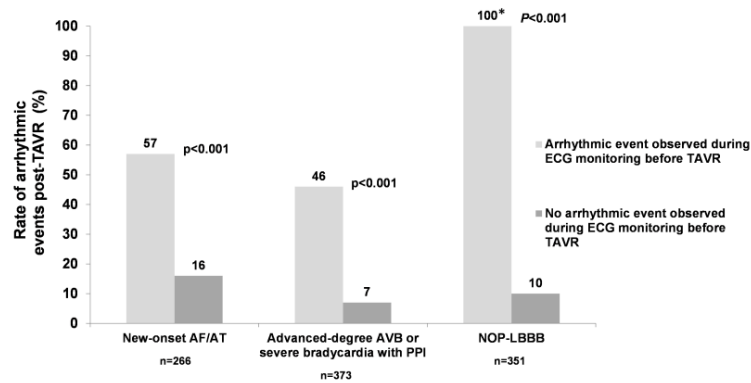
* Intermittent LBBB

FIGURE 5-4. Arrhythmic events before (24-hour ECG monitoring) and following TAVR

A.   Patients with new-onset AF/AT, advanced AVB or severe bradycardia requiring PPI or NOP-LBBB following TAVR, according to the occurrence of newly diagnosed arrhythmic events during the 24-hour ECG monitoring before the procedure.

B.   Total and "real" incidence of new-onset AF/AT, new advanced AVB or severe bradycardia requiring PPI and NOP-LBBB after TAVR.

C.   Incidence of new-onset AF/AT, advanced AVB or severe bradycardia requiring PPI and NOP-LBBB after TAVR according to the occurrence of previously unknown arrhythmias during 24-hour ECG monitoring before TAVR among patients at risk for each type of arrhythmia.

5.6. DISCUSSION

Previously unknown paroxysmal arrhythmias or transient conduction disturbances, most of them asymptomatic, were encountered in up to 16.1% of candidates for TAVR as evaluated by a 24-hour ECG monitoring before the procedure. These newly diagnosed arrhythmic events led to changes in treatment in about half of the patients, and were more frequently observed in patients with a higher $CHADS_2$ score and a lower LVEF. In about a third of patients with episodes of AF/AT or advanced AVB or severe bradycardia requiring PPI following TAVR, the presence of these arrhythmic events had already been diagnosed during the 24-hour ECG monitoring before the procedure, leading to a significant reduction in the occurrence of arrhythmias directly attributable to the TAVR procedure. About 1 out of 10 patients with NOP-LBBB following TAVR had paroxysmal episodes of LBBB before the procedure. Finally, the occurrence of AF/AT during the 24-hour ECG monitoring before the procedure was associated with an increased rate of cerebrovascular events post-TAVR.

There is evidence supporting the frequent association between aortic stenosis and conduction disturbances, supraventricular and ventricular arrhythmias.[143, 219, 233, 234] Several mechanisms have been proposed to explain this association: first, the deposit of calcium on the conduction system as result of its proximity to the aortic valve complex[148] and the development of left ventricular dysfunction, both of which have been associated with the occurrence of LBBB and advanced AVB in patients with aortic stenosis;[146] second, the increase in left ventricular pressure overload leading to left ventricular hypertrophy and left atrium overload.[234] Indeed, in addition to aortic stenosis, candidates for TAVR nowadays usually have a high co-morbidity burden which further increases the risk of arrhythmic events and conduction disorders.[143, 219-223, 227, 235] In fact, and consistent with previous studies, [85, 86, 236, 237] 38% of patients included had known AF/AT and 14.3% of them had advanced AVB or severe bradycardia with PPI before TAVR. In addition, previously unknown events were encountered in nearly 1 out of 5 patients during 24-hour ECG monitoring, leading to a real prevalence of AF/AT and advanced AVB or severe bradycardia before TAVR (previously and newly diagnosed) in this study of 45% and 17%, respectively. This represents one of the highest rates of supraventricular arrhythmias ever reported in TAVR patients.[85, 86, 236, 237] It is well known that 24-hour ECG monitoring has a relatively low sensitivity in the detection of paroxysmal arrhythmias,[238, 239] and this suggests that the rate of silent arrhythmic events in

TAVR candidates may be even higher. Nonetheless, no control group was available in this study, and the rate of unknown arrhythmias detected by ECG monitoring in an age- and risk-matched population without aortic stenosis might have been similar.

A lower LVEF and a higher CHADS2 score were associated with the occurrence of newly diagnosed arrhythmic events, attributable perhaps to a higher arrhythmia burden in these patients due to a more advanced stage of cardiac disease or a higher overall burden of disease. Previous studies have shown that the presence of left ventricular dysfunction in patients with aortic stenosis is associated with longer HV intervals[146] as well as with a higher incidence of ventricular tachycardia and AF.[233, 240] Likewise, a higher CHADS2 score has been associated with a higher prevalence of AF. [241]

Although the clinical impact of these previously unknown arrhythmias in TAVR candidates remains to be elucidated, short episodes of AF/AT have been associated with an increased risk of stroke in patients with implantable devices and in the overall population[226, 242] and the occurrence of ventricular arrhythmias and paroxysmal AVB have been described as predictors of sudden cardiac death and adverse cardiac events.[224, 234, 243] Interestingly, about 1 in 10 TAVR candidates had a change in therapy related to the diagnosis of previously unknown arrhythmic events, highlighting the importance of monitoring such patients before the TAVR procedures. Whether or not early therapy in patients with paroxysmal events may be associated with a potential benefit in patients undergoing TAVR should be evaluated in future studies. Also, the fact that no treatment was implemented in about 50% of the patients with newly diagnosed arrhythmias suggests that more data and clear guidelines are needed for the treatment of silent arrhythmic events in this group of patients.

Pre-existing AF and new-onset AF have been associated with an increased risk of stroke after TAVR,[244, 245] and the occurrence of previously unknown paroxysmal AF/AT may also be associated with an increased rate of 30-day stroke if anticoagulation therapy is not prescribed early on. In fact, the occurrence of AF/AT during 24-hour ECG recording was associated with an 18-fold increase in the rate of cerebrovascular events when compared to patients with no AF/AT and almost a two-fold increase when compared to patients with previously known AF/AT. Importantly, none of the patients with newly diagnosed AF and stroke had received anticoagulation therapy upon the detection of the arrhythmia, despite antiarrhythmic therapy had been started. Nonetheless, although these differences were significant, these results should be interpreted with caution due to the low number of events.

A total of 9 out of the 10 cerebrovascular events observed in this study occurred in patients with previously known or newly diagnosed AF/AT (before TAVR). Also, almost 1/3 of patients with new-onset AF/AT, which has been independently associated with the occurrence of sub-acute cerebrovascular events after TAVR in previous studies[244], had newly diagnosed AF/AT before TAVR and, therefore, AF/AT would have preceded the occurrence of cerebrovascular events in those cases. The temporal sequence between the presence of AF/AT and the occurrence of cerebrovascular events makes the causal association plausible. Also, the timing of such cerebrovascular events (after the initial 72 hrs) makes the contribution of procedural aspects such as catheter manipulation or valve implantation unlikely. However, considering the relatively low number of events, these data should be interpreted as hypothesis-generating and would have to be confirmed in larger studies in the future. Likewise, the occurrence of unknown AVB might have led to an increased rate of sudden cardiac death after TAVR if it occurs after the discontinuation of ECG monitoring.

The rates of new-onset AF, PPI and LBBB following TAVR have been reported in 30%, 12-49% and 18-65%, respectively, with wide differences across studies.[225, 246] Accordingly, ~20%, ~10% and ~11% of patients had new-onset AF, PPI and NOP-LBBB after TAVR in our study. However, ~ 1/3 of patients with new AF/AT or advanced AVB or severe bradycardia requiring PPI had this arrhythmia before the procedure as determined by 24-hour ECG monitoring, meaning that the real incidence of these events attributable to the TAVR procedure per se would in fact be reduced by about a third. This may have a major impact on the evaluation of these complications with different transcatheter valve systems, and highlight once again the importance of monitoring such patients before the procedure in order to have a more accurate idea of the real effect of transcatheter valves on the occurrence of arrhythmic events. Also, as expected, the occurrence of AF/AT and advanced AVB or severe bradycardia during 24-hour ECG monitoring was associated with a much higher risk of suffering the arrhythmic event following the procedure. Three patients also had intermittent LBBB before TAVR and all of them developed NOP-LBBB after the procedure. The presence of underlying disease of the conduction system might explain, at least in part, the fact that a significant proportion of these conduction disorders persist at hospital discharge, despite having appeared before valve implantation.[175]

5.6.1. Clinical implications

The results of this study suggest that performing continuous ECG monitoring for at least 24 hours before the TAVR procedure can be useful for detecting previously unknown paroxysmal arrhythmias, such as paroxysmal AF/atrial tachycardia and advanced degree of atrioventricular block and this, in turn, may translate into the implementation of specific therapies to prevent the complications associated with such arrhythmias (e.g. stroke, sudden death). Because of the potential major clinical benefit without increased risks and low cost, it seems reasonable to recommend the use of ECG monitoring for at least 24 hours before the TAVR procedures. In patients with newly detected arrhythmias, appropriate therapy according to current recommendations should be initiated promptly. Particularly in patients with newly diagnosed AF and high cardioembolic risk, anticoagulation therapy should probably be started (and continued indefinitely) early upon the detection of the AF episode in order to prevent the possible occurrence of cerebrovascular events after TAVR. Nonetheless, the optimal timing for the initiation of anticoagulation therapy in such patients needs to be determined on a patient-by-patient basis according to the risk of both bleeding and thromboembolic events. Also, this strategy may lead to a reduction in the length of hospital stays by allowing an earlier indication of definitive therapy (e.g. PPI in case of advanced AV block). Also, it would allow us to determine the real incidence of tachy- and brady-arrhythmias attributable to the transcatheter prosthesis and to the TAVR procedure itself, which may indeed be of major importance when evaluating newer transcatheter valve systems and/or new indications of TAVR (e.g. lower risk, younger patients). However, these recommendations need to be interpreted bearing in mind that it is a hypothesis-generating study regarding the association between newly diagnosed arrhythmias and cerebrovascular events and, therefore, these results would need to be confirmed in larger studies.

Limitations. All centers but one enrolled consecutive patients into the study and, therefore, some selection bias cannot be completely ruled out. The sensitivity of 24- hour ECG monitoring is low and the rate of unknown events might therefore be higher than reported. Telemetry strips or Holter recorders were analyzed by different cardiologists with no centralized laboratory, and consequently variations in the interpretation of these disorders cannot be ruled out. Also, although current recommendations for the treatment of arrhythmias were followed in all centers, the indication of therapy in patients with newly diagnosed events before and after TAVR was left to the discretion of the physician responsible for the patient

and some variability in the clinical decision-making process may have occurred. The results regarding the association between newly diagnosed arrhythmias and 30-day cerebrovascular events need to be interpreted with caution due to the relatively small number of events. More than 90% of patients included in this study underwent TAVR using a balloon-expanding valve system, and the results of the study regarding post-TAVR arrhythmias may not be applicable to patients receiving a self-expanding valve. Further studies will be needed in patients undergoing TAVR with a self-expanding valve system.

Conclusions

The occurrence of previously unknown paroxysmal arrhythmias and transient conduction disorders was very frequent in TAVR candidates and led to a significant overestimation of the real rate of new-onset AF, advanced AVB or severe bradycardia requiring PPI and NOP-LBBB following TAVR. The occurrence of previously unknown AF/AT was associated with a higher risk for cerebrovascular events. The diagnosis of these previously unknown events may have an impact on the rate of complications and the length of hospital stays following TAVR by allowing the implementation of prophylactic measures and an early indication of definitive therapy. Nonetheless, further studies with a larger number of patients are necessary to determine the best diagnostic and therapeutic strategies in patients with arrhythmic events.

5.7. FUNDING SOURCES

5.8. CONFLICT OF INTEREST DISCLOSURES

Dr. Josep Rodés-Cabau is consultant for Edwards Lifesciences and St-Jude Medical. Eric Dumont is consultant for Edwards Lifesciences. The rest of the authors had no conflict of interest to disclose.

SUPPLEMENTAL TABLE 5-1. Individual Characteristics of Patients with Unknown Events, Associated Symptoms and the Recommended Therapy

Age	Event	Symptoms	Recommended therapy	Anticoagulation therapy	CVE	CHADS$_2$
40	Non-sustained VT, paroxysmal AT/AF	None	None	None	No	1
64	Non-sustained VT	None	None	None	No	2
65	Paroxysmal AF/AT	None	None	None	No	1
65	Paroxysmal AF/AT, advanced degree AVB, Non-sustained VT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	1
66	Paroxysmal AF/AT	None	None	None	No	4
67	Non-sustained VT	None	None	None	No	1
72	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	3
72	Paroxysmal AF/AT	None	None	None	No	3
74	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	2
75	Advanced-degree AVB	None	Medical therapy	None	No	6
75	Paroxysmal AF/AT	None	None	None	No	4
76	Advanced degree AVB	None	Medical therapy	None	No	2
76	Non-sustained VT, intermittent LBBB	None	None	None	No	3
76	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	5
76	Severe bradycardia	None	Medical therapy	None	No	4
77	Non-sustained VT	None	None	None	No	3
77	Severe bradycardia	None	Medical therapy	None	No	3
77	Severe bradycardia , Non-sustained VT	None	Medical therapy	None	No	4
77	Non-sustained VT	None	None	None	No	4
78	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	5
78	Paroxysmal AF/AT	None	None	None	No	2
78	Paroxysmal AF/AT, Advanced-degree AVB, Non-sustained VT	None	PPI	None	No	4
79	intermittent LBBB	None	None	None	No	3
79	Severe bradycardia	None	Medical therapy	None	No	3
80	Non-sustained VT	None	None	None	No	2
80	Paroxysmal AF/AT, Non-sustained VT	None	None	None	No	4
80	Paroxysmal AF/AT	None	None	None	No	5
81	Non-sustained VT	None	None	None	No	3
81	Severe bradycardia	None	Medical therapy	None	No	3

81	Paroxysmal AF/AT, Non-sustained VT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	3
81	Severe bradycardia	None	None	None	No	3
81	Intermittent LBBB	None	None	None	No	3
82	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	3
82	Paroxysmal AF/AT	None	Medical therapy	None	No	3
82	Non-sustained VT	None	None	None	No	5
82	Advanced-degree AVB	None	PPI	None	No	2
83	Severe bradycardia	None	None	None	No	2
83	Non-sustained VT	None	None	None	No	3
83	Paroxysmal AF/AT	None	None	None	No	4
83	Paroxysmal AF/AT, Non- sustained VT	None	None	None	No	3
83	Non-sustained VT	None	None	None	No	1
84	Paroxysmal AF/AT	Shortness of breath	Medical therapy	None	Yes	2
84	Non-sustained VT , Severe bradycardia	None	PPI	None	No	3
84	Advanced-degree AVB	None	None	None	No	3
85	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	4
85	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	2
85	Paroxysmal AF/AT	None	Medical therapy	None	Yes	2
85	Severe bradycardia	None	Medical therapy	None	No	3
85	Severe bradycardia	None	Medical therapy	None	No	6
85	Paroxysmal AF/AT	None	None	None	No	6
85	Advanced-degree AVB	None	None	None	No	2
86	Non-sustained VT	None	None	None	No	3
86	Severe bradycardia	None	None	None	No	2
86	Non-sustained VT	None	None	None	Yes	5
87	Non-sustained VT	None	None	None	No	3
87	Advanced-degree AVB	None	PPI	None	No	2
87	Non-sustained VT	None	None	None	No	3
87	Advanced-degree AVB	None	PPI	None	No	3
87	Non-sustained VT	None	None	None	Yes	3
88	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	3
88	Advanced-degree AVB	None	Temporary pacing wire	None	No	3
88	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment with a target INR of 2-3	No	5
89	Severe bradycardia	None	Medical therapy	None	No	3
89	Advanced-degree AVB	None	None	None	No	2
89	Non-sustained VT	None	None	None	No	3
89	Advanced-degree AVB	None	None	None	No	6
90	Paroxysmal AF/AT	None	Medical therapy	Warfarin indefinitely with dose adjustment	No	2

				with a target INR of 2-3		
90	Non-sustained VT	None	None	None	No	3
92	Non-sustained VT	None	None	None	No	2
93	Paroxysmal AF/AT	None	None	None	No	3

AVB : atrio-ventricular block , AF: atrial fibrillation, AT : atrial tachycardia, CVE: cerebrovascular events, INR: international normalized ratio, LBBB : left bundle branch block, LVEF: left ventricular ejection fraction, PPI: permanent pacemaker implantation VT: ventricular tachycardia.

CHAPTER 6- Article 2

Predictive Factors and Long-Term Clinical Consequences of Persistent Left Bundle Branch Block Following Transcatheter Aortic Valve Implantation with a Balloon-Expandable Valve

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6.1. RESUME

Objectifs: Évaluer les facteurs prédictifs et la valeur pronostique du bloc de branche gauche (BBG) de novo chez les patients (subissant) traités par implantation d'une valve aortique transcathéter (TAVI) avec une valve déployée par ballonnet (BEV).

Contexte: Les facteurs prédictifs de la persistance du BBG (vs. transitoire ou absent) après un TAVI avec un BEV et ses conséquences cliniques sont inconnus.

Méthodes: Un total de 202 patients consécutifs sans troubles de conduction et sans pacemaker (PPM) traités par TAVI avec un BEV ont été inclus. Une surveillance électrocardiographique continue a été réalisée pendant l'hospitalisation ainsi qu'un ECG 12 dérivations quotidien jusqu'à la sortie de l'hôpital. Aucun patient n'a été perdu de vue au terme d'un suivi médian de 12 mois (6-24) et un ECG était disponible chez 97% des patients. Les critères d'implantation d'un PPM ont été limités à l'apparition d'un bloc auriculo-ventriculaire de haut degré (BAV) ou d'une bradycardie symptomatique sévère.

Résultats: Un BBG de novo a été observé chez 61 patients (30.2%) au décours immédiat du TAVI, résolutif chez 37.7% et 57.3% des patients à la sortie de l'hôpital et à 6 -12 mois de suivi, respectivement. La durée de base du QRS (P = 0.037) et la profondeur de la prothèse (P = 0.017) étaient des facteurs prédictifs indépendants de l'apparition d'un BBG persistant. La présence d'un BBG persistant à la sortie de l'hôpital a été associée à une diminution de la fraction d'éjection ventriculaire gauche (P = 0.001) et à un moins bon état fonctionnel (P = 0.034) à 1 an de suivi. Les patients ayant un BBG persistant sans PPM à la sortie de l'hôpital ont eu une incidence plus élevée de syncope (16.0% vs. 0.7%, P = 0.001) et de BAV complet nécessitant un PPM (20.0% vs. 0.7%, P < 0.001), mais sans impact sur la mortalité globale ou cardiaque pendant la période de suivi (P > 0.20 pour toutes). Un BBG de novo était le seul facteur associé à PPM après TAVI (P < 0.001).

Conclusion: Au moins 30% des patients sans troubles de la conduction développent un BBG de novo après TAVI avec une BEV, bien que transitoire chez plus d'un tiers d'entre eux. La durée du QRS et un positionnement plus ventriculaire de la prothèse sont associés à un taux plus élevé de BBG de novo persistant. Ce dernier entraine un risque plus élevé de progression

vers un BAV complet nécessitant l'implantation PPM, sans impact sur la mortalité globale à 1 an.

6.2. ABSTRACT

Objectives: This study evaluated the predictive factors and prognostic value of new-onset persistent left bundle branch block (LBBB) in patients undergoing transcatheter aortic valve implantation (TAVI) with a balloon-expandable valve.

Background: The predictors of persistent (vs. transient or absent) LBBB after TAVI with a balloon-expandable valve and its clinical consequences are unknown.

Methods: A total of 202 consecutive patients with no baseline ventricular conduction disturbances or previous permanent pacemaker implantation (PPI) who underwent TAVI with a balloon-expandable valve were included. Patients were on continuous electrocardiographic (ECG) monitoring during hospitalization and 12-lead ECG was performed daily until hospital discharge. No patient was lost at a median follow-up of 12 (range: 6 to 24) months, and ECG tracing was available in 97% of patients. The criteria for PPI were limited to the occurrence of high degree atrioventricular block (AVB) or severe symptomatic bradycardia.

Results: New-onset LBBB was observed in 61 patients (30.2%) after TAVI, and had resolved in 37.7% and 57.3 % of them at hospital discharge and at 6 to 12-months follow-up, respectively. Baseline QRS duration ($P = 0.037$) and ventricular depth of the prosthesis ($P = 0.017$) were independent predictors of persistent LBBB. Persistent LBBB at hospital discharge was associated with a decrease in left ventricular ejection fraction ($P = 0.001$) and poorer functional status ($P = 0.034$) at 1-year follow-up. Patients with persistent LBBB and no PPI at hospital discharge had a higher incidence of syncope (16.0% vs. 0.7%, $P = 0.001$) and complete AVB requiring PPI (20.0% vs. 0.7%, $P < 0.001$), but not of global or cardiac mortality during the follow-up period ($P > 0.20$ for all). New-onset LBBB was the only factor associated with PPI following TAVI ($P < 0.001$).

Conclusion: Up to 30% of the patients with no prior conduction disturbances developed new LBBB following TAVI with a BEV, although it was transient in more than one third. Longer baseline QRS duration and a more ventricular positioning of the prosthesis were associated with a higher rate of persistent LBBB, which in turn determined higher risks for complete AVB and PPI but not mortality, at 1-year follow-up.

6.3. INTRODUCTION

New-onset left bundle branch block (LBBB) is the most frequent conduction alteration associated with TAVI.[175, 179, 180, 185-189, 191, 192] Several studies have evaluated the predictive factors of new-onset LBBB following TAVI, but most of them have focused on patients undergoing TAVI with the self-expandable system (CoreValve, Medtronic Inc, Minneapolis, Minnesota). [175, 179, 180, 186-188] Furthermore, all studies to date have included patients with conduction disturbances prior to TAVI (including patients with prior pacemaker in some), which may indeed lead to a more difficult interpretation of the exact role of TAVI on the development of new conduction disturbances and its predictors. Importantly, while it has been shown that the vast majority of conduction disturbances occur during the TAVI procedure, a significant number resolve within the first days following the procedure, especially with the use of balloon-expandable valves. [191, 192] However, no data exist on the factors associated with persistent (vs. transient) new-onset LBBB following TAVI and its clinical consequences. It is therefore unknown whether patients leaving the hospital with a new LBBB following TAVI have a higher risk for clinical events, particularly new complete atrioventricular block (AVB) and/or sudden death.

The objectives of this study were therefore to: 1) determine the incidence and predictors of new-onset persistent LBBB in patients without baseline intraventricular conduction abnormalities undergoing TAVI with a balloon-expandable valve, and 2) evaluate the long-term prognostic significance of persistent LBBB in this population.

6.4. METHODS

6.4.1. Study population

Of 348 consecutive patients (Quebec Heart & Lung Institute: n = 263 patients, Vall d'Hebron hospital: n = 85), who underwent TAVI with a balloon-expandable Edwards SAPIEN or SAPIEN XT valve (Edwards Lifesciences, Irvine, CA) 146 patients were excluded because of the following reasons: prior pacemaker (n = 57), prior intraventricular conduction abnormalities (complete or incomplete right or left bundle branch block, n = 83), death or

conversion to open heart surgery before the first ECG (4 and 2 patients, respectively). The final study population consisted of 202 patients. Details about the TAVI procedure have been previously reported. [99] All baseline, procedural and post-operative data were prospectively recorded. Peri-procedural complications were defined according to the VARC criteria.[247] The degree of native aortic valve calcification was measured (Agatston units) in all patients who had non-contrast ECG-gated computed tomography (CT) prior to the procedure (n = 131, 65%). Patients underwent a transthoracic echocardiography at baseline, at hospital discharge, and at 6- to 12-month follow-up. The position of the transcatheter valve after implantation was evaluated by transesphageal echocardiography (long axis view) as previously described. [191]

6.4.2. ECG Data and Criteria for Pacemaker Implantation

ECG tracings were recorded at baseline (within 24 hrs prior to the procedure), immediately after the procedure and then every 24 hours up to hospital discharge. Furthermore, patients were on continuous ECG monitoring during the entire hospitalization period following the procedure. All ECG tracings were analyzed by a cardiologist blinded to clinical data. The diagnosis of intraventricular conduction abnormalities was based on AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. [134] The policies for PPI were in accordance to the ACC/AHA/HRS guidelines for device-based therapy of cardiac rhythm abnormalities. [164]

Transient LBBB was defined as the occurrence of new LBBB that resolved before hospital discharge. *Persistent* LBBB was defined as any new LBBB that persisted at hospital discharge. Those patients who developed LBBB after the procedure and required a PPI or died before hospital discharge (without proven resolution of the LBBB) were also included in the group of persistent LBBB.

6.4.3. Follow-up

Follow-up was carried out by clinical visits or phone contact at 30 days, 6 months, 1 year, and yearly thereafter. The minimum follow-up for the study population was of 6 months (median: 12 [6-24] months), and no patient was lost at follow-up. An ECG tracing was obtained at 6- to 12-month follow-up in 97% of the patients alive at that time point).

6.4.4. **Statistical Analysis**

Categorical variables were compared with Chi-square or Fisher's exact tests as appropriate. Continuous variables were compared using T-student or Wilcoxon rank sum test and one-way analysis of variance if comparisons involved >2 groups. A repeated measures model with interaction was used to compare the changes in LVEF at different time points between groups (persistent LBBB vs. absent or transient LBBB). Post-hoc comparisons were performed using the Tukey's test. The predictors of new-onset persistent LBBB (vs. absent or transient LBBB) were determined using a binary logistic regression model including variables with p-value ≤0.10 in the univariate analysis. Age, baseline QRS duration, and ventricular depth of the prosthesis were the variables included in the analysis. The predictors of significant LVEF changes over time were determined using a multivariate regression linear model including variables with p-value <0.10 in the univariate analysis. Hypertension, new-onset persistent LBBB and peak troponin T were the variables included in the analysis. Cumulative outcomes at 1-year follow-up were assessed by Kaplan-Meier estimates and compared using the log-rank test. A 30-day landmark analysis was also performed. The results were considered significant with p-values <0.05. All analyses were conducted using the statistical package SAS, version 9.2 (SAS Institute Inc, Cary, North Carolina, U.S.A.).

6.5. **RESULTS**

Baseline and procedural characteristics of the study population are shown in Table 6-1.

TABLE 6-1. Baseline and Procedural Characteristics of the Study Population (n=202)

Clinical characteristics	
Age (years)	80 ± 8
Female	121 (59.9)
Body mass index (kg/m^2)	27 ± 5
Hypertension	178 (88.1)
Diabetes mellitus	67 (33.2)
COPD	50 (24.8)
Coronary artery disease	118 (58.4)
eGFR (ml/min)	56.8 ± 23.0
Baseline treatment	
Beta-blockers	94 (46.5)
Calcium channel blockers	58 (28.7)
Amiodarone	13 (6.4)
STS-PROM score (%)	7.5 ± 3.7
ECG	
PR interval (ms)	174 ± 38
QRS duration (ms)	92 ± 10
Echocardiography	
LVEF (%)	57 ± 12
Mean gradient (mmHg)	47 ± 18
Aortic valve area (cm^2)	0.64 ± 0.22
Computed tomography	
Aortic valve calcification (Agatston units)	3227 ± 2121
Procedural findings	
Success	190 (94.1)
Approach	
Transapical	117 (57.9)
Transfemoral	85 (42.1)
Ratio valve prosthesis size/aortic annulus	1.17 ± 0.07
Prosthesis ventricular depth* (mm)	1.87 ± 2.62
In-hospital outcomes	

Death	14 (6.9)
Stroke	4 (2.0)
Myocardial infarction	2 (1.0)
Major bleeding	23 (11.4)
Major vascular complications	7 (3.5)
Pacemaker implantation	14 (6.9)
Hospitalization length (days)	7 (5-10)

*Distance between the hinge point of the mitral valve and the ventricular end of the valve prosthesis frame (TEE, long-axis view)

Values are expressed as n (%), mean (±SD) or median (25-75th percentile).

COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration ratio, STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; LVEF: left ventricular ejection fraction

6.5.1. New-Onset Conduction Disturbances and LBBB Following TAVI.

New-onset LBBB and overall conduction disturbances following TAVI are shown in Figure 6-1. New complete LBBB was observed in 57 patients (28.2%) in the first ECG following the procedure and another 4 patients developed new LBBB at a mean of 24 ± 17 hours (range: 12 to 48 hours) following TAVI, leading to a global incidence of new-onset LBBB during the hospitalization period of 30.2%. The ECG performed at hospital discharge showed the persistence and resolution of LBBB in 25 and 23 patients, respectively (Figure 6-1).
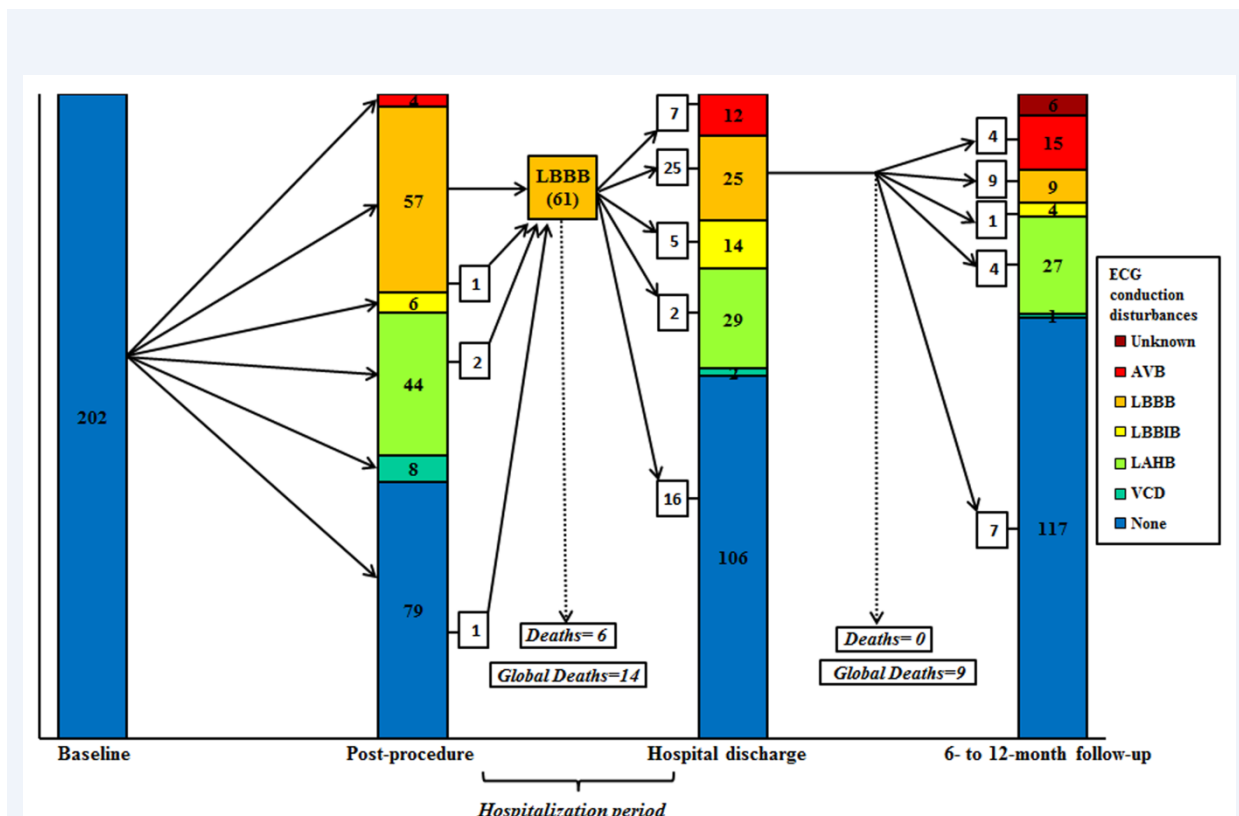
FIGURE 6-1. Conduction Abnormalities Following TAVI

Flowchart showing the occurrence of intraventricular conduction abnormalities following transcatheter aortic valve implantation immediately after the procedure, during the hospitalization period and up to 6- to 12-month follow-up.

CAVB: complete atrioventricular block; ILBBB: incomplete left bundle branch block; LBBB: left bundle branch block; IVCD: non-specific intraventricular conduction disturbances; LAHB: left anterior hemiblock; LBBB: left bundle branch block, TAVI: transcatheteraortic valve implantation

At 6- to 12-month follow-up, no conduction disorders were observed in 65% of survivors at that time point (Figure 6-1). In patients with persistent LBBB at hospital discharge (n = 25), LBBB had resolved in 12 patients (48%), 4 patients required PPI because of 3rd degree AVB (16%), and LBBB persisted in 9 patients (36%) (Figure 6-1). No new-onset LBBB was documented in any patient after hospital discharge. The mean changes in QRS duration throughout the study period are shown in Figure 6-2.
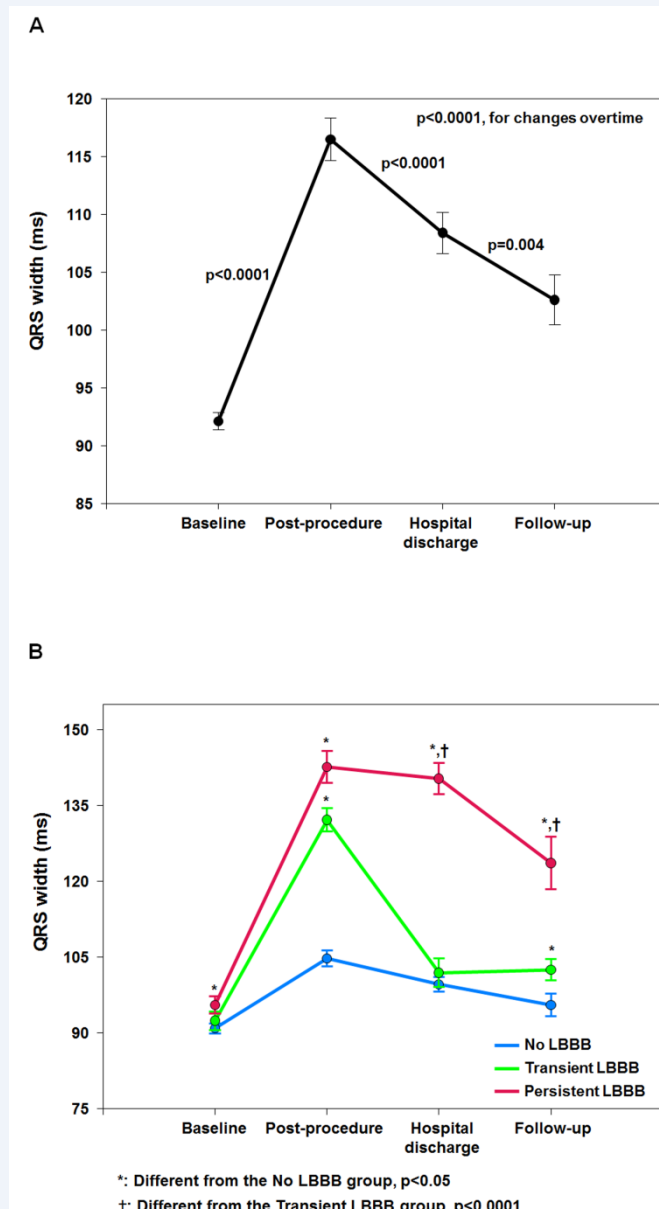
FIGURE 6-2. Changes in QRS Width Following TAVI

Changes in mean QRS duration following transcatheter aortic valve implantation and up to 6-to 12-month follow-up in overall population (**A**) and according to the occurrence of new-onset left bundle branch block (**B**).

Error bars indicate standard errors
*Different from the No LBBB group, p<0.05; †different from the Transient LBBB group, p<0.0001.
Abbreviation as in Figure 6-1

TABLE 6-2. Baseline and procedural findings, according to the occurrence of new-onset left bundle branch block following transcatheter aortic valve implantation

	No LBBB (n=141)	Transient LBBB (n=23)	Persistent LBBB (n=38)	p* value
Clinical Characteristics				
Age (years)	81 ± 8	79 ± 6	77 ± 9†	0.019
Female	83 (58.9)	17 (73.9)	21 (55.3)	0.328
Body mass index (kg/m^2)	26 ± 5	26 ± 5	28 ± 6	0.125
Hypertension	119 (84.4)	22 (95.7)	37 (97.4)	0.041
Diabetes mellitus	44 (31.2)	8 (34.8)	15 (39.5)	0.615
COPD	35 (24.8)	3 (13.0)	12 (31.6)	0.261
Coronary artery disease	79 (56.0)	17 (73.9)	22 (57.9)	0.277
eGFR (ml/min)	56.6 ± 22.5	54.6 ± 20.4	59.1 ± 26.3	0.742
Baseline treatment				
Betablockers	64 (45.4)	14 (60.9)	16 (42.1)	0.332
Calcium channel blockers	38 (27.0)	8 (34.8)	12 (31.6)	0.648
Amiodarone	8 (5.7)	2 (8.7)	3 (7.9)	0.729
STS-PROM score (%)	7.6 ± 3.8	6.1 ± 3.7	7.4 ± 3.4	0.476
ECG				
PR interval	176 ± 36	158 ± 23	174 ± 45	0.114
QRS duration (ms)	90 ± 10	92 ± 9	96 ± 10†	0.033
Echocardiography				
LVEF (%)	57 ± 12	54 ± 15	58 ± 11	0.440
Mean gradient (mmHg)	46 ± 17	47 ± 19	49 ± 19	0.696
Aortic valve area (cm^2)	0.65 ± 0.22	0.63 ± 0.28	0.61 ± 0.17	0.547
Computed tomography				
Aortic valve calcification (Agatston units)	2544(1600-4442)	2045(1666-4209)	3150(1944-5358)	0.412
Procedural variables				
Approach				
Transapical	79 (56.0)	12 (52.2)	26 (68.4)	0.335
Transfemoral	62 (44.0)	11 (47.8)	12 (31.6)	

Ratio aortic prosthesis size/ aortic annulus	1.16 ± 0.07	1.18 ± 0.09	1.18 ± 0.07	0.097
Prosthesis ventricular depth‡ (mm)	1.64 ± 2.85	1.22 ± 2.23	3.04 ± 1.72†§	0.028

*P value by one-way analysis of variance for continuous variables and Fisher's exact test for categorical variables. † $P<0.05$ vs. no LBBB by Tukey post hoc test; § $P<0.05$ vs. transient LBBB by Tukey post hoc test. ‡Distance between the hinge point of the mitral valve and the ventricular end of the valve prosthesis frame (TEE, long-axis view).
Values are expressed as n (%), mean (±SD) or median (25-75th percentile)
COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration ratio, STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; LVEF: left ventricular ejection fraction

6.5.2. Predictive Factors of New-Onset Persistent LBBB

Baseline and procedural characteristics of the patients, grouped according to the occurrence of persistent LBBB (vs. transient or no LBBB) following the TAVI procedure are shown in Table 6-2. Factors associated with persistent LBBB (vs. no or transient LBBB) in the univariate analysis, were prosthesis ventricular depth (3.04 ± 1.72 vs. 1.56 ± 2.73, $P=0.009$), longer baseline QRS duration (96±10 vs. 91± 9, $P=0.005$) and younger age (77±9 vs. 80±7, $P=0.010$). In the multivariate analysis, prosthesis ventricular depth (OR 1.37 for each increase of 1 mm [95% CI: 1.06-1.77], $P=0.017$) and baseline QRS duration (OR: 1.24 for each increase of 4 ms [95% CI: 1.01-1.51], $P=0.037$) were independent predictors of persistent LBBB. No predictors of transient LBBB were identified.

6.5.3. Prognostic Value Of New-Onset and Persistent LBBB

Clinical outcomes during the hospitalization period according to the occurrence of new-onset LBBB are shown in Table 6-3.

At a median (range) follow-up of 12 [6-24] months, a total of 32 patients had died, with no differences between patients with and without persistent LBBB. There was only 1 case of sudden death during the follow-up period, which occurred 9 months after TAVI in a patient with no LBBB at hospital discharge. Survival curves at 1-year follow-up are shown in Figure 6-3 (A, B). The overall rate of PPI was higher in patients with persistent LBBB compared to the rest of the study population (34.2% vs. 4.3%, $P=0.001$). Freedom from PPI curves up to 1-

year follow-up are shown in Figure 6-3C. Thirty-day landmark analyses for cumulative outcomes are shown in Figure 6-3D to, F.

TABLE 6-3. In-Hospital Outcomes, According to the Occurrence of New-Onset Left Bundle Branch Block

	New LBBB (n=61)	No LBBB (n=142)	*P* value
Complete atrioventricular block	8 (13.1)	6 (4.3)	0.023
Need for PPI	8 (13.1)	6 (4.3)	0.023
Major vascular complications	4 (6.6)	3 (2.1)	0.202
Major bleeding	9 (14.8)	14 (9.9)	0.194
Myocardial infarction	0	2 (1.4)	0.998
Stroke	3 (4.9)	1 (0.7)	0.083
Death	6 (9.8)	8 (5.7)	0.285
Hospital Stay (days)	8 (5-13)	7 (6-9)	0.091

LBBB: left bundle branch block; PPI: permanent pacemaker implantation

Baseline and procedural characteristics of the patients grouped according to the need for PPI are shown in Table 6.4. The occurrence of new-onset LBBB following the procedure (HR: 5.99; 95% CI: 2.93 to 15.61; $P < 0.001$) was the only factor associated with PPI during the entire study period.
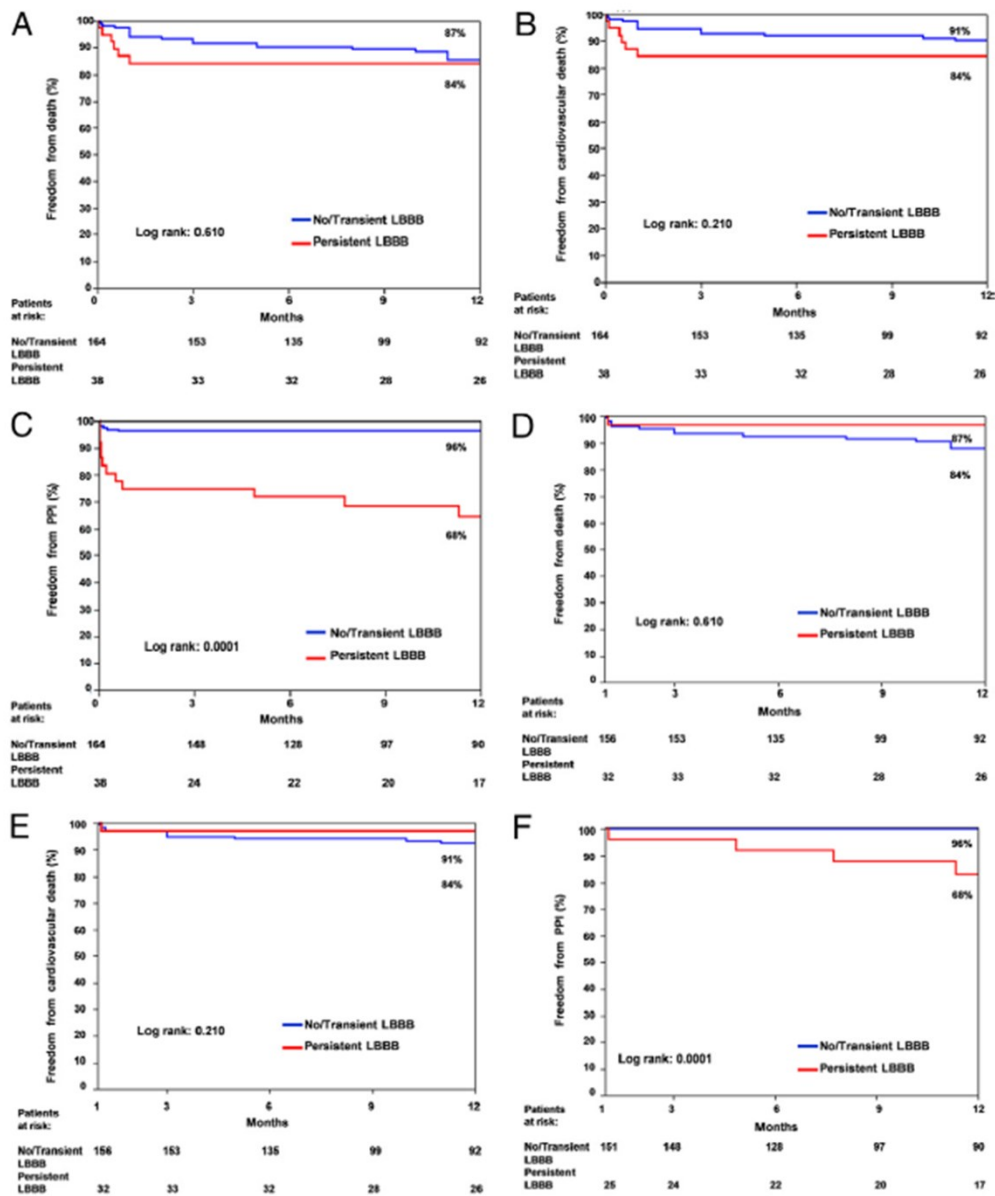
FIGURE 6-3. Survival curves and landmark analysis survival curves at one-month in patients with and without persistent LBBB following TAVI

Kaplan-Meier curves up to 1-year follow-up for overall mortality (**A**), cardiac mortality (**B**), and permanent pacemaker implantation (**C**) for patients with and without persistent left bundle branch block following transcatheter aortic valve implantation. Kaplan-Meier curves from 30 days following transcatheter aortic valve implantation to 12 months for overall mortality (**D**), cardiac mortality (**E**), and permanent pacemaker implantation (**F**) in patients with and without persistent left bundle branch block

LBBB:left bundle branch block

TABLE 6-4. Baseline and Procedural Findings, According to the Need for Permanent Pacemaker Implantation (In-Hospital or During the Follow-Up Period)

	PPI (cumulative) (n=20)	No PPI (n=182)	HR	*P* value
Clinical characteristics				
Age (years)	81 ± 6	80 ± 8	1.02 (0.96-1.09)	0.454
Female	12 (60.0)	109 (59.9)	0.90 (0.37-2.22)	0.803
Body mass index (kg/m^2)	27 ± 6	27 ± 5	1.01 (0.92-1.11)	0.762
Hypertension	17 (85.0)	161 (88.5)	0.59 (0.17-2.04)	0.406
Diabetes mellitus	6 (30.0)	61 (33.5)	0.96 (0.37-2.51)	0.938
COPD	5 (25.0)	45 (24.7)	1.16 (0.42-3.22)	0.778
Coronary artery Disease	11 (55.0)	107 (58.8)	0.95 (0.39-2.30)	0.903
eGFR (ml/min)	51.9 ±20.6	57.3 (23.2)	0.99 (0.97-1.01)	0.343
Baseline treatment				
Betablockers	8 (40.0)	86 (47.3)	0.70 (0.28-1.72)	0.434
Calcium channel blockers	8 (40.0)	50 (27.5)	1.64 (0.67-4.01)	0.281
Amiodarone	2 (10.0)	11 (6.0)	1.80 (0.41-7.81)	0.433
STS-PROM score (%)	6.9 ± 2.8	7.6 ± 3.8	0.94 (0.79-1.11)	0.457
ECG				
PR interval (mseg)	191 ± 59	172 ± 35	1.01 (0.99-1.02)	0.354
QRS duration (mseg)	94 ± 10	92 ± 10	1.02 (0.97-1.07)	0.500
Echocardiography				
LVEF (%)	62 ± 8	57 ± 12	1.03 (0.99-1.08)	0.137
Mean gradient (mmHg)	44 ± 21	47 ± 17	0.99 (0.97-1.02)	0.491
Aortic valve area (cm^2)	0.61±0.19	0.64±0.22	0.50 (0.40-6.26)	0.591
Computed tomography				
Aortic valve calcification	3362 ± 2345	3209 ± 2104	-	0.854

(Agatston units)				
Procedural variables				
Approach				
Transapical	14 (70.0)	103 (56.6)	1.66 (0.63-4.33)	0.303
Transfemoral	6 (30.0)	79 (43.4)		
Ratio prosthesis/aortic annulus	1.17 ± 0.09	1.16 ± 0.07	-	0.407
Prosthesis ventricular depth* (mm)	3.19 ± 1.65	1.71 ± 2.68	1.27 (0.96-1.68)	0.100
Residual AR≥2	1 (5.0)	27 (14.8)	1.02 (0.79-1.31)	0.877
New-onset LBBB	14 (70.0)	47 (25.8)	5.99 (2.29-15.61)	<0.001

* Distance between the hinge point of the mitral valve and the ventricular end of the valve prosthesis frame (TEE, long-axis view).
Values are expressed as n (%), mean (±SD) or median (25-75th percentile)
AR: aortic regurgitation; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration ratio; PPI: pacemaker implantation. STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; LVEF: left ventricular ejection fraction. AR: aortic regurgitation. LBBB: left bundle branch block

Late clinical outcomes of the 25 patients with persistent LBBB and no PPI at hospital discharge are detailed in Table 6-5. None of these patients had sudden death at a median of 12 (6-24) months. However, the rates of syncope and need for PPI during the follow-up period were higher in this group than in the rest of the study population (syncope: 16.0% vs. 0.7%, P=0.001; PPI: 20.0% vs. 0.7%, P<0.001). The individual characteristics of the patients requiring PPI during the follow-up period are shown in Table 6-6.

TABLE 6.5. Late Clinical Outcomes, According to the Presence of New Persistent Left Bundle Branch Block (with no Pacemaker Implantation) at Hospital Discharge

	Overall (n=176)	Persistent LBBB (n=25)	No / Transient LBBB (n=151)	*P* value
Median follow-up (months)	12 (6-24)	12 (5-24)	12 (5-24)	0.164
Syncope	5 (2.8)	4 (16.0)	1 (0.7)	0.001
Heart failure requiring hospitalization	26 (14.8)	7 (28.0)	19 (12.6)	0.124
PPI	6 (3.4)	5 (20.0)	1 (0.7)	<0.001
Death				
Overall	32 (18.2)	4 (16.0)	28 (18.5)	0.998
Cardiac death	14 (8.0)	1 (4.9)	13 (8.6)	0.696
Sudden death	1 (0.7)	0	1 (0.6)	0.999

Values are expressed as n (%) or median (25-75th percentile)
LBBB: left bundle branch block; PPI: permanent pacemaker implantation.

TABLE 6-6. Individual Characteristics of the Patients Requiring Permanent Pacemaker Implantation during the Follow-Up Period

Age (years)	STS-PROM (%)	Persistent LBBB	Timing of PPI	Reason for PPI
69	6.8	yes	7 months	Complete AVB (+syncope)
70	5.2	yes	4 months	Complete AVB (+heart failure)
76	3.5	no	19 months	Complete AVB (+presyncope)
77	4.5	yes	1 month	Complete AVB (+syncope)
78	7.9	yes	11 months	Complete AVB (+syncope)
79	10.8	yes	43 months	Complete AVB (+syncope)

PPI: permanent pacemaker implantation. STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; LBBB: left bundle branch block; PPI: permanent pacemaker implantation; AVB: atrioventricular block.

At 1-year follow-up, patients with persistent LBBB had a poorer NYHA functional class compared to patients with no or transient LBBB (P=0.034) (Figure 6-4).
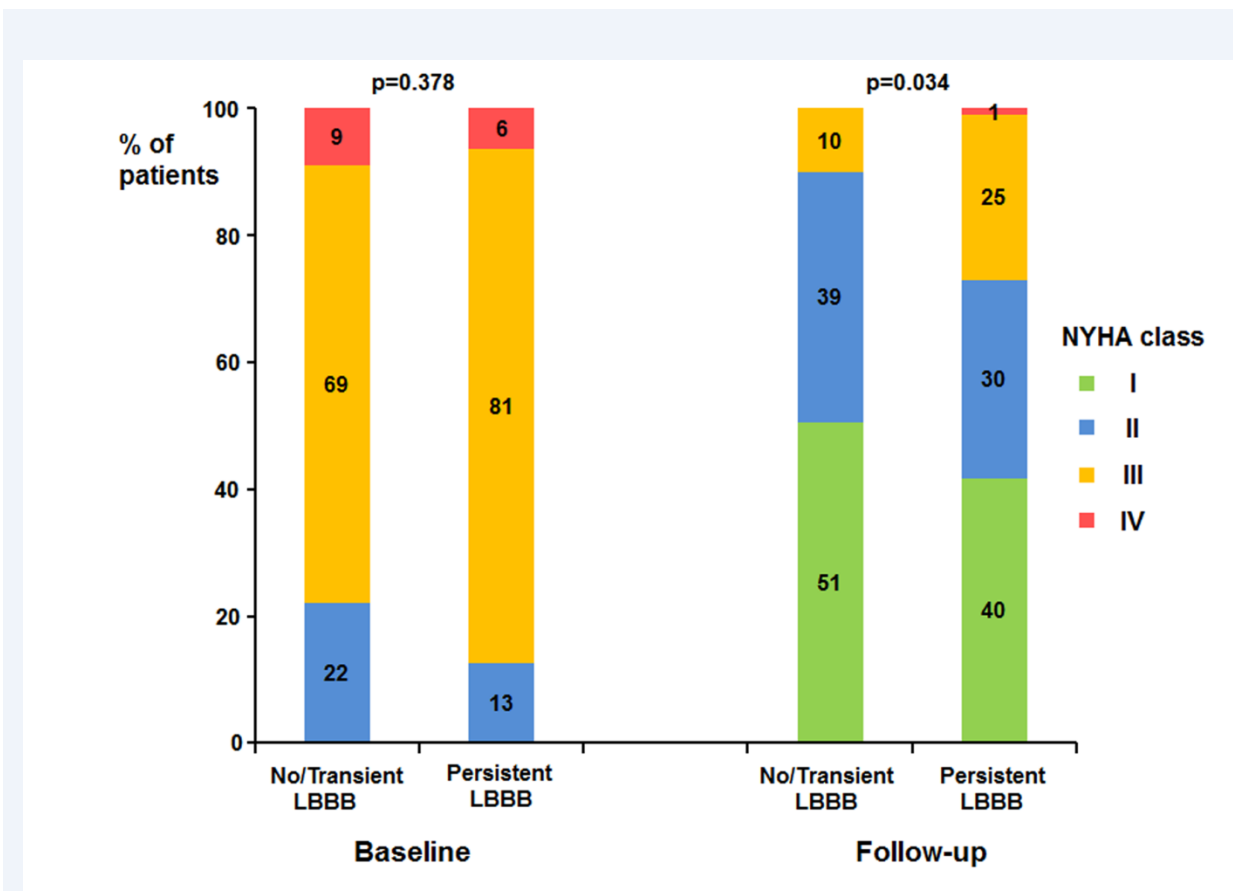
FIGURE 6-4. **Changes in functional class following TAVI**

Changes in NYHA functional class in patients with and without persistent LBBB following transcatheter aortic valve implantation.

Abbreviation as in Figure 6-1

6.5.4. Echocardiographic data

Valve hemodynamics of the patients with and without new-onset LBBB are shown in Figure 6-5.
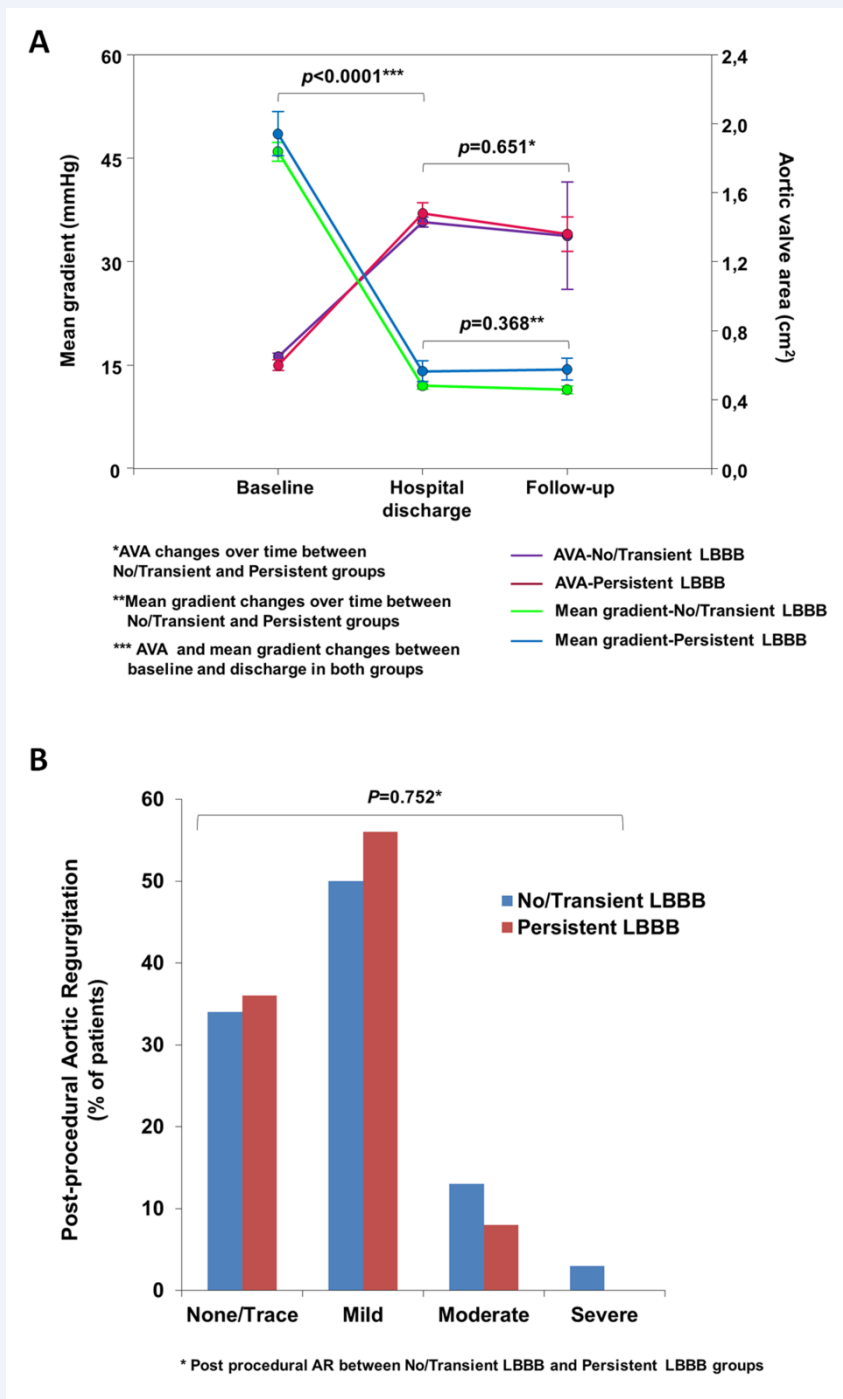
FIGURE 6-5. Valve hemodynamics following TAVI

  A. Changes in mean transvalvular gradient and aortic valve area, according to the occurrence on new-onset LBBB

  B. Degree of residual aortic regurgitation, according to the presence of new-onset LBBB.

Abbreviations as in Figure 6-1

The changes in LVEF throughout the study period are shown in Figure 6-6.
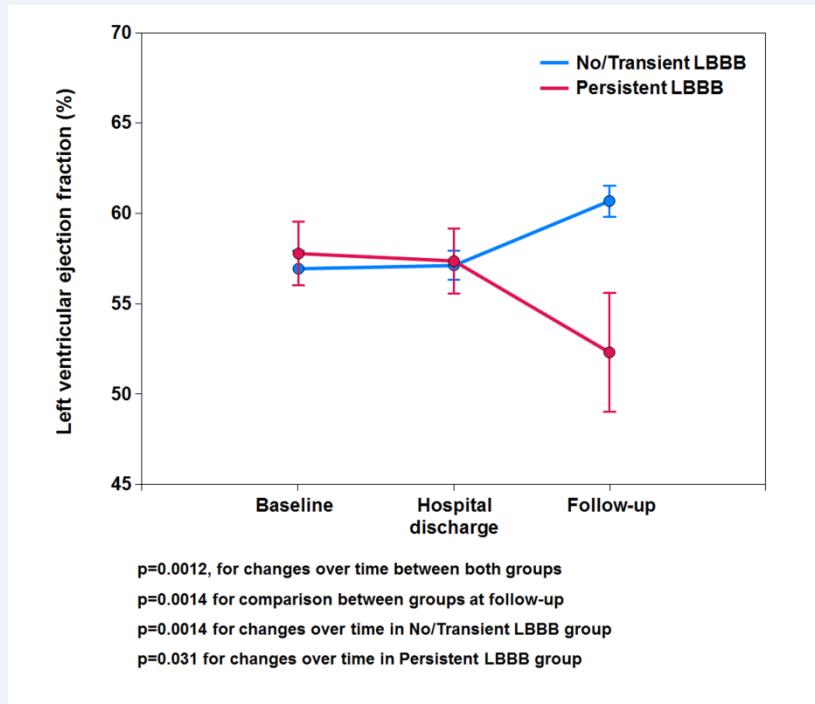
FIGURE 6-6. Changes in left ventricular ejection fraction following TAVI

Changes in left ventricular ejection fraction following transcatheter aortic valve implantation in patients with and without persistent left bundle branch block following transcatheter aortic valve implantation

LBBB: left bundle branch block

Patients with persistent LBBB at hospital discharge exhibited a decrease in LVEF of $4.75 \pm 8.02\%$ (95% CI: 0.99-8.50, $P = 0.031$) at 1-year follow-up, whereas patients with no/transient LBBB had an increase in LVEF of $2.52 \pm 11.32\%$ (95% CI: 0.27-4.77, $P = 0.0014$), $P = 0.0012$ for comparison between groups. The LVEF at 1-year follow-up was lower in the persistent LBBB group compared to the no/transient LBBB group ($53 \pm 13\%$ vs. $62 \pm 9\%$, $P = 0.0014$). The changes in LVEF over time depending on baseline and procedural variables are shown in Table 6-7. In the multivariate linear regression analysis the occurrence of persistent LBBB was the only independent predictive factor of LVEF decrease at 1-year follow-up (estimate $\pm$SE: -8.6 ± 2.6, R^2:0.14, $P = 0.001$).

TABLE 6-7. Left Ventricular Ejection Fraction Changes between Hospital Discharge and 6- to 12-Month Follow-Up, According to Baseline and Procedural Variables

	Δ LVEF	*P* value
Clinical variables		
Age		
≥ Median (81 yrs)	1.18 ± 9.42	0.907
< Median (81 yrs)	1.42 ± 12.68	
Sex		
Male	1.64 ± 9.14	0.824
Female	1.15 ± 11.98	
Hypertension		
Yes	0.56 ± 11.10	0.035
No	7.46 ± 9.80	
Diabetes mellitus		
Yes	0.26 ± 10.53	0.104
No	3.94 ± 12.34	
COPD		
Yes	2.04 ± 10.57	0.202
No	-1.00 ± 12.71	
Prior CAD		
Yes	2.50 ± 14.06	0.385
No	0.51 ± 8.70	
Baseline eGFR		
≥Median (55ml/min)	2.54 ± 12.02	0.235
<Median (55ml/min)	0.11 ± 10.19	
STS-PROM score (%)		
≥ Median (7.20 %)	1.11 ± 10.39	0.655
< Median (7.20%)	2.01 ± 9.62	
ECG		
PRinterval		
≥ Median (168 ms)	2.07 ± 9.27	0.974
< Median (168 ms)	2.14 ± 11.92	
QRS duration		
≥ Median (92 ms)	0.80 ± 10.86	0.645

< Median (92 ms)	1.75 ±11.46	
Echocardiography		
LVEF		
≥ Median (60%)	0.63 ± 9.79	0.420
< Median (60%)	2.51 ± 13.27	
Mean gradient		
≥ Median (43mmHg)	1.03 ± 11.57	0.784
< Median (43mmHg)	1.59 ± 10.78	
Aortic valve area		
≥ Median (0.60cm^2)	0.95 ± 8.18	0.424
< Median (0.60cm^2)	2.47 ± 11.96	
Procedural variables		
Transcatheter approach		
Transapical	1.10 ± 10.70	0.784
Transfemoral	1.69 ± 12.05	
New LBBB		
No/Transient LBBB	2.52 ± 11.32	0.001
Persistent LBBB	-4.75 ± 8.02	
Residual aortic regurgitation:		
≥ 2	1.09 ± 11.38	0.625
< 2	2.50 ± 9.88	
Peak CK-MB		
≥Median (19.30μg/dL)	0.95 ± 10.95	0.446
<Median (19.30μg/dL)	2.59 ± 7.73	
Peak Troponin T		
≥ Median (0.50μg/dL)	0.20 ± 9.64	0.092
< Median (0.50μg/dL)	3.97 ± 9.91	

Values are expressed as n (%) or mean (±SD).
CAD: coronary artery disease, CK-MB: creatinin kinase-myocardial band, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration ratio, IVS: interventricular septum, LBBB: left bundle branch block, LVEF: left ventricular ejection fraction, STS-PROM: Society of Thoracic surgeons predicted risk of mortality.

6.6. DISCUSSION

New-onset LBBB has been reported in 29% to 65% of the patients following TAVI with a self-expandable valve [175, 179, 180, 185-189], and in 12% to 18% following TAVI with a balloon-expandable valve [185, 191, 192, 248]. The rate of 30% of new LBBB observed in the present study might be related mainly to the exclusion of patients with conduction abnormalities (including LBBB) or pacemaker prior to TAVI. In fact, the rate of new LBBB in previous studies would have increased up to ~75% and 30% for self-expandable and balloon-expandable valves, respectively, if patients with complete bundle branch block and/or pacemaker had been excluded [175, 179, 180, 185-188, 191, 192]. Importantly, and in accordance with prior studies using balloon-expandable valves, a significant number of these conduction abnormalities resolved within the first few days following the intervention.[191, 192] In a further step, our study also shows that up to about half of the new LBBBs present at hospital discharge (median of 7 days after TAVI) had resolved at 1-year follow-up. This clearly differs from the experience with the self-expandable CoreValve system, in which LBBB persisted in the vast majority of patients up to 6-month follow-up .[181] Nuis et al [175] showed that about 50% of conduction disturbances occurring during the TAVI procedure took place before valve implantation and were related to wire manipulation or balloon valvuloplasty. It is therefore not surprising that in the absence of permanent damage or mechanical stress of the left bundle branch a significant number of these conduction disturbances disappear within the few days following the procedure. Another important finding of the present study is the fact that no new intraventricular conduction disturbances were observed either after day 2 in the periprocedural period or later during the follow-up period.

6.6.1. Predictive Factors of New-Onset Persistent LBBB

Unlike all prior studies evaluating the predictive factors of LBBB (transient and persistent) following TAVI, this study specifically focused in the prediction of persistent LBBB as compared to transient or absent LBBB. Of note, no predictive factors were encountered for transient LBBB, whereas both a lower (ventricular) valve positioning and longer QRS duration were associated with persistent LBBB following balloon-expandable valve implantation. A longer QRS duration might be associated with an early stage of the conduction system disease which, in turn, can increase the vulnerability of this system to any

trauma during the TAVI procedure. [142, 249]A more ventricular positioning of the valve prosthesis might increase the risk of mechanical stress and direct damage of the conduction system leading to a higher rate of conduction disturbances. In accordance with our results, a lower positioning of the valve prosthesis has been shown to be a predictor of conduction disturbances and PPI in patients following TAVI with the CoreValve device. [188, 206]

6.6.2. Prognostic Value of New-Onset Persistent LBBB

This study showed that the occurrence of new persistent LBBB following TAVI is associated with a much higher risk of complete AVB requiring PPI. It is of high clinical relevance that the higher risk of complete AVB started very soon (hours-days) after the appearance of LBBB, and continued during the follow-up period in those patients with persistent LBBB. In fact, all cases but one of complete AVB leading to PPI during the follow-up period occurred in patients with persistent LBBB, and syncope was the clinical presentation in most patients. We found no relation between the occurrence of LBBB and acute or late mortality following TAVI, and no cases of sudden death were observed among the patients with persistent LBBB. However, further studies with a larger number of patients will be needed to confirm the lack of association between new persistent LBBB following TAVI and sudden death. Furthermore, the potential usefulness of a closer follow-up (serial ECGs, 24-48 hrs ECG monitoring within the first months following TAVI) and/or systematic electrophysiological studies in such cases should probably be investigated in the future.

Patients with persistent LBBB had a significant impairment in LVEF during the follow-up period and exhibited a poorer functional class as compared to those with no/transient LBBB. Tzikas et al [197] reported the lack of postprocedural improvement in LVEF in patients with new conduction disturbances (LBBB and/or pacemaker implantation) after CoreValve prosthesis implantation. It is known that the presence of LBBB generates a ventricular contraction asynchrony secondary to an abnormal electrical activation, which in turn causes left ventricular remodeling and further ventricular dysfunction [135]. The potential beneficial effects of resynchronization therapy[250] might merit to be evaluated in future studies.

Limitations. The results regarding the lack of relation between persistent LBBB and cardiac mortality, and particularly sudden death, should be interpreted with caution due to the

112

relatively small sample size. These results will therefore have to be confirmed by larger studies in the future.

In conclusion, in patients with aortic stenosis and no prior conduction abnormalities, new-onset LBBB occurred in up to 30% of the patients following TAVI with a balloon-expandable valve, although this conduction disturbance was persistent in less than half of them at 6-to 12-month follow-up. The prosthesis ventricular depth and QRS duration predicted the occurrence of persistent LBBB, which was associated with a higher rate of AVB and PPI, and a poorer functional status and ventricular function at midterm follow-up. These results highlight the importance of close monitoring and follow-up of patients with persistent LBBB following TAVI, and support the performance of larger studies to further evaluate the prognostic value of these conduction abnormalities following TAVI.

CHAPTER 7-Article 3

Impact of New-Onset Persistent Left Bundle Branch Block on Late Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Implantation with a Balloon-Expandable Valve

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7.1.   RESUME

Objectifs. Déterminer l'impact du bloc de branche gauche de novo persistent (NOP-LBBB) sur les résultats tardifs après l'implantation de la valve aortique par cathéter (TAVI).

Contexte: L'impact de NOP-LBBB suivante TAVI reste controversé**.**

Méthodes: Un total de 668 patients consécutifs qui ont subi TAVI d'une valve expansible par ballonnet (BEV) sans BBG ou pacemaker ont été inclus. Un ECG a été réalisé avant l'intervention, immédiatement après la procédure et de façon quotidienne jusqu'à la sortie de l'hôpital. Les patients ont été suivis à 1, 6 et 12 mois, puis annuellement.

Résultats: Un BBG est apparu chez 128 patients (19.2%) immédiatement après TAVI, persistant à la sortie de l'hôpital chez 79 patients (11.8%). À un suivi médian de 13 mois (3-27), il n'y avait pas différences dans les taux de mortalité entre les patients avec NOP-LBBB et ceux sans NOP-LBBB (27.8% vs. 28.4%; HR: 0.87 [IC 95%: 0.55 à 1.37], $P = 0,54$). Aucune différence a été observée entre les deux groupes en ce qui concerne la mortalité cardiovasculaire ($P = 0.82$), la mort subite ($P = 0.87$), ré-hospitalisations pour toutes causes (p = 0.11) ou l'insuffisance cardiaque ($P = 0.55$). NOP-LBBB était le seul facteur associé à un taux accru d'implantation de pacemaker pendant la période de suivi (13.9% vs. 3.0%, HR: 3.88 [IC 95%: 1.86 à 8.05], $P < 0.001$). NOP-BBG a également été associée à une absence d'amélioration de la FEVG et une mauvais évolution de la classe NYHA ($P < 0.02$ pour les deux).

Conclusion: NOP-LBBB est survenu dans environ 1 sur 10 patients qui avaient subi une TAVI avec une BEV. NOP-LBBB a été associé à un taux accru d'implantation de pacemaker, l'absence d'amélioration de la FEVG et de l'état fonctionnel, mais pas à la mortalité cardiovasculaire global ou ré-hospitalisations à 1 an de suivi.

7.2. ABSTRACT

Objectives. The aim of this study was to determine the impact of new-onset persistent left bundle branch block (NOP-LBBB) on late outcomes after transcatheter aortic valve implantation (TAVI).

Background: The impact of NOP-LBBB after TAVI remains controversial.

Methods: A total of 668 consecutive patients who underwent TAVI with a balloon-expandable valve without pre-existing LBBB or permanent pacemaker implantation (PPI) were included. ECGs were obtained at baseline, immediately after the procedure and daily until hospital discharge. Patients were followed at 1, 6, and 12 months and yearly thereafter.

Results: New-onset LBBB occurred in 128 patients (19.2%) immediately after TAVI and persisted at hospital discharge in 79 patients (11.8%). At a median follow-up of 13 months (range 3 to 27 months), there were no differences in mortality rate between the NOP-LBBB and no NOP-LBBB groups (27.8% vs. 28.4%; adjusted-hazard ratio [HR]: 0.87 [95% CI: 0.55 to 1.37]; P = 0.54). There were no differences between groups regarding cardiovascular mortality (P = 0.82), sudden death (P = 0.87), rehospitalization for all causes (P =0.11), or heart failure (P = 0.55). NOP-LBBB was the only factor associated with an increased rate of PPI during the follow-up period (13.9% vs. 3.0%; HR: 4.29 [95% CI: 2.03–9.07], P < 0.001. NOP-LBBB was also associated with a lack of left ventricular ejection fraction improvement and poorer New York Heart Association functional class at follow-up (P < 0.02 for both).

Conclusion: NOP-LBBB occurred in ~1 of 10 patients who had undergone TAVI with a balloon-expandable valve. NOP-LBBB was associated with a higher rate of PPI, a lack of improvement in left ventricular ejection fraction, and a poorer functional status, but did not increase the risk of global or cardiovascular mortality or rehospitalizations at 1-year follow-up.

7.3. INTRODUCTION

The dismal prognosis associated with symptomatic severe aortic stenosis when left untreated is dramatically improved by surgical aortic valve replacement (SAVR). However, despite relieving valvular obstruction, some studies have shown that patients undergoing SAVR have a poorer survival than that expected for the general population, due partially to an excess of cardiovascular mortality and specifically sudden death. [251] Among the factors associated with increased late mortality following SAVR, the occurrence of new-onset left bundle branch block (LBBB) has been associated with a higher risk of sudden death.[155, 160]

Transcatheter aortic valve implantation (TAVI) has been established as a therapeutic option for aortic stenosis patients considered to be at high or prohibitive surgical risk. [99] The occurrence of new-onset LBBB is one of the most frequent complications following TAVI. [246] While the incidence and predictive factors of new conduction disturbances following TAVI have been well studied, data on the potential prognostic value of this conduction abnormality are scarce and controversial. Recently, 2 studies using mainly or exclusively the self-expandable CoreValve system (Medtronic, Minneapolis, MN) reported opposite results: while Houthuizen et al [252] showed a higher mortality rate at 1-year follow-up in patients who had a new-onset LBBB after TAVI, Testa et al [169] failed to show any impact of new-onset LBBB after TAVI on mortality, nor on the rate of re-hospitalizations for heart failure, unlike other prior studies showing that the appearance of new LBBB may trigger heart failure even in patients without overt cardiac disease. [135, 137] It is known that major differences exist between the self-expandable and balloon-expandable valves regarding the incidence and evolution of conduction disturbances overtime [181, 246, 253] and little evidence exists regarding balloon-expandable valves. [253] The aim of this study was therefore to determine the impact of NOP-LBBB on late clinical outcomes in a large cohort of patients who had undergone TAVI with a balloon-expandable valve.

7.4. METHODS

7.4.1. Study Population

A total of 985 consecutive patients with symptomatic aortic stenosis considered not suitable or at very high risk for SAVR underwent TAVI with a balloon-expandable valve in 4 centers. Of them, a total of 317 patients were excluded for the following reasons: aborted procedure without valve implantation (n = 20), procedural death (n = 7), previous permanent pacemaker implantation (PPI) (n = 152), pre-existing LBBB (n = 83), and PPI during hospitalization (n = 55). The final study population consisted of 668 patients (St-Paul's hospital: 303 patients; Quebec Heart and Lung Institute: 220 patients; St-Michael's hospital: 86 patients; Hospital Universitari Vall d'Hebron: 59 patients). Of these, 168 patients from both the Quebec Heart and Lung Institute and Hospital Universitari Vall d'Hebron had already been included in a prior study. [253] Details on the TAVI procedure have been provided elsewhere .[99] Data were prospectively collected in a dedicated database in each center. All patients signed informed consent form before procedures and the study was conducted in accordance with recommendations of institutional ethics committees of each center. The need for consent to participate in this research study was waived in view of its observational and anonymous nature. Periprocedural events were defined according to the VARC-2 criteria.[112]

7.4.2. Electrocardiographic Data

Electrocardiographic (ECG) records were obtained from all patients at baseline, immediately after the procedure and daily until hospital discharge. ECG tracings were analyzed by a cardiologist in each center. The diagnosis of intraventricular conduction abnormalities was based on AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram.[134] PPI was indicated if third-degree or advanced second-degree atrio-ventricular block (AVB) was found at any anatomic level that was not expected to resolve after the intervention and for sinus node dysfunction with documented symptomatic bradycardia, in agreement with the ACC/AHA/HRS guidelines for device-based therapy of cardiac rhythm abnormalities.[164]

NOP-LBBB was defined as any new LBBB occurring during the hospitalization period after the TAVI procedure that persisted at hospital discharge, including patients who died during hospitalization period without proven resolution of the LBBB.

7.4.3. Follow-up

Follow-up was carried out by clinical outpatient visits or telephonic interviews at 30 days, 6 months, 1 year, and yearly thereafter. The median follow-up was 13 (interquartile range [IQR]: 3 to 27) months, and no patient was lost to follow-up. All clinical events were defined according to the VARC criteria and any death was recorded and further classified as of cardiovascular or non-cardiovascular origin. [112] Any death of unknown cause was considered cardiovascular mortality, as recommended by the VARC criteria and any death was recorded and further classified as of cardiovascular or non-cardiovascular cause. Any death of unknown case was considered cardiovascular mortality as recommended by VARC 2 criteria. Sudden cardiac death was defined as any unexpected death due to cardiac disease that occurs within 1 hour after of the onset of symptoms[254]. Re-hospitalization for all causes and heart failure were recorded during the follow-up period. Physicians responsible for the patients were contacted and/or medical charts reviewed in order to determine the causes of re-hospitalization and/or death when necessary.

Transthoracic echocardiography exams were performed at baseline, at hospital discharge and at 6- to 12-month follow-up. Echocardiography data at follow-up were available in 341 patients (83% of the patients that reached the 6- to 12-month follow-up).

7.4.4. Statistical Analysis

Qualitative variables are expressed as percentages and compared using the Chi-Square or Fisher exact test as appropriate. Continuous variables are displayed as mean (standard deviation) or median (IQR) and compared using 2 sided t-test or Wilcoxon rank-sum test depending on the variable distribution.Comparisons of clinical outcomes between NOP-LBBB and no NOP-LBBB patients were adjusted for baseline differences between groups using a logistic regression analysis (30-day mortality) or proportional hazard model (late mortality) that included variables with P value <0.10 in the univariate analysis. The following variables were included in the model: age, hypertension, diabetes, approach and prosthesis

size. A landmark analysis with a landmark cut-off at 30 days was used to further investigate the impact of NOP-LBBB on late mortality. To analyze factors associated with late PPI a Fine-Gray Cox model was constructed to account for death as a competing risk event for the need of PPI. Survival curves were constructed using Kaplan-Meier estimates and the long-rank test was used for comparison between groups. Changes in left ventricular ejection fraction (LVEF) over time between groups were compared using a repeated-measures model with interactions. Further comparisons were performed using the Tukey's technique. The predictors of significant LVEF changes over time were determined using a multivariate regression linear model including variables with P value <0.10 in the univariate analysis. Variables included were: LVEF at baseline, transapical/transaortic approach and NOP-LBBB. A P value <0.05 was considered statistically significant. Analyses were conducted using the statistical package SAS, version 9.2 (SAS Institute Inc., Cary, NC)

7.5. RESULTS

New-onset LBBB occurred in 128 (19.2%) patients immediately after the procedure. Of these, LBBB persisted at hospital discharge in 79 patients (11.8 %; 56.4% of patients with new-onset LBBB). Baseline clinical characteristics, ECG and echocardiographic findings, procedural variables and in-hospital outcomes according to the occurrence of NOP-LBBB are shown in Table 7-1.

TABLE 7-1. Baseline and Procedural Variables, According to the Occurrence of New-Onset Persistent LBBB (n=668)

	No NOP-LBBB (n=589)	NOP-LBBB (n=79)	P value
Clinical Characteristics			
Age (years)	81 ± 8	78 ± 9	0.006
Male	286 (48.6)	39 (49.4)	0.905
Body mass index (kg/m^2)	26 ± 6	27 ± 6	0.200
Hypertension	473 (80.3)	71 (89.9)	0.040
Diabetes mellitus	169 (28.7)	35 (44.3)	0.005
COPD	161 (27.3)	22 (27.8)	0.923
NYHA class >II	452 (76.7)	62 (78.5)	0.730
eGFR<60 (ml/min)	260 (44.1)	33 (41.8)	0.719
Coronary artery disease	401 (68.1)	58 (73.4)	0.261
Previous CABG	189 (32.1)	32 (40.5)	0.135
STS-PROM score (%)	7.9 ± 4.9	7.6 ± 4.6	0.568
Log EuroSCORE (%)	21.2 ±14.1	20.8 ± 13.9	0.844
Echocardiography			
LVEF (%)	56 ± 13	56 ± 11	0.841
Mean gradient (mmHg)	47 ±17	45 ± 17	0.380
Aortic valve area (cm^2)	0.60 (0.50-0.77)	0.62 (0.55-0.78)	0.504
PSAP>60 (mmHg)	75 (12.7)	12 (15.2)	0.508
Procedural variables			
Procedural success	531 (90.2)	70 (88.6)	0.668
Valve-inValve	25 (4.2)	3 (3.8)	0.999
Approach			
Transfemoral	333 (56.5)	30 (38.0)	
Transapical	237 (40.2)	49 (62.0)	0.001
Transaortic	19 (3.2)	0	
Prosthesis type			
Cribier-Edwards	37 (6.3)	2 (2.5)	
Edwards SAPIEN	299 (50.8)	46 (58.2)	0.440
SAPIEN XT	247 (41.9)	31 (39.2)	
SAPIEN 3	6 (1.0)	0	
Prosthesis size (mm)			
20-23	274 (46.5)	35 (44.3)	0.041

26	294 (49.9)	36 (45.6)	
29	21 (3.6)	8 (10.1)	
In-hospital Outcomes			
Mild or more residual AR	74 (12.5)	9 (11.4)	0.763
Myocardial infarction	9 (1.5)	1 (1.3)	0.999
Major vascular complications	50 (8.4)	7 (8.9)	0.922
Major or life-threatening bleeding	124 (21.1)	13 (16.5)	0.342
Dialysis	5 (0.8)	1 (1.3)	0.532
Stroke	14 (2.4)	4 (5.1)	0.254
Death	29 (4.9)	5 (6.3)	0.594

Values are expressed as n (%), mean (±SD) or media (IQR)
AR: aortic regurgitation, CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration ratio; Log EuroSCORE: Logistic EuroSCORE predicted risk of mortality; LVEF: left ventricular ejection fraction; NOP-LBBB: new-onset persistent LBBB; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality.

Patients who had NOP-LBBB were younger (P = 0.006), had a higher prevalence of hypertension (P=0.040) and diabetes mellitus (P = 0.005), underwent more frequently the TAVI procedure through transapical approach (P = 0.005), and received more frequently a 29mm valve (P = 0.041). Transapical approach (odds ratio (OR): 1.90[95% confidence interval (CI): 1.15-3.16,] P = 0.013) and a larger valve size -29mm valve- (OR: 3.12[1.22-7.97, P = 0.017] remained as independent predictors of NOP-LBBB in the multivariate analysis.

7.5.1. NOP-LBBB and mortality

At a median follow-up of 13 (IQR: 3-27) months, a total of 189 patients (28.3%) had died; causes of death were classified as non-cardiovascular in 75 patients (39.7%), and cardiovascular in 114 patients (60.3%). Sudden death occurred in 7 patients (1.0%, all during the follow-up period).

A total of 22 (27.8%) patients with NOP-LBBB died during the study period, 16 from cardiovascular causes (20.3%, sudden death: 1.3%). There were no differences between NOP-LBBB and no NOP-LBBB groups regarding overall mortality (NOP-LBBB: 27.8% , no

NOP-LBBB: 28.4%, hazard ration [HR]: 0.83 [95% CI: 0.53-1.29], P = 0.401; P = 0.431 after adjusting for age differences; P = 0.538 after adjusting for baseline differences), cardiovascular mortality (NOP-LBBB: 20.3%, no NOP-LBBB: 16.6%, HR: 1.03 [95% CI: 0.61-1.76], P = 0.906; P = 0.888 after adjusting for age differences; P=0.820 after adjusting for baseline differences) or sudden death (NOP-LBBB: 1.3%, no NOP-LBBB: 1.0%, HR: 0.91 [95% CI: 0.11-7.65], P = 0.932, P = 0.974 after adjusting for age differences; P = 0.872 after adjusting for baseline differences) (Table 7-2). This lack of association between NOP-LBBB and mortality persisted when a landmark analysis with a cut-off at 30 days (before and after 30 days) was performed (Table 7-2).

TABLE 7-2. New-Onset Persistent LBBB and Mortality Following TAVI

Cause of death	No NOP-LBBB (n=589)	NOP-LBBB (n=79)	P value
All-cause			
Univariate HR/OR			
Cumulative	1.00	0.83 (0.53-1.29)	0.401
≤30 days	1.00	1.26 (0.51-3.01)	0.611
>30 days to max	1.00	0.73 (0.44-1.23)	0.240
Age-adjusted HR/OR			
Cumulative	1.00	0.84 (0.53-1.31)	0.431
≤30 days	1.00	1.32 (0.53-3.25)	0.552
>30 days to max	1.00	0.73 (0.43-1.24)	0.244
Multivariate-adjusted HR/OR			
Cumulative	1.00	0.87 (0.55-1.37)	0.538
≤30 days	1.00	1.47 (0.57-3.75)	0.423
>30 days to max	1.00	0.75 (0.44-1.29)	0.300
Cardiovascular			
Univariate HR/OR			
Cumulative	1.00	1.03 (0.61-1.76)	0.906
≤30 days	1.00	1.26 (0.47-3.35)	0.644
>30 days to max	1.00	0.88 (0.45-1.71)	0.702
Age-adjusted HR/OR			
Cumulative	1.00	1.04 (0.61-1.78)	0.888

≤30 days	1.00	1.26 (0.47-3.37)	0.643
>30 days to max	1.00	0.88 (0.45-1.73)	0.718
Multivariate-adjusted HR/OR			
Cumulative	1.00	1.07 (0.62-1.85)	0.820
≤30 days	1.00	1.46 (0.53-4.04)	0.468
>30 days to max	1.00	0.90 (0.44-1.75)	0.704
Sudden death			
Univariate HR/OR			
Cumulative	1.00	0.91 (0.11-7.65)	0.932
≤30 days	-	-	-
>30 days to max	-	-	-
Age-adjusted HR/OR			
Cumulative	1.00	0.97 (0.11-8.20)	0.974
≤30 days	-	-	-
>30 days to max	-	-	-
Multivariate-adjusted HR/OR			
Cumulative	1.00	0.84 (0.10-7.39)	0.872
≤30 days	-	-	-
>30 days to max	-	-	-

HR: hazard ratio; OR: odds ratio. Other abbreviations as Table 7-1.

Survival curves for all-cause mortality, cardiovascular mortality and sudden death are shown in Figure 7-1.
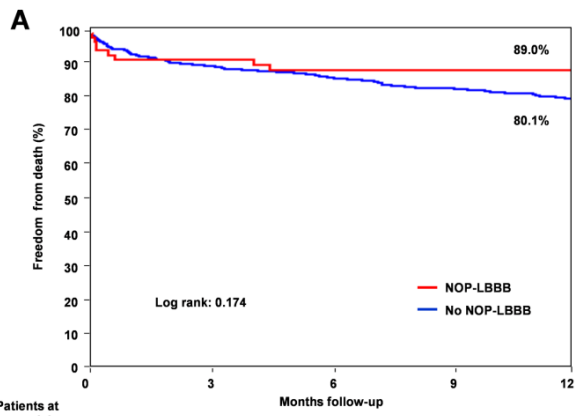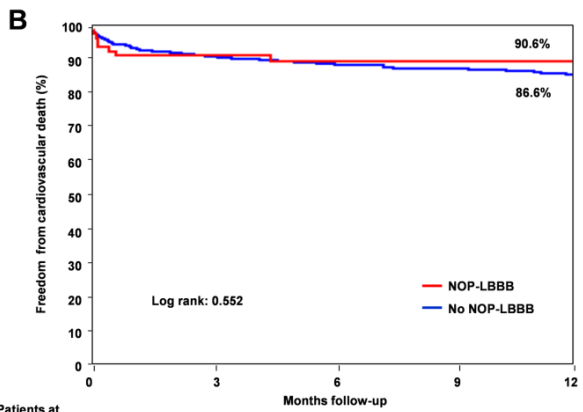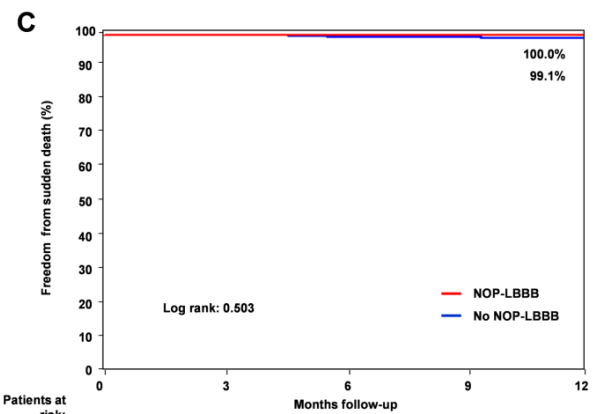
FIGURE 7-1. Survival curves at 1-year follow-up

Kaplan-Meier survival curves at 1-year follow-up for overall mortality (A), cardiac mortality (B) and sudden cardiac death (C), according to the occurrence of NOP-LBBB

Abbreviations as in Figure 7-1

7.5.2. NOP-LBBB and PPI

Of the 668 patients discharged alive without pacemaker implantation following TAVI, 29 patients (4.3%), 11 (13.4%) patients with NOP-LBBB and 18 (3.0%) of patients without NOP-LBBB required PPI after a median follow-up of 13 (IQR: 3 to 27) months. The median time for PPI was 12 (IQR: 5 to 38) months. PPI was indicated for high degree or complete AVB, sinus node dysfunction, symptomatic bradycardia and slow AF in 16 (55.5%), 6 (20.7%), 4 (13.8) and 3 (10.3%) patients, respectively. In 8 out 9 patients with new-onset persistent LBBB who underwent PPI during the follow-up period, PPI was indicated due to the occurrence of high degree or complete AVB. Individual characteristics of patients requiring PPI are shown in the Supplemental Table 7-1.

NOP-LBBB was the only independent predictor of PPI during the follow-up period, even when considering death as a competing risk event (HR: 4.29 [95% CI: 2.03-9.07], $P < 0.001$). Survival curves showing freedom from PPI over time are shown in Figure 7-2.

7.5.3. NOP-LBBB, re-hospitalizations and functional status

A total of 281 (42.1%) patients needed a re-hospitalization at a median follow-up of 13 (IQR: 3 to 27) months, 85 of them (12.7%; 30.2% of total hospitalizations) due to heart failure. There was no association between NOP-LBBB and hospitalizations for all causes (55.7 vs. 40.2%; HR: 1.27 [95% CI: 0.91-1.77], $P = 0.154$; $P = 0.138$ after adjusting by age differences and P=0.112 after adjusting by baseline differences), or heart failure (16.5 vs. 12.2; HR: 1.30 [95% CI: 0.72-2.35], $P = 0.390$; $P = 0.409$ after adjusting for age differences; $P = 0.546$ after adjusting for baseline differences) (Table 7-3).
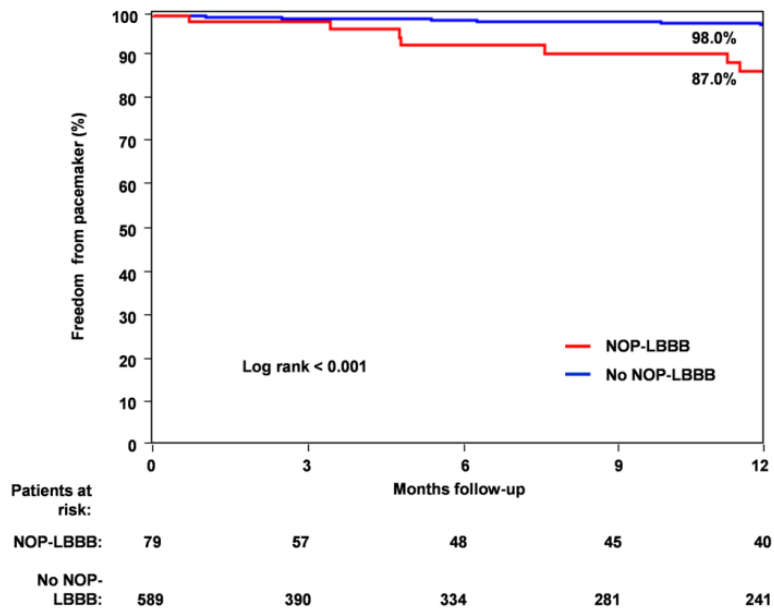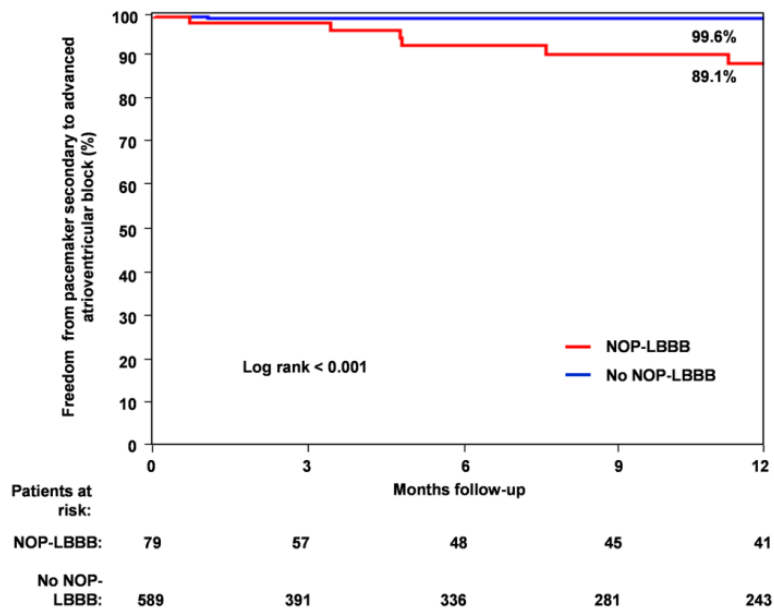
FIGURE 7-2. Permanent pacemaker implantation at 1-year follow-up

Kaplan-Meier curves at 1-year follow-up showing freedom from permanent pacemaker implantation (A) and freedom from pacemaker implantation due to advanced or complete atrioventricular block (B), according to the occurrence of NOP-LBBB

Abbreviations as in Figure 7-1

TABLE 7-3. New-Onset Persistent LBBB and the Risk of Re-Hospitalization

	No NOP-LBBB (n=589)	NOP-LBBB (n=79)	*P* value
Re-hospitalizations for all causes			
Univariate HR/OR	1.00	1.27 (0.91-1.77)	0.154
Age-adjusted HR/OR	1.00	1.29 (0.92-1.79)	0.138
Multivariate-adjusted HR/OR	1.00	1.32 (0.94-1.86)	0.112
Re-hospitalizations for heart failure			
Univariate HR/OR	1.00	1.30 (0.72-2.35)	0.390
Age-adjusted HR/OR	1.00	1.29 (0.71-2.34)	0.409
Multivariate-adjusted HR/OR	1.00	1.21 (0.66-2.22)	0.546

HR: hazard ratio; OR: odds ratio
Other abbreviations as Table 7-1

Differences in NYHA class at baseline and follow-up period across the study groups are shown in Figure 7-3. NOP-LBBB was associated with a poorer NYHA class at the 6- to 12-month follow-up (*P* = 0.015).
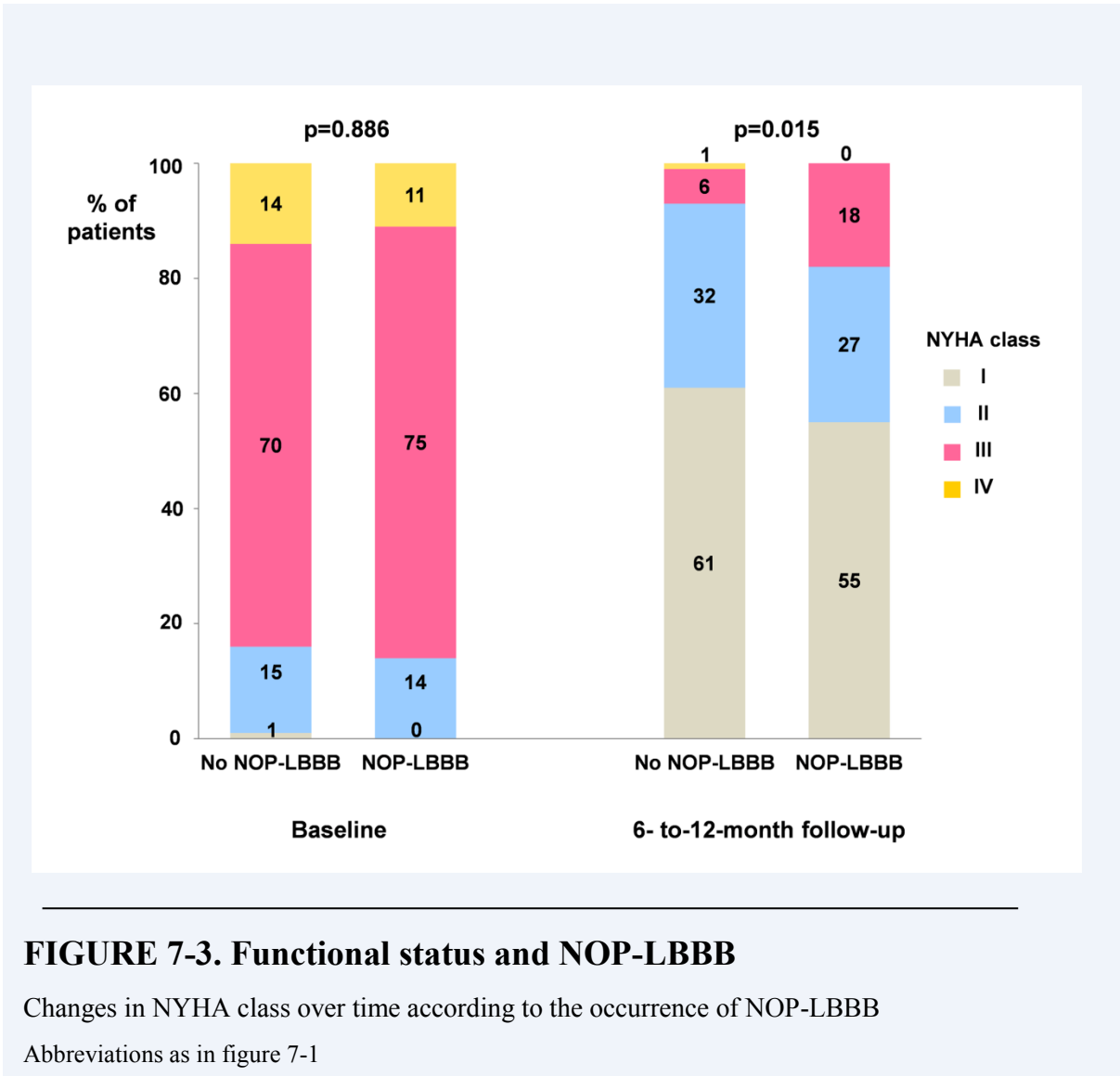
FIGURE 7-3. Functional status and NOP-LBBB

Changes in NYHA class over time according to the occurrence of NOP-LBBB

Abbreviations as in figure 7-1

7.5.4. NOP-LBBB, valve hemodynamics and LVEF

Changes in LVEF between baseline and follow-up are shown in Figure 7-4

The presence of hypertension (estimated coefficient [95% IC]: -3.37 [-6.66 to -0.76], $P = 0.045$), LVEF at baseline (estimated coefficient [95% IC]: -7.69 [-.8.72 to -6.66], $P < 0.001$), the use of transapical approach (estimated coefficient [95% IC]: -2.89 [-5.45 to -0.31], $P = 0.028$) and the occurrence of NOP-LBBB (estimated coefficient [95% IC]: -4.70 [-8.41 to -0.99], $P = 0.006$) were predictors of changes in LVEF over time. In the multivariate analysis,

LVEF at baseline and the occurrence of NOP- LBBB were the only independent predictors of lack of improvement in LVEF (estimated coefficients [95% IC]: -7.58 [8.60 to -6.55] and -4.00 [-6.91 to –1.10], $P = 0.007$, R^2: 0.422, respectively)
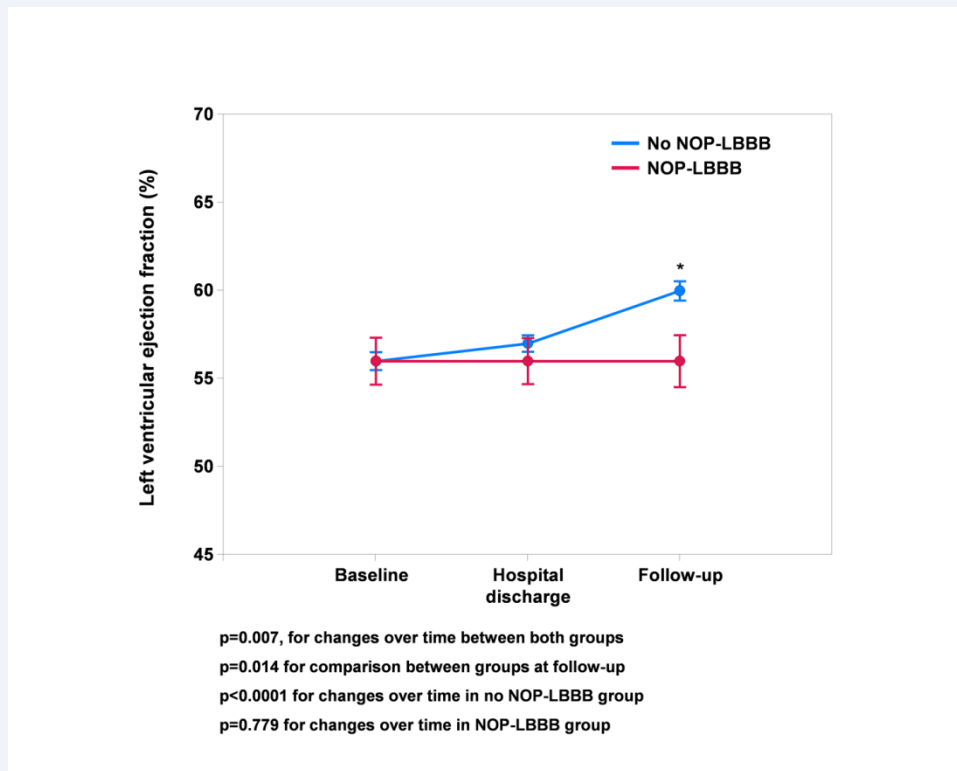
FIGURE 7-4. Left ventricular ejection fraction and NOP-LBBB

Changes in left ventricular ejection fraction following TAVI, according to the occurrence of NOP-LBBB

Abbreviations as in figure 7-1

7.6. DISCUSSION

NOP-LBBB following TAVI with a balloon-expandable valve occurred in 11.8% of patients without preexisting LBBB or PPI. NOP-LBBB was not associated with cumulative all-cause mortality, cardiovascular mortality, sudden death or re-hospitalizations for all-cause or heart failure after a median follow-up of 13 months. However, NOP-LBBB was associated with a higher rate of PPI, a lack of improvement in LVEF, and a poorer functional status at follow-up.

The rate of new-onset LBBB of about 20% observed in the present study is similar to that reported in previous studies of TAVI using balloon-expandable valves [246, 253, 255]. Also coherent with previous studies, about half of the conduction disturbances occurring after balloon-expandable valve implantation resolved within the few days following the procedure [253]. Previous studies have shown that unlike transient conduction disturbances, NOP-LBBB is partially determined by factors such as a lower (more ventricular) implantation of the stent valve frame, which is probably associated with more permanent mechanical damage of the left conduction system [119, 180, 253]. Also, the use of both transapical approach and 29-mm valves was associated with a higher incidence of NOP-LBBB, probably due to a greater damage of the ventricular septum in these cases. However, these observations have to be interpreted with caution, since this study was not designed to evaluate the predictors of NOP-LBBB.

7.6.1. NOP-LBBB and Mortality

The presence of LBBB has been classically considered a marker of poorer long-term survival in patients with preexisting cardiac disease [135, 137] and in apparently healthy individuals without overt disease [135, 256]. It has been shown that LBBB can affect the hemodynamic and electrical performance of the heart, leading to mechanical ventricular asynchrony, which in turn can result into increased end-systolic volumes, septal hypertrophy, abnormal perfusion, and an impairment of systolic and diastolic ventricular performance [257]. It is not known however, whether the presence of LBBB is directly associated with higher mortality or is merely an indicator of the severity of underlying cardiac disorders. Importantly, in most of studies showing a relationship between LBBB and mortality the follow-up was very long, ranging from 3 to 30 years [155, 160, 162, 256].

The occurrence of new-onset LBBB following SAVR has been a matter of concern, and studies on the impact of new LBBB on late mortality following SAVR have provided different results [153, 155, 160, 162, 167]. While some studies have suggested an association between the occurrence of LBBB and mortality after SAVR[155, 160, 165], others have failed to show any impact of this conduction abnormality on clinical outcomes following SAVR [153, 167]. The relatively limited sample size of all these studies, differences between studies regarding inclusion criteria (any new LBBB vs. only NOP-LBBB), and considerable variability in the length of follow-up may partially explain these differences.

Very few data exist on the clinical impact of new-onset LBBB following TAVI. Three previous studies have shown a negative effect of new-onset LBBB on left ventricular function at 1-year follow-up, with either a lack of improvement or even reduction in LVEF in those patients with new LBBB [197, 253, 258], in accordance with the results of this study. However, the clinical relevance of these changes in ventricular function remains to be determined. More recently, Houthuizen et al [252] reported a higher rate of all-cause mortality and cardiovascular mortality at 1-year follow-up in those patients who developed new LBBB after TAVI. These results clearly differ from those reported in the present study, where NOP-LBBB was not associated with any increase in overall or cardiovascular mortality. While the sample size and length of follow-up were similar in the 2 studies, some significant differences should be highlighted. First, the global risk of the patients included in this study was higher (logistic EuroSCORE of about 21% vs.16%), most likely related to a higher prevalence of cardiac and non-cardiac co-morbidities, and this also translated into a higher cumulative mortality rate (28.3% vs. 20.6%). The potential clinical impact of new conduction abnormalities after TAVI may differ between moderate- and high-risk patients, partially due to differences in the relative weight of co-morbidities in clinical outcomes. Second, the present study included only patients with new LBBB that persisted at hospital discharge, whereas the Houthuizen's study included patients with any new LBBB within 7 days after TAVI. This may be particularly relevant when using the balloon-expandable Edwards system, for which the occurrence of new LBBB is transient (recovery within a few hours or days) in about half of the cases.[253] Finally, another important difference between the 2 studies is the use of different transcatheter valve systems. Whereas the present study evaluated only patients who underwent TAVI with a balloon-expandable transcatheter heart valve system, Houthuizen et al [252] included a mix of self-expandable and balloon-expandable valves, with the majority of patients receiving a self-expandable CoreValve system and the incidence and evolution over

time of conduction disturbances are different between the 2 –balloon- and self-expandable-valve systems [181, 253]. In accordance with the results of our study, Testa et al.[169] did not find any association between new LBBB and all-cause and cardiovascular mortality at 1-year follow-up in a large cohort of patients who underwent self-expandable transcatheter valve implantation. Two of the main differences with respect to Houthuizen's study were the inclusion of higher risk patients (mean logistic EuroSCORE of ~23%) and the inclusion of persistent LBBB (vs. new-onset LBBB). These differences between studies may partially explain the controversial results regarding the clinical impact of new LBBB after TAVI, but this will have to be further evaluated in future studies.

7.6.2. NOP-LBBB and PPI at 1-Year Follow-Up

A high risk of AVB has been observed in patients and individuals without overt cardiac disease in the presence of LBBB.[259, 260] Previous studies including a relatively small number of patients showed a higher rate of PPI at follow-up among those patients who developed a new LBBB following either SAVR or TAVI. [155, 253, 261] The present study confirmed these results in a large cohort of patients who had received a balloon-expandable valve. Of note, cases with NOP-LBBB that progressed towards an advanced or complete AVB accounted for almost half (43%) of PPIs required during the first year after TAVI and 59% of PPIs due to complete AVB during the study period. Following the immediate mechanical injury of the left bundle branch after valve implantation, a further late injury of the conduction system related to an inflammatory or cicatrisation process may explain these late conduction disturbances. Also, the occurrence of NOP-LBBB may identify a group of patients more prone to developing conduction abnormalities which would require PPI at midterm follow-up. Testa et al. [169] found a higher rate of PPI in the NOP-LBBB group at 1 month after TAVI, but this difference was no longer significant at 1-year follow-up. Interestingly, the rate of PPI among patients with new LBBB was of 18%, slightly higher than the 13% observed in our study. However, the rate of PPI at 1-year follow-up among patients with no conduction disturbances at hospital discharge was as high as 17%, and this was much higher as compared to the 3% observed in our study. Therefore, the differences between the 2 studies may be explained by the very high rate of PPI during the follow-up period in patients without conduction disturbances after self-expandable valve implantation, much higher than that expected according to the age of the study population. Future studies including a much larger number

of patients will be needed to elucidate the factors associated with the progression of conduction disturbances and the need for PPI late after TAVI with balloon- and self-expandable transcatheter valves.

7.6.3. NOP-LBBB, LVEF, Functional Status and Re-hospitalizations

Prior studies have shown the deleterious effect of NOP-LBBB on LVEF following TAVI, with either a lack of improvement or even a decrease in LVEF as compared to patients with no new conduction abnormalities [197, 253, 258]. In accordance with these studies, a lack of improvement in LVEF at 6-to-12 months after TAVI was also observed in the present study in those patients with NOP-LBBB, as compared to an increase in LVEF in patients with no NOP-LBBB. Also, patients with NOP-LBBB exhibited an impaired functional status at follow-up, with 18% of the patients in NYHA class >II, as compared to only 7% of the patients with no new conduction abnormalities after TAVI. These results differ from those reported by Testa et al.[169] showing the lack of differences in LVEF changes and NYHA class at follow-up between patients with and without new LBBB after TAVI with a self-expandable valve [169]. As mentioned above, in the work of Testa et al. there was a rate of PPI as high as 17% within the year following TAVI in patients with no new LBBB (similar to the 18% in patients with new LBBB) and this may have been associated with LV mechanical dyssynchronism similar to that of LBBB. In addition, a tendency towards a higher rate of moderate or severe paravalvular leaks was also observed in the new LBBB group, and this might also have mitigated the potential differences in LVEF and NYHA class between patients NOP-LBBB and no NOP-LBBB groups.

The appearance of a new LBBB has been associated with a higher incidence of re-hospitalizations secondary to decompensated heart failure in patients diagnosed with heart failure[135] and in those without overt cardiac disease. [137]. NOP-LBBB was not associated with a higher rate of re-hospitalizations due to heart failure in the present study, and this was in accordance with prior studies in the TAVI field. [169, 253]Most patients had normal LVEF pre-TAVI and longer term follow-up may be necessary to detect an increase in re-hospitalizations secondary to LV mechanical dyssynchrony in these patients. Also, the number of events was limited and a larger sample size with a longer follow-up may be needed to detect differences between groups.

Limitations. The study was not designed to confirm the null hypothesis. Although the ECGs were evaluated by experienced cardiologists in each center, there was no centralized core lab for ECG analysis. There was no central committee to adjudicate clinical events, and although centers followed the VARC definitions, this might be relevant for the classification of mortality events as cardiovascular vs. non-cardiovascular. However, this probably has only minor importance with respect to overall mortality or PPI (yes/no) events. Finally, the duration of the follow-up was relatively short and this might have led to an underestimation of the impact of LBBB, especially in view of the fact that studies evaluating the relationship between LBBB and mortality in non-TAVI candidates had a follow-up ranging from 3 up to 30 years.[135, 155, 160, 165]

Conclusions

The occurrence of conduction disturbances, and particularly of LBBB, remains an important issue in the TAVI field. Determining the prognostic value of these conduction disturbances is of major clinical relevance, especially considering that specific therapies (PPI, resynchronization) might be applied to potentially modify clinical outcomes. The present study showed that NOP-LBBB following TAVI with a balloon-expandable valve was not associated with any increased risk of mortality (overall and cardiovascular) or re-hospitalization (any cause or heart failure) at 1-year follow-up. However, NOP-LBBB was associated with a higher rate of advanced or complete AVB requiring PPI and predicted a lack of LVEF improvement and poorer functional status after TAVI. Future studies will have to further evaluate both the clinical impact of LV changes and the factors associated with the further progression of conduction disturbances in patients developing LBBB after TAVI. Continuous follow-up of these patients over time is mandatory in order to determine the impact of NOP-LBBB at longer term follow-up.

7.7. ACKNOWLEDGMENTS

7.8. CONFLICT OF INTEREST DISCLOSURES

Drs. Webb, Cheung, Dumont and Ye are consultants for Edwards Lifesciences. Dr Rodés-Cabau is consultant for Edwards Lifesciencies and St Jude Medical. Dr. DeLarochellière is consultant for St. Jude Medical. The other authors reported no conflict of interest.

SUPPLEMENTAL TABLE 7-1. Individual Characteristics of Patients Requiring Permanent Pacemaker Implantation during the Follow-Up Period (n=29)

Age (years)	Gender	Baseline QRS morphology	QRS morphology at hospital discharge	Reason for PPI	Days after TAVI
65	Male	IVCD	IVCD	Symptomatic bradycardia	415
65	Female	Normal	LIBBB	Sinus node dysfunction	165
65	Female	Normal	LBBB	Complete AVB	147
68	Male	Normal	Normal	Sinus node dysfunction	1195
69	Male	Normal	LBBB	Complete AVB	232
70	Female	Normal	LBBB	Complete AVB	146
70	Female	IVCD	LBBB	Complete AVB	1841
72	Female	Normal	Normal	Sinus node dysfunction	300
75	Male	Normal	Normal	Symptomatic slow AF	1941
76	Female	Normal	Normal	Symptomatic bradycardia	578
77	Female	Normal	LBBB	Complete AVB	22
78	Male	Normal	LBBB	High degree AVB	340
79	Female	Normal	Normal	Symptomatic slow AF	895
79	Male	IVCD	LBBB	Sinus node dysfunction	347
79	Female	Normal	LBBB	High degree AVB	1296
80	Male	Normal	Normal	Mobitz II AVB	305
81	Male	RBBB	RBBB+LAHB	Trifascicular block + symptomatic bradycardia	359
81	Male	RBBB	RBBB	Complete AVB	32
81	Female	Normal	Normal	Sinus node dysfunction	814
83	Female	Normal	Normal	Complete AVB	105
85	Female	RBBB	RBBB+LAHB	Complete AVB	1197
86	Male	Normal	Normal	Complete AVB	387
87	Male	IVCD	IVCD	Complete AVB	1268

87	Male	Normal	Normal	Complete AVB	192
89	Male	IVCD	IVCD	Sinus node dysfunction	1204
89	Male	RBBB	RBBB	Symptomatic bradycardia	1123
89	Male	Normal	LBBB	Complete AVB	921
93	Female	Normal	Normal	Symptomatic slow AF	77
93	Female	RBBB+LAHB	RBBB+LAHB	Complete AVB	13

AVB: atrio-ventricular block; IVCD: intraventricular conduction delay; PPI: permanent pacemaker implantation; LAHB: left anterior hemiblock; LBBB: left bundle branch block; LIBBB: left incomplete bundle branch block; RBBB: right bundle branch block; TAVI: transcatheter aortic valve implantation

CHAPTER 8-Article 4

Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Implantation: Impact on Late Clinical Outcomes and Left Ventricular Function

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8.1. RESUME

Contexte: Très peu de données existent sur l'impact clinique de l'implantation d'un stimulateur cardiaque permanent (PPI) après implantation d'une valve aortique par cathéter (TAVR). L'objectif de cette étude était d'évaluer l'impact d'une PPI après un TAVR sur les résultats à long terme dans une grande cohorte de patients.

Méthodes et résultats: Un total de 1556 patients consécutifs sans PPI traités par TAVR (valve déployée par ballonnet [BEV]: 858 patients; valve auto-extensible [SEV]: 698 patients) ont été inclus. Au total, 239 patients (15.4%) ont nécessité une PPI dans les 30 premiers jours suivant le TAVR (groupe BEV: 7.1%; groupe SEV: 25.5%). La raisons de la PPI était un bloc auriculo-ventriculaire complet ou de haut degré dans la plupart des cas (75%). Au terme d'un suivi moyen de 22 ± 17 mois, aucune association n'a été observée entre la nécessité d'IPP à 30 jours et la mortalité toutes causes confondues (HR: 0.98 [0.74 à 1.30], $P = 0.871$), la mortalité cardiovasculaire (HR: 0.81 , IC 95%: 0.56 à 1.17, $P = 0.270$) et la mortalité toutes causes confondues ou les réhospitalisations pour insuffisance cardiaque (HR: 1.00, IC à 95%: 0.77 à 1.30, $P = 0.980$). Une diminution du taux de morts subites ou de cause inconnue a été observée chez les patients avec PPI (1.7% contre 5.4% chez les patients sans PPI, HR: 0,31, IC à 95%: de 0.11 à 0.85, $P = 0.023$). Les patients ayant eu une nouvelle PPI ont eu une mauvaise évolution de leur FEVG avec le temps ($P = 0.017$), et une nouvelle PPI était un facteur prédictif indépendant de diminution de la FEVG à 6 et 12 mois de suivi (coefficient estimé: -2.26, IC à 95%: -4.07 à -0.44, $P = 0.013$, R2: 0.121).

Conclusion: La PPI est une complication fréquente du TAVR, mais n'est pas associée à un taux accru de décès ou de réhospitalisation globale ou cardiovasculaire pour l'insuffisance cardiaque après un suivi de ~ 2 ans en moyenne. En effet, la PPI à 30 jours était un facteur de protection de la survenue de mort inattendue (subite ou inconnue). Cependant, elle a eu un effet négatif sur l'évolution de la fonction ventriculaire gauche.

8.2. ABSTRACT

Background: Very few data exist on the clinical impact of permanent pacemaker implantation (PPI) following transcatheter aortic valve implantation (TAVI). The objective of this study was to assess the impact of new PPI following TAVI on late outcomes in a large cohort of patients.

Methods and Results: A total of 1,556 consecutive patients without prior PPI undergoing TAVI (balloon-expandable valve [BEV]: 858 patients; self-expandable valve [SEV]: 698 patients) were included. A total of 239 patients (15.4%) required a new PPI within the first 30 days following TAVI (BEV group: 7.1%; SEV group: 25.5%). Reasons for PPI were high degree or complete atrioventricular block in most (75%) cases. At a mean follow-up of 22 ± 17 months, no association was observed between the need for 30-day PPI and all-cause mortality (HR: 0.98 [0.74-1.30], $P = 0.871$), cardiovascular mortality (HR: 0.81, 95% CI: 0.56-1.17, $P = 0.270$), and all-cause mortality or rehospitalization due to heart failure (HR: 1.00, 95% CI: 0.77-1.30, $P=0.980$). A lower rate of sudden or unknown death was observed in patients with PPI (1.7% vs. 5.4% in patients with no PPI, HR: 0.31, 95% CI: 0.11-0.85, $P = 0.023$). Patients with new PPI showed a poorer evolution of LVEF over time ($P = 0.017$), and new PPI was an independent predictor of LVEF decrease at 6- to 12-month follow-up (estimated coefficient: -2.26, 95% CI:-4.07 to -0.44, $P = 0.013$, R^2: 0.121).

Conclusion: The need for PPI was a frequent complication of TAVI, but it was not associated with any increase in overall or cardiovascular death or rehospitalization due to heart failure after a mean follow-up of ~ 2 years. Indeed, 30-day PPI was a protective factor for the occurrence of unexpected (sudden or unknown) death. However, new PPI did have a negative effect on left ventricular function over time.

8.3.   INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become the treatment of choice for patients with aortic stenosis who are considered to be non-operable and a good alternative for those at high surgical risk.[99] However, the occurrence of some periprocedural complications remains a concern. The need for permanent pacemaker implantation (PPI) following the procedure is one of the most frequent complications associated with TAVI, with an overall incidence of about 15% (~25% and 7% following TAVI with self-expandable (SEV) and balloon-expandable valves (BEV), respectively).[99]

Strong evidence supports the potential negative impact of right ventricular apical pacing, which has been associated with an increased rate of the combined endpoint of mortality and rehospitalization due to heart failure in patients with left ventricular dysfunction,[212-214] ventricular tachyarrhythmias[215, 216] and pacing-induced cardiomyopathy in patients without overt structural heart disease.[133] However, evidence on the clinical impact of PPI following TAVI remains scarce and based on small studies with limited ($\leq$ 1 year) follow-up.[187, 262-264] While these studies did not find any impact of PPI on mortality, concerns that they may have been underpowered due to inadequate sample size have been raised.[265] Also, no studies to date have evaluated the impact of PPI on rehospitalizations due to heart failure, left ventricular function changes and sudden death. Finally, the vast majority of patients included in studies evaluating the impact of PPI following TAVI had received a SEV,[187, 262-264] and very few data exist on those patients receiving a BEV. The aims of this study were, therefore, to assess, in a large cohort of patients undergoing TAVI with BEV and SEV, the impact of new PPI on i) late outcomes (including mortality and rehospitalization due to heart failure) and ii) left ventricular function and functional status changes after the intervention.

8.4. METHODS

8.4.1. Study Population

A total of 1,811 consecutive patients who underwent TAVI with either BEV or SEV in 8 centers between January 2005 and February 2013 were screened. Of these, 233 patients were excluded due to pre-existing pacemaker implantation, and 22 patients due to an unsuccessful procedure without valve implantation. The final study population consisted of 1,556 patients (SEV: 698 patients; BEV: 858 patients).

Patients were considered candidates for TAVI if they were at high or prohibitive predicted perioperative risk as evaluated by a heart team composed of cardiac surgeons and interventional cardiologists at each center. TAVI procedures were performed as previously described[99]. The study was conducted in accordance with the institutional ethics committee of each participating center, and all patients provided signed informed consent for the procedures. Data were collected prospectively in each center. Procedural complications for the purpose of this study were defined according to Valve Academic Research Consortium (VARC)-2 criteria.[112]

8.4.2. Indications for PPI

In agreement with the ACC/AHA/HRS recommendations, PPI was indicated if third-degree or advanced second-degree atrio-ventricular block (AVB) at any anatomical level occurred and was not expected to resolve, or in the presence of sinus node dysfunction and documented symptomatic bradycardia.[230] The indication of PPI in the presence of left bundle branch block (LBBB) with PR prolongation (>200 ms) not expected to normalize was at the discretion of the physician. The selection of a single-chamber or dual-chamber pacemaker was left to the implanter's choice.

8.4.3. Follow-up

Follow-up was carried out through clinical outpatient visits and/or phone contacts at 30 days, 6 months, 12 months and yearly afterwards. No patient was lost during the follow-up period.

Echocardiographic examinations at baseline were available in all patients, in 1279 patients at hospital discharge, and in 902 patients at 6- to 12-month follow-up (83% of patients alive at that point of time, 89% and 78% in the BEV and SEV groups, respectively, $P = 0.002$). Left ventricular ejection fraction (LVEF) was calculated using the biplane modified Simpson's method and left ventricular dysfunction was defined as LVEF $\leq$ 50%.[266]

8.4.4. Endpoints and Definitions

The primary endpoint was defined as a composite of all-cause mortality and hospitalization due to heart failure at last follow-up. Secondary endpoints were: all cause-mortality, cardiovascular mortality, sudden cardiac death, composite of sudden cardiac death and death of unknown cause, rehospitalization due to heart failure, functional class changes, and LVEF changes. Several sources of information were used to investigate endpoints: outpatient clinical visits, phone contacts with patients, families or physicians and review of medical records to determine causes of death when necessary. All events were defined according to the VARC-2 criteria.[112] Sudden cardiac death was defined as any unexpected death due to cardiac disease occurring within 1 hour after of the onset of symptoms[254]. Death was classified as of unknown cause if the unexpected death failed to meet the confirmation criteria of sudden cardiac death, and the cause of death could not be determined after contact with the responsible physician or the patient's family. Death of unknown cause was classified as cardiovascular death.[112] Only readmissions with a primary diagnosis of heart failure at hospital discharge were considered as rehospitalizations due to heart failure. For patients with several hospitalizations due to heart failure, only the first episode was included in the analysis.

8.4.5. Statistical Analysis

Qualitative variables are expressed as percentages and quantitative variables as mean ± standard deviation or median (interquartile range) according to variable distribution, and compared using Chi-Square or Fisher exact test and sided t-test or Wilcoxon signed-rank test as appropriate. The primary composite endpoint and secondary endpoints were compared between PPI and no PPI and BEV and SEV groups using proportional hazard models (cumulative outcomes). All multivariate models were adjusted for baseline differences in the univariate analysis including variables with a P value $\leq$ 0.10. A landmark analysis with a

landmark cut-off at 30 days was used to further investigate the impact of PPI on study outcomes. Thirty-day outcomes were assessed with a logistic regression model. Survival rates were summarized using Kaplan-Meier estimates and the log-rank test was used for comparison between groups. A linear general model for repeated measures with interaction was used to compare the changes in LVEF at different time points between PPI and no PPI groups. Further comparisons were performed using the Tukey's technique. Predictors of LVEF changes over time were analyzing using a univariate and a multivariable linear regression model. The results were considered significant with p-values <0.05. Analyses were conducted using the statistical package SAS, version 9.2 (SAS Institute Inc., Cary, NC)

8.5. RESULTS

A total of 239 patients (15.4%) received a PPI within 30 days following TAVI (25.5% vs. 7.1% in the SEV and BEV groups, respectively, P <0.001). Baseline and procedural characteristics of the study population, according to the need for PPI following TAVI are shown in Table 8-1.

TABLE 8-1. Baseline and Procedural Findings, According to the Need for 30-day New Pacemaker Implantation Following Transcatheter Aortic Valve Implantation (n=1556)

	No Pacemaker (n=1317)	30-day Pacemaker Implantation (n=239)	*P* value
Clinical Characteristics			
Age (years)	80 ± 8	81 ± 5	0.074
Male	629 (47.8)	111 (46.4)	0.708
Body mass index (kg/m²)	26 (23-29)	27 (24-30)	0.134
NYHA class ≥3	1014 (77.0)	175 (73.2)	0.206
Hypertension	1067 (81.1)	199 (83.3)	0.354
Diabetes mellitus	418 (31.7)	67 (28.0)	0.282
COPD	409 (31.1)	73 (30.5)	0.864

eGFR <60 ml/min	741 (56.3)	141 (59.0)	0.433
Paroxysmal/chronic AF	372 (28.4)	62 (26.3)	0.499
Coronary artery Disease	765 (58.1)	112 (46.8)	0.001
Porcelain aorta	192 (14.6)	29 (12.1)	0.246
Logistic EuroScore (%)	20.5 ± 14.0	20.3 ± 14.0	0.776
STS-PROM score (%)	7.7 ± 5.4	7.2 ± 4.9	0.237
Echocardiography			
LVEF (%)	55 ± 14	56 ± 13	0.283
LVEF≤50%	397 (30.2)	70 (29.3)	0.785
Mean gradient (mmHg)	47 ± 16	49 ± 16	0.085
Aortic valve area (cm^2)	0.60 (0.50-0.80)	0.64 (0.50-0.79)	0.178
Procedural findings			
Procedural success*	1128 (85.6)	198 (82.8)	0.261
Approach			
Transapical/Transaortic	362 (27.5)	32 (13.4)	<0.001
Transfemoral/Subclavian	955 (72.5)	207 (86.6)	
Prosthesis type			
Self-expandable	520 (39.5)	178 (74.5)	<0.001
Balloon-expandable	797 (60.5)	61 (25.5)	
Prosthesis size (mm)			
20-23	368 (27.9)	32 (13.4)	
26	678 (51.5)	118 (49.4)	<0.001
29-31	271 (20.6)	89 (37.2)	
Need for a second valve	32 (2.4)	15 (6.3)	0.001
≥Moderate AR	174 (13.9)	40 (17.2)	0.187

*Following Valve Academic Research Consortium-2 criteria.
Values are expressed as n (%), mean (±SD) or median (25-75th percentile) when appropriate.
AR: aortic regurgitation, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration ratio, LVEF: left ventricular ejection fraction, NOP-LBBB: new-onset persistent left bundle branch block, NYHA: New York Heart Association, STS-PROM: Society of Thoracic Surgeons predicted risk of mortality.

The timing, clinical indications and pacemaker models implanted overall, and according to the type of transcatheter valve (SEV or BEV) are shown in Table 8-2. The 30-day outcomes according to study group (PPI vs. no PPI) are shown in Table 8-3. There were no differences between groups in 30-day mortality or major complications following TAVI (*P*>0.20 for all).

A resting ECG was performed at 6- to 12-month follow-up in 133 patients with 30-day PPI (62% of patients at risk, 61.7% and 62.5% in the SEV and BEV groups, respectively, P=0.707) with the aim of assessing the presence of pacemaker activity. Pace rhythm was observed in 89 of these patients (66.9%), and it was more frequent in patients who had received a SEV (72.8% vs. 46.7% in patients with a BEV, P=0.007).

TABLE 8-2. Timing, Type and Indications for 30-day Permanent Pacemaker Implantation, Overall and According to the Transcatheter Valve Type

	Overall (n=239)	Self-expandable (n=178)	Balloon-expandable (n=61)	P value
Days after TAVI	3 (1-6)	2 (1-6)	3 (2-6)	0.188
PPI timing				
≤24 hours	86 (36.0)	71 (39.9)	15 (24.6)	
24 hours- 7 days	128 (53.6)	93 (52.2)	35 (57.4)	0.025
>7 days	25 (10.4)	14 (7.9)	11 (18.0)	
Indications				
Complete or high degree AVB	180 (75.3)	135 (75.8)	45 (73.8)	
Sinoatrial node disease	17 (7.1)	14 (7.9)	3 (4.9)	
Symptomatic bradycardia	19 (7.9)	9 (5.1)	10 (16.4)	0.030
LBBB + first degree AVB	23 (9.6)	20 (11.2)	3 (4.9)	
Type of pacemaker				
Single-chamber	96 (40.2)	78 (43.8)	18 (29.5)	
Dual-chamber	143 (59.8)	100 (56.2)	43 (70.5)	0.051

Values are expressed as n (%) or median (25-75th percentile) when appropriate.
AVB: atrioventricular block, LBBB: left bundle branch block, PPI: permanent pacemaker implantation, TAVI: transcatheter aortic valve implantation

TABLE 8-3. Thirty-Day Outcomes According to the Need for Permanent Pacemaker Implantation within the First 30 Days after the Procedure

	No PPI (n=1317)	30-day PPI (n=239)	OR	*P* value
30-day outcomes				
Death	92 (7.0)	16 (6.7)	0.96 (0.55-1.66)	0.892
Stroke	38 (2.9)	10 (4.2)	1.49 (0.73-3.03)	0.274
Myocardial infarction	25 (1.9)	3 (1.3)	0.59 (0.14-2.60)	0.485
Major vascular complications	95 (7.2)	22 (9.2)	1.31 (0.80-2.12)	0.282
Major or life-threatening bleeding	206 (15.6)	33 (13.8)	0.85 (0.57-1.27)	0.434

OR: odds ratio, PPI: permanent pacemaker implantation

8.5.1. 30-Day PPI and Late Outcomes

Cumulative late clinical events, grouped according to the need for PPI within 30 days following TAVI are shown in Table 8-4. After a mean follow-up of 22±17 months, a total of 525 patients (33.7%) had either died or required a rehospitalization due to heart failure, with no differences between PPI and no PPI groups (34.1% vs. 31.8%; HR: 1.00, 95% CI: 0.77-1.30, *P* = 0.980). There were no differences between groups in the secondary endpoints of late overall and cardiovascular mortality, or rehospitalization due to heart failure (Table 8-4). There was however a lower rate of unexpected (sudden or unknown) death among patients who had a PPI within 30 days following TAVI (HR: 0.31, 95% CI: 0.11-0.85, *P* = 0.023). This protective effect of 30-day PPI on unexpected death persisted following a landmark analysis with a cut-off at 30 days (Table 8-4).

The Kaplan-Meier curves at 3-year follow-up according to the study group (PPI vs. no PPI) are shown in Figure 8-1.

TABLE 8-4. Risk of Mortality and Heart Failure According to the Need for 30-day Permanent Pacemaker Implantation

Outcome	No PPI	30-day PPI	Univariate HR (95% CI)	P value	Multivariate HR* (95% CI)	P value
All patients						
No. of patients	1317	239				
Primary Outcome						
Death or rehospitalization for heart failure	449 (34.1)	76 (31.8)	0.81 (0.64-1.04)	0.097	1.00 (0.77-1.30)	0.980
Secondary Outcomes						
Death from any cause	364 (27.6)	62 (25.9)	0.83 (0.63-1.09)	0.178	0.98 (0.74-1.30)	0.871
Death from cardiovascular causes	254 (19.3)	37 (15.5)	0.72 (0.51-1.02)	0.063	0.81 (0.56-1.17)	0.270
Sudden cardiac death	26 (2.0)	1 (0.4)	0.19 (0.03-1.39)	0.101	0.15 (0.02-1.08)	0.059
Sudden cardiac death/Unknown death	71 (5.4)	4 (1.7)	0.27 (0.10-0.75)	0.011	0.31 (0.11-0.85)	0.023
Rehospitalization for heart failure	134 (10.2)	24 (10.0)	0.86 (0.55-1.32)	0.482	1.16 (0.73-1.85)	0.529
>30 days to maximun						
No. of patients	1225	223				
Primary Outcome						
Death or rehospitalization for heart failure	357 (29.1)	60 (26.9)	0.78 (0.60-1.03)	0.082	1.05 (0.78-1.40)	0.762
Secondary Outcomes						
Death from any cause	272 (22.2)	46 (20.6)	0.80 (0.58-1.09)	0.160	1.02 (0.74-1.42)	0.895
Death from cardiovascular causes	162 (13.2)	21 (9.4)	0.61 (0.39-0.96)	0.034	0.79 (0.49-1.27)	0.331
Sudden cardiac death	17 (1.4)	1 (0.4)	0.27 (0.04-2.07)	0.209	0.19 (0.03-1.47)	0.112
Sudden cardiac death/Unknown death	63 (5.1)	4 (1.8)	0.31 (0.11-0.85)	0.022	0.36 (0.13-1.00)	0.047
Rehospitalization for heart failure	132 (10.8)	24 (10.8)	0.87 (0.56-1.34)	0.521	1.17 (0.74-1.87)	0.500

* Adjusted for baseline differences between groups;PPI: permanent pacemaker implantation: HR: hazard ratio, CI: confidence interval
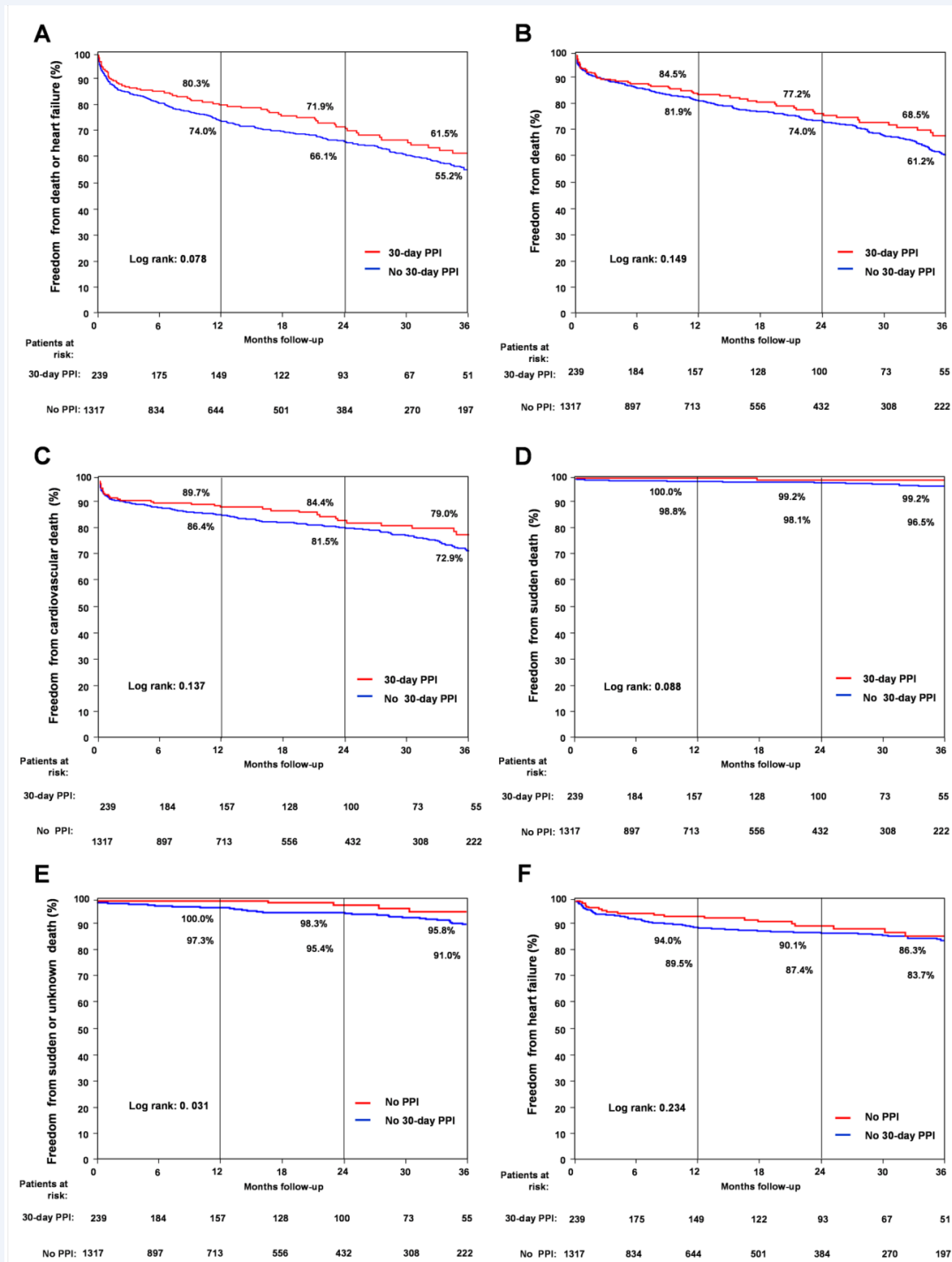
FIGURE 8-1. Kaplan-Meier curves at 1-year follow-up for the combined endpoint of all-cause mortality and rehospitalization for heart failure (A), all-cause mortality (B), cardiovascular mortality (C), sudden cardiac death (D), sudden cardiac death or death of unknown cause (E), and rehospitalization for heart failure (F)

150

The individual characteristics of the 76 patients who suffered sudden or unknown death are detailed in Supplement data Table 8-1. Clinical, echocardiographic and electrocardiographic univariate and multivariate predictors of unexpected (sudden and unknown) death and sudden cardiac death in the study population are shown in Table 8-5. New-onset persistent left bundle branch block (NOP-LBBB) was observed in 269 patients (20.4% of patients without 30-day PPI, 39.5% and 10.2% in the SEV and BEV groups, respectively, $P < 0.001$). The mean QRS at discharge in patients with NOP-LBB was 145±19 ms. Pre-existing paroxysmal/chronic AF (HR: 1.76, 95% CI: 1.09-2.86, $P = 0.021$) and the lack of 30-day-PPI (HR: 3.22, 95% CI: 1.16-9.09, $P = 0.024$) were the independent predictors of unexpected death. The occurrence of NOP-LBBB (HR: 2.77, 95% CI: 1.09-7.07, $P = 0.033$) and a lower LVEF at baseline (5.25 for each decrease in 5%, 95% CI: 5.15-5.45, $P < 0.001$) were the independent predictors of sudden cardiac death. No association was observed between NOP-LBBB and overall mortality (HR: 1.30, 95% CI: 0.86-1.89, $P = 0.226$) or cardiovascular mortality (HR: 1.31, 95% CI: 0.74-2.34, $P = 0.357$).

8.5.2. Subgroups Analyses (Low LVEF, Transcatheter Valve Type)

Late outcomes according to the need for PPI following TAVI in patients with low (≤50%) and normal (>50%) LVEF at baseline are shown in Table 8-6. There were no differences in all- cause mortality and rehospitalization due to heart failure, all-cause mortality, cardiovascular mortality and sudden cardiac death between patients with and without LVEF ≤ 50% ($P > 0.10$ for all). However, a higher rate of unexpected (sudden or unknown) death was observed in patients with no PPI and normal left ventricular function ($P = 0.043$). Also, no negative impact of PPI was encountered in patients with at least moderate left ventricular dysfunction (LVEF ≤ 40%) ($P > 0.10$ for all), with a protective effect on unexpected death in patients with normal or mildly depressed left ventricular function ($P = 0.023$).

TABLE 8-5. Univariate and Multivariate Predictive Factors of Unexpected (Sudden/Unknown) Death and Sudden Death in the Study Population (n= 1556)

	Unexpected (Sudden/Unknown) Death				Sudden Cardiac death			
	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	P value	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	P value
Clinical and echocardiographic variables								
Age (years)	1.02 (0.99-1.06)	0.260			0.97 (0.93-1.02)	0.292		
Male	1.09 (0.69-1.71)	0.717			1.34 (0.63-2.86)	0.446		
Hypertension	0.71 (0.42-1.18)	0.191			1.07 (0.41-2.82)	0.893		
Diabetes mellitus	0.85 (0.51-1.42)	0.542			1.87 (0.87-4.00)	0.107		
COPD	1.11 (0.67-1.82)	0.677			0.83 (0.35-1.97)	0.671		
eGFR <60 ml/min	1.11 (0.70-1.76)	0.646			1.31 (0.60-2.86)	0.502		
Paroxysmal/chronic atrial fibrillation	1.71 (1.06-2.74)	0.027	1.76 (1.09-2.86)	0.021	1.02 (0.43-2.41)	0.972		
Coronary artery Disease	1.88 (1.14-3.09)	0.013	1.61 (0.95-2.74)	0.079	1.19 (0.55-2.58)	0.660		
LVEF (%)*	5.10 (5.05-5.15)	0.027	5.05 (5.00-5.25)	0.060	5.20 (5.10-5.30)	0.001	5.25 (5.15-5.45)	<0.001
STS-PROM score (%)	1.04 (1.00-1.08)	0.061	1.02 (0.98-1.07)	0.330	0.96 (0.87-1.05)	0.353		
Procedural findings								
Balloon-expandable valve	1.51 (0.95-2.41)	0.083	1.04 (0.62-1.73)	0.881	0.34 (0.14-0.81)	0.014	0.47 (0.17-1.33)	0.154
≥Moderate AR	1.43 (0.78-2.61)	0.248			2.09 (0.83-5.26)	0.119		
Lack of 30-day PPI	3.70 (1.33-10.00)	0.011	3.22 (1.16-9.09)	0.024	5.26 (0.71-3.84)	0.101		
NOP-LBBB	1.00 (0.57-1.74)	0.994			2.51 (1.13-5.60)	0.024	2.77 (1.09-7.07)	0.033

NOP-LBBB: new-onset persistent left bundle branch block. Other abbreviations as Table8-1.For each decrease of 5% in LVEF

TABLE 8-6. Risk of Mortality and Hospitalization for Heart Failure, According to the Need for 30-Day Permanent Pacemaker Implantation in Patients with Normal and Low Left Ventricular Ejection Fraction

Outcome	No PPI	30-day PPI	Univariate HR (95% CI)	p value
LVEF>50%				
No. of patients	920	169		
Primary Outcome				
Death or rehospitalization for heart failure	296 (32.2)	52 (30.8)	0.83 (0.62-1.12)	0.218
Secondary Outcomes				
Death from any cause	235 (32.2)	43 (25.4)	0.83 (0.62-1.12)	0.385
Death from cardiovascular causes	158 (17.2)	22 (13.0)	0.67 (0.43-1.10)	0.081
Sudden cardiac death	13 (1.4)	1 (0.6)	0.36 (0.05-2.75)	0.324
Sudden cardiac death/ Unknown death	46 (5.0)	3 (1.8)	0.30 (0.09-0.98)	0.043
Rehospitalization for heart failure	87 (9.5)	16 (9.5)	0.87 (0.51-1.48)	0.603
LVEF≤50%				
No. of patients	395	70		
Primary Outcome				
Death or rehospitalization for heart failure	152 (38.3)	24 (34.3)	0.78 (0.51-1.20)	0.259
Secondary Outcomes				
Death from any cause	128 (32.2)	19 (27.1)	0.77 (0.47-1.24)	0.277
Death from cardiovascular causes	95 (23.9)	15 (21.4)	0.81 (0.47-1.40)	0.447
Sudden cardiac death	13 (3.3)	0	-	-
Sudden cardiac death/unknown death	26 (6.5)	1 (1.4)	0.20 (0.03-1.47)	0.114
Rehospitalization for heart failure	47 (11.8)	8 (11.4)	0.85 (0.40-1.79)	0.663

LVEF: left ventricular ejection fraction. Other abbreviations as Table8- 3.

Baseline clinical characteristics and procedural findings and clinical outcomes during the follow-up period according to the type of valve implanted are displayed in Data Supplement Table 8-2 and 8-3, respectively. Death or heart failure, death from any cause and from cardiovascular causes, sudden cardiac death, sudden /unknown death, and hospitalizations due to heart failure were similar in the SEV and BEV groups ($P > 0.10$ for all).

The late outcomes according to the need for PPI following TAVI for the patients who had received a BEV or a SEV are shown in Table 8-7. There were no differences in any of the late outcomes between patients with and without PPI in each of the transcatheter valve type groups. In the SEV group, a trend towards a lower rate of sudden cardiac /unknown death was observed in patients with PPI (HR: 0.30, 95%CI: 0.09-1.02, $P = 0.053$). In the BEV group, the risk of sudden cardiac/unknown death was similar in patients with and without PPI (HR: 0.28, 95% CI: 0.04-2.05, $P = 0.212$). However, no significant interaction was found between the need of PPI and the type of valve implanted for unexpected death ($P = 0.997$) and sudden cardiac death ($P = 0.984$).

8.5.3. PPI, LVEF and Functional Status

Changes in valve hemodynamics according to the need for PPI are shown in Supplement Figure. LVEF significantly increased in overall population at 6-to 12-month follow-up (from $56 \pm 13\%$ to $59 \pm 11\%$, $P < 0.001$). LVEF changes over time according to the need for PPI are shown in Figure 8-2A. Whereas LVEF increased over time in patients with no PPI, LVEF decreased at follow-up in those patients who had PPI following TAVI ($P = 0.017$ for comparison between groups), without differences between BEV and SEV groups ($P = 0.668$) (Supplement Figure 8-2). The poorer evolution of LVEF in patients who needed PPI was observed in those patients who received a dual-chamber (vs. single-chamber) PPI ($P = 0.043$; $P = 0.023$ after adjusting for the presence of AF; Figure 8-2B).

TABLE 8-7. Risk of Mortality and Rehospitalization for Heart Failure Following TAVI with Balloon-Expandable and Self-Expandable Valves, According to the Need for 30-Day Permanent Pacemaker

Outcome	No PPI	30-day PPI	Univariate HR (95% CI)	*P* value
Balloon-expandable valve				
No. of patients	797	61		
Primary Outcome				
Death or hospitalization for heart failure	313 (39.3)	26 (42.6)	1.11 (0.75-1.66)	0.600
Secondary Outcomes				
Death from any cause	251 (31.5)	22 (36.1)	1.08 (0.70-1.67)	0.737
Death from cardiovascular causes	174 (21.8)	13 (21.3)	0.93 (0.53-1.64)	0.803
Sudden cardiac death	7 (0.9)	0	-	-
Sudden cardiac death/unknown death	45 (5.6)	1 (1.6)	0.28 (0.04-2.05)	0.212
Hospitalization for heart failure	109 (12.7)	7 (11.5)	0.92 (0.43-2.00)	0.840
Self-expandable valve				
No. of patients	520	178		
Primary Outcome				
Death or hospitalization for heart failure	136 (26.2)	50 (28.1)	0.99 (0.72-1.37)	0.965
Secondary Outcomes				
Death from any cause	113 (21.7)	40 (22.5)	0.97 (0.68-1.39)	0.859
Death from cardiovascular causes	80 (15.4)	24 (13.5)	0.82 (0.52-1.29)	0.386
Sudden cardiac death	19 (3.7)	1 (0.6)	0.15 (0.2-1.09)	0.060
Sudden cardiac death/unknown death	26 (5.0)	3 (1.7)	0.30 (0.09-1.02)	0.053
Hospitalization for heart failure	32 (6.2)	17 (9.6)	1.41 (0.78-2.54)	0.252

Abbreviations as Table 8-3.

A
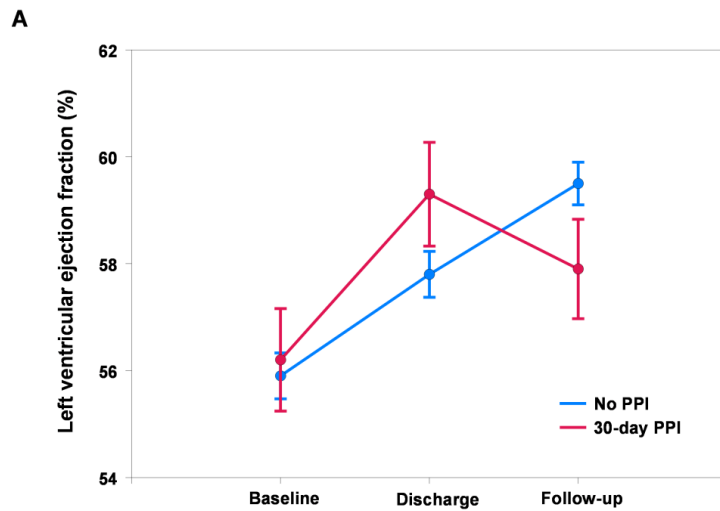
P=0.017, between both groups
P=0.412, between baseline and discharge across groups
P=0.003, between discharge and follow-up across groups
P=0.001, between discharge and follow-up for no PPI groups
P=0.061, between discharge and follow-up for 30-day PPI group

B
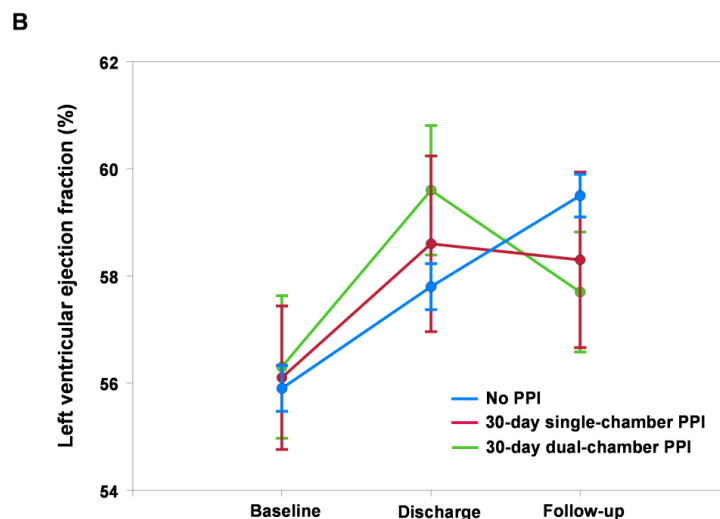
P=0.043 between groups
P=0.407, between baseline and discharge accross groups
P=0.007 between discharge and follow-up accross groups
P=0.020 no PPI vs dual chamber for change between discharge and follow-up
P=0.333 no PPI vs single chamber for change between discharge and follow-up

FIGURE 8- 2. LVEF changes between baseline and 6- to- 12 month follow-up according to the need for 30-day permanent pacemaker implantation (A) and the type of pacemaker implanted (B)

Of note, only the 855 patients with echocardiographic exams at the 3 points of time have been included.

156

The variables associated with LVEF changes over time are displayed in Table 8-8. LVEF at baseline and the need for PPI within 30 days were the only independent predictors of LVEF decrease over time (estimated coefficient: -3.43, 95% CI: -4.10 to -2.76, $P < 0.001$ and -2.26, 95% CI: -4.07 to -0.44, $P = 0.013$, R^2: 0.121, respectively).

TABLE 8-8. Univariate and Multivariate Predictors of Left Ventricular Ejection Fraction Changes Over Time (Hospital Discharge and 6- to 12-Month Follow-Up)

	Univariate		Multivariate	
	B coefficient (95% CI)*	***P* value**	**B coefficient (95% CI)***	***P* value**
Clinical variables				
Age (years)	0.23 (-0.51 to 0.97)	0.534		
Male	0.94 (-0.49 to 2.37)	0.197		
Hypertension	-0.50 (-2.27 to 1.28)	0.584		
Diabetes mellitus	0.11 (-1.42 to 1.63)	0.892		
eGFR <60 ml/min	-0.53 (-1.96 to 0.90)	0.470		
Paroxysmal/chronic AF	-1.54 (-3.13 to 0.50)	0.058	-1.32 (-2.82 to 0.18)	0.084
Coronary artery disease	1.57 (0.15 to 2.99)	0.030	0.29 (-1.09 to 1.66)	0.681
Echocardiography				
LVEF (%)	-3.49 (-4.15 to -2.83)	<0.001	-3.44 (-4.11 to -2.77)	<0.001
Mean gradient (mmHg)	-0.50 (-1.21 to 0.21)	0.170		
Aortic valve area (cm²)	0.04 (-0.64 to 0.72)	0.914		
Procedural variables				
Approach Transapical/ Transaortic	1.76 (0.17 to 3.34)	0.030	0.67 (-0.87 to 2.21)	0.395
≥ Moderate AR	-1.21 (-3.29 to 0.87)	0.253		
30-day PPI	-2.63 (-4.52 to -0.74)	0.006	-2.26 (-4.07 to -0.44)	0.013

* per 1-SD increase or categorical change; Abbreviations as Table 8-1

Changes in NYHA class over time are shown in **Figure 8-3**. A marked improvement in NYHA class was observed in patients with and without 30-day PPI ($P < 0.001$ for both groups) without differences in NYHA class changes between PPI and no PPI groups ($P = 0.672$).
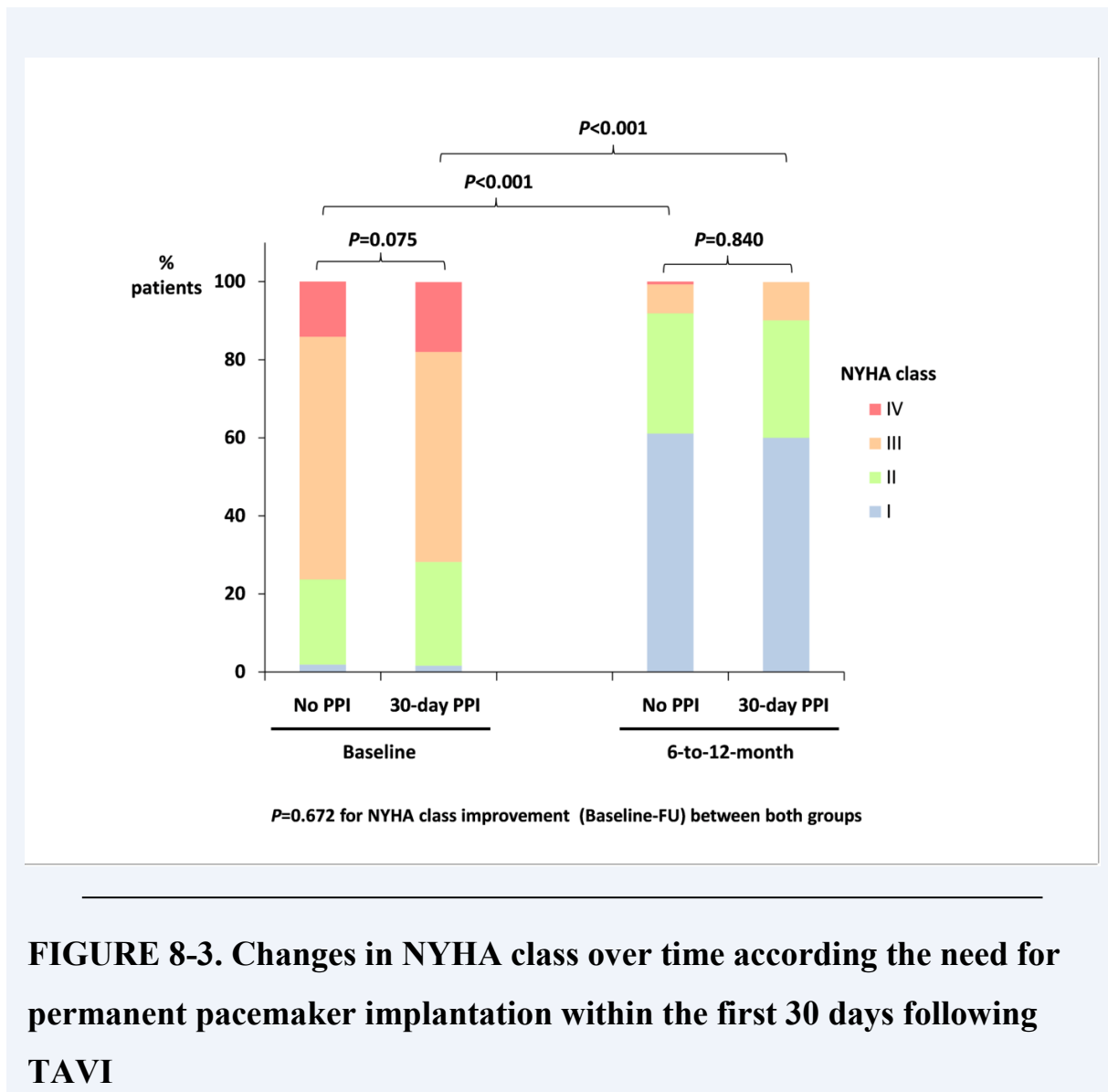
FIGURE 8-3. Changes in NYHA class over time according the need for permanent pacemaker implantation within the first 30 days following TAVI

8.6. DISCUSSION

Injury to the conduction system is one of the more frequent complications of TAVI.[246] Although there is wide variability in the incidence of pacing requirements across studies,[246] an analysis of the literature showed that 1 out 7 patients (less than 10% and up to ~25% when using BEV and SEV, respectively) require a PPI periprocedurally,[267] which is consistent with the results of the present study. Also in accordance with prior studies,[267] almost 90% of PPIs at 30 days were implanted within the first week following the procedure, with a much lower risk thereafter, and 75% were secondary to high degree or complete AVB.

8.6.1. PPI Following TAVI and Clinical Outcomes

There is strong evidence that the need for a paced rhythm increases the risk of late mortality and heart failure.[212-214, 268-270] In contrast to these results, we failed to find any deleterious effect of PPI on mortality or heart failure status in patients undergoing TAVI, even in patients with left ventricular dysfunction at baseline. However, these finding are consistent with prior studies in the cardiac surgery field,[168] as well as with some prior smaller TAVI series.[187, 262-264]

Results from the DAVID, MOST and MADIT-II trials showed that the deleterious impact of pacing on heart failure and/or mortality depends on cumulative percent time ventricular paced. Specifically, a right ventricular pacing during ≥40-50% of the time was associated with increased risk of heart failure and/or mortality.[212, 213, 271] Several studies on TAVI have shown that new conduction disturbances following TAVI may resolve over time in about 50% of patients,[169, 253] especially with the use of BEV. Indeed, it has been shown that more than 50% of patients requiring periprocedural PPI are not pacing-dependent at follow-up.[187, 272, 273] In the present study, more than one third of patients with PPI (more than 50% in patients who had received a BEV) did not exhibit pacing activity on the ECG performed at the 6- to 12-month follow-up. Since most PPIs were implanted due to high degree or complete AVB, this observation suggests that a significant proportion of AVBs have resolved over time. This is consistent with the situation observed after surgical aortic valve replacement,[154, 274] and in fact, current surgical guidelines recommend the implantation of a permanent pacemaker in patients with postoperative AVB only if the conduction abnormality persists at least 7 days after cardiac surgery and/or is not expected to resolve.[230] Interestingly, Simms et

al.[272] reported similar rates of late pacing-dependency in patients undergoing SAVR and TAVI.

It has been suggested that the deleterious impact of PPI might differ between young and older patients;[275] while a poorer survival has been observed in younger patients requiring PPI, some studies have shown that PPI has no impact on mortality in octogenarians and nonagenarians,[276] who in fact represent the vast majority of patients undergoing TAVI nowadays. Also, the presence of left ventricular dysfunction has been reported as an independent predictor of a deleterious clinical impact of PPI,[277, 278], whereas LVEF remained stable over time in most patients without structural heart disease receiving a PPI.[279] However, we did not find differences between patients with and without PPI when analyzing the data by subgroups according to left ventricular function. The severity of comorbidities and concomitant structural heart disease in patients undergoing TAVI led to a high rate of death and heart failure, and this might mitigate the potential negative effect of PPI in these patients. Furthermore, the immediate hemodynamic improvement due to aortic stenosis release resulted into significant improvement of left ventricular function in patients with pre-existing ventricular dysfunction ($36 \pm 8\%$ to $50 \pm 13\%$, $P \leq 0.001$), as previously reported,[280] and this may also have compensated the potential deleterious effect of ventricular pacing in such patients.

The fact that PPI following TAVI resulted in a significant decrease in unexpected (sudden cardiac and unknown) death during the follow-up period merits further discussion. Pre-existing AF and the lack of 30-day PPI were predictors of unexpected death and the occurrence of NOP-LBBB and a lower LVEF at baseline predicted the occurrence of sudden death. Left ventricular dysfunction and AF are well recognized predictors of sudden death[281, 282] and NOP-LBBB after TAVI has been associated with an increased risk of late overall and cardiac mortality,[252] although this has not been confirmed in other studies.[169, 253] In this study, the occurrence of NOP-LBBB was not associated with overall or cardiac death, but it increased by > 2 times the risk of sudden death during the follow-up period. NOP-LBBB following TAVI has been associated with a higher risk of PPI and complete complete AVB,[253] which in turn, might lead to sudden death if a pacemaker is not implanted. However, the number of sudden death events in the present study was relatively low and these results need therefore to be interpreted with caution. Future studies are needed to assess the impact of

NOP-LBBB after TAVI on sudden death as well as to evaluate the potential predictors of increased death in these patients.

8.6.2. PPI and LVEF

After an initial improvement in LVEF immediately after valve obstruction relief, those patients who required PPI exhibited a significant decrease in LVEF over time as compared to a continuous improvement in ventricular function in the rest of the study population. In fact, PPI was the only factor determining a deleterious effect on ventricular function following TAVI. Importantly, this negative effect of PPI was more pronounced in those patients receiving a dual-chamber (vs. single-chamber) PPI. It is well known that pacing induces electrical and mechanical dysynchrony, which in turn, may lead to an adverse LV remodeling, and ultimately to the development of heart failure.[133, 283, 284] The occurrence and extent of pacing-induced heart disease has been associated with ventricular pacing burden and duration,[277] and dual-chamber pacemakers have been associated with a higher percentage of cumulative pacing, leading to a higher risk of re-hospitalization due to heart failure.[133, 213] Interestingly, the implantation of a biventricular pacemaker in patients with preserved LVEF and symptomatic bradycardia, and in those with AVB and left ventricular dysfunction has been shown to prevent the adverse effects of pacing on LVEF.[284, 285] The potential usefulness of biventricular pacing in patients requiring PPI after a TAVI procedure should be evaluated in future studies.

The negative impact of PPI on LVEF did not translate into a deleterious effect on the heart failure status, which may be related to the mild degree of LVEF deterioration in most patients and the positive hemodynamic effects related to aortic stenosis release.
Limitations. While data were collected prospectively in each center, data analyses were performed retrospectively, and there was no event-adjudication committee for the study. Echocardiographic examinations at follow-up were not completed in about 15% of patients and this may have had an impact on the results regarding LVEF changes over time. Pacing-dependency and right ventricular pacing burden were not systematically evaluated. Finally, a bias cannot be ruled out when comparing outcomes between balloon- and self-expandable valve groups due to the lack of randomization.

Conclusions

This study including a large cohort of patients undergoing TAVI with BEV and SEV showed that periprocedural PPI remains a frequent complication of TAVI. The need for PPI periprocedurally had no impact on overall and cardiovascular death, or on functional status and heart failure decompensation requiring rehospitalization after a mean follow-up of ~2 years. Indeed, 30-day PPI was a protective factor for the occurrence of unexpected (sudden cardiac or unknown) death during the follow-up period, which indirectly raises questions about the most appropriate management of new conduction disturbances that do not meet the criteria for PPI following TAVI. However, PPI, particularly with a dual-chamber pacemaker, was associated with a negative effect on left ventricular function. Further efforts will be important to determine the long-term impact of this decrease in LVEF and the potential benefits of resynchronization therapies in some patients.

8.7. ACKNOWLEDGMENTS

8.8. FUNDING SOURCES

8.9. CONFLICT OF INTEREST DISCLOSURES

Dr. Josep Rodés-Cabau is consultant for Edwards Lifesciences and St-Jude Medical. Drs. John G. Webb and Eric Dumont are consultants for Edwards Lifesciences. Dr. Conrado Tamburino is consultant of Edwards, Medtronic, CeloNova and Abbott. The rest of the authors had no conflict of interest to disclose.

SUPPLEMENTAL TABLE 8-1. Individual Characteristics of the 76 Patients Having Unexpected Death (Sudden Cardiac Death or Death of Unknown Cause)

Age (years)	Gender	STS-PROM (%)	LVEF (%)	Prosthesis type	30-day PPI	QRS morphology at baseline	QRS morphology at discharge/death	Cause of death	Days after TAVI
63	female	2.4	65	BEV	no	RBBB + LAHB	RBBB + LAHB	unknown	963
65	female		72	SEV	no	IVCD	unknown	sudden cardiac death	1
67	male	7.5	50	BEV	no	normal	LBBB	unknown	1624
68	male	7.0	63	SEV	no	normal	LBBB	sudden cardiac death	93
69	female	3.5	55	SEV	no	LAHB	LAHB	sudden cardiac death	1158
69	female	2.2	20	SEV	no	normal	normal	sudden cardiac death	18
70	female	3.0	35	SEV	no	LBBB	LBBB	sudden cardiac death	406
71	female	2.5	30	SEV	no	normal	LBBB	sudden cardiac death	168
72	female	2.5	60	SEV	yes	LIBBB	LBBB	unknown	915
73	male	6.4	45	BEV	no	IVCD	IVCD	sudden cardiac death	25
73	female	6.5	58	SEV	no	normal	unknown	sudden cardiac death	1
74	male	5.6	60	BEV	no	normal	normal	unknown	1461
75	male	14.1	30	BEV	no	IVCD	IVCD	unknown	94
75	male	26.8	35	BEV	no	IVCD	IVCD	unknown	395
76	male	4.3	40	SEV	no	RBBB	RBBB	sudden cardiac death	3
76	male	3.5	56	SEV	no	normal	LBBB	unknown	1631
78	female	4.5	60	BEV	no	normal	normal	unknown	300
78	female	7.9	50	BEV	no	normal	LBBB	unknown	440
79	male	12.2	45	BEV	no	IVCD	IVCD	sudden cardiac death	3
79	male	6.3	20	SEV	no	normal	LBBB	sudden cardiac death	35
79	male	14.7	65	SEV	no	RBBB	RBBB	unknown	168
79	female	4.2	55	SEV	no	normal	normal	unknown	726
79	female	22.0	45	BEV	no	normal	normal	unknown	356
79	female	3.7	54	BEV	no	normal	normal	unknown	1105
79	female	11.9	25	BEV	no	LBBB	LBBB	unknown	476
80	male	3.8	65	SEV	no	normal	LAHB	sudden cardiac death	819
80	male	4.6	55	SEV	no	IVCD	LBBB	sudden cardiac death	746
80	female	15.1	54	SEV	yes	normal	paced	unknown	825
80	female	5.1	58	SEV	no	normal	LBBB	unknown	1071
81	female	2.8	37	SEV	no	normal	LBBB	sudden cardiac death	92
81	female	6.5	10	SEV	no	LBBB	LBBB	sudden cardiac death	1
81	female	2.7	60	BEV	no	normal	normal	unknown	1422
81	male	5.3	65	BEV	no	normal	normal	unknown	219

81	male	4.7	50	BEV	no	RBBB	RBBB + LAHB	unknown	149
81	male	5.3	25	BEV	no	RBBB	RBBB	unknown	1039
82	male	11.2	20	BEV	no	RBBB + LAHB	RBBB + LAHB	sudden cardiac death	3
82	male	2.1	50	SEV	no	normal	LBBB	sudden cardiac death	895
82	female	4.3	60	SEV	yes	IVCD	paced	sudden cardiac death	501
82	male	3.7	60	SEV	no	normal	LBBB	sudden cardiac death	1031
82	male	6.5	55	BEV	no	normal	normal	unknown	853
82	male	6.8	30	BEV	no	IVCD	IVCD	unknown	169
82	male	5.3	65	BEV	no	normal	normal	unknown	219
83	female	2.6	58	SEV	no	normal	LBBB	sudden cardiac death	9
83	female	22.4	70	BEV	no	normal	normal	unknown	1782
83	female	8.3	60	BEV	no	normal	normal	unknown	1273
83	female	4.7	59	SEV	no	normal	normal	unknown	1034
84	male	10.2	40	BEV	no	IVCD	IVCD	sudden cardiac death	387
84	male	15.1	25	BEV	yes	RBBB	paced	unknown	692
85	male	7.1	60	BEV	no	IVCD	LBBB	sudden cardiac death	1610
85	female	8.1	62	SEV	no	normal	LAHB	sudden cardiac death	1765
85	male	6.2	60	SEV	no	IVCD	IVCD	unknown	2158
85	female	16.8	25	BEV	no	normal	LAHB	unknown	31
86	female	9.4	54	SEV	no	normal	LAHB	sudden cardiac death	659
86	male	6.5	58	SEV	no	normal	LBBB	sudden cardiac death	486
86	female	5.1	60	BEV	no	normal	normal	unknown	1382
86	female	5.6	65	BEV	no	normal	normal	unknown	1137
86	male	10.3	75	BEV	no	normal	normal	unknown	1171
86	male	11.4	35	BEV	no	normal	LBBB	unknown	458
86	male	9.3	65	BEV	no	RBBB + LAHB	RBBB + LAHB	unknown	105
86	female	17.5	45	BEV	no	IVCD	IVCD	unknown	343
87	female	7.1	60	BEV	no	normal	normal	unknown	1905
87	female	31.7	65	BEV	no	LBBB	LBBB	unknown	402
88	male	13.2	55	BEV	no	LBBB	LBBB	sudden cardiac death	253
88	female	7.9	65	BEV	no	normal	normal	unknown	1257
88	male	9.7	60	BEV	no	normal	normal	unknown	856
88	female	5.5	78	SEV	no	normal	normal	unknown	996
89	male	5.2	65	BEV	no	normal	normal	unknown	423
89	female	6.9	68	BEV	no	normal	normal	unknown	428
90	female	7.1	60	BEV	no	normal	normal	unknown	67
91	female	12.3	65	BEV	no	RBBB + LAHB	RBBB + LAHB	unknown	467
92	female	14.8	65	BEV	no	normal	normal	unknown	1972
92	female	7.9	65	BEV	no	normal	normal	unknown	1423

92	male	10.4	65	BEV	no	normal	normal	unknown	822
92	female	13.7	45	BEV	no	RBBB	RBBB	unknown	1795
93	male	8.0	60	BEV	no	LAHB	LAHB	unknown	215
97	female	21.9	50	BEV	no	RBBB + LAHB	RBBB + LAHB	sudden cardiac death	946

IVCD: intraventricular conduction delay, LAHB: left anterior hemiblock, LBBB: left bundle branch block, LIBBB: left incomplete bundle branch block LVEF: left ventricular ejection fraction, PPI: permanent pacemaker implantation, RBBB: right bundle branch block, STS-PROM: Society of Thoracic Surgeons predicted risk of mortality, TAVI: transcatheter aortic valve implantation.

SUPPLEMENTAL TABLE 8-2. Baseline and Procedural Findings According to the Type of Valve Implanted (n=1556)

	Balloon-expandable valve (n=858)	Self-expandable valve (n=698)	*P* value
Clinical Characteristics			
Age (years)	81 ± 8	80 ± 6	0.199
Male	423 (49.3)	317 (45.4)	0.127
Body mass index (kg/m^2)	26 (23-29)	27 (24-30)	0.004
NYHA class ≥3	644 (75.1)	545 (78.1)	0.163
Hypertension	699 (81.5)	567 (81.5)	0.999
Diabetes mellitus	259 (30.2)	226 (32.3)	0.315
COPD	228 (26.6)	254 (36.1)	<0.001
eGFR <60 ml/min	473 (55.1)	409 (58.6)	0.170
Paroxysmal/chronic AF	286 (33.3)	148 (21.2)	<0.001
Coronary artery disease	590 (68.8)	286 (41.0)	<0.001
Logistic EuroScore (%)	21.3 ± 14.4	19.5 ± 13.2	0.014
STS-PROM score (%)	8.0 ± 5.0	7.2± 5.6	0.006
Echocardiography			
LVEF (%)	55 ± 13	56 ± 14	0.055
LVEF≤40%	149 (17.4)	120 (17.2)	0.932
Mean gradient (mmHg)	46 ± 17	50 ± 17	<0.001
Aortic valve area (cm^2)	0.60 (0.50-0.78)	0.62 (0.41-0.79)	0.358
Procedural findings			
Procedural success*	769 (89.6)	557 (79.8)	<0.001
Approach			
Transapical/Transaortic	385 (44.9)	9 (1.3)	<0.001
Transfemoral/Subclavian	473 (55.1)	687 (98.7)	
Prosthesis size (mm)			
20-23	388 (45.2)	12 (1.7)	
26	425 (49.5)	371 (53.2)	<0.001
29-31	45 (5.2)	315 (45.1)	
Need for a second valve	18 (2.1)	29 (4.2)	0.018
≥Moderate AR	82 (9.6)	132 (18.9)	<0.001

	61 (7.1)	178 (25.5)	<0.001
30-day PPI	61 (7.1)	178 (25.5)	<0.001
30-day mortality	61 (7.1)	47 (6.7)	0.772

*According VARC-2 criteria.
AR: aortic regurgitation, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration ratio, LVEF: left ventricular ejection fraction, NOP-LBBB: new-onset persistent left bundle branch block, NYHA: New York Heart Association, STS-PROM: Society of Thoracic surgeons predicted risk of mortality

SUPPLEMENTAL TABLE 8-3. Cumulative Outcomes of the Study Population According to the Type of Valve Implanted (n=1556)

	Univariate HR* (95% CI)	P value	Multivariate HR*† (95% CI)	P value
Death or hospitalization for heart failure	1.96 (1.64-2.35)	<0.001	1.26 (0.75-2.13)	0.382
Death from any cause	1.76 (1.45-2.15)	<0.001	0.99 (0.55-1.77)	0.960
Death from cardiovascular causes	1.72 (1.35-2.19)	<0.001	0.94 (0.45-1.99)	0.807
Sudden cardiac death	0.34 (0.14-0.81)	0.014	0.19 (0.02-1.94)	0.163
Sudden death/unknown death	1.51 (0.95-2.41)	0.083	0.76 (0.27-2.13)	0.598
Hospitalization for heart failure	2.42 (1.72-3.39)	<0.001	1.65 (0.63-4.31)	0.311

*Compared to self-expandable valve group; † Adjusted for baseline and procedural differences.
CI: confidence interval, HR: hazard ratio,
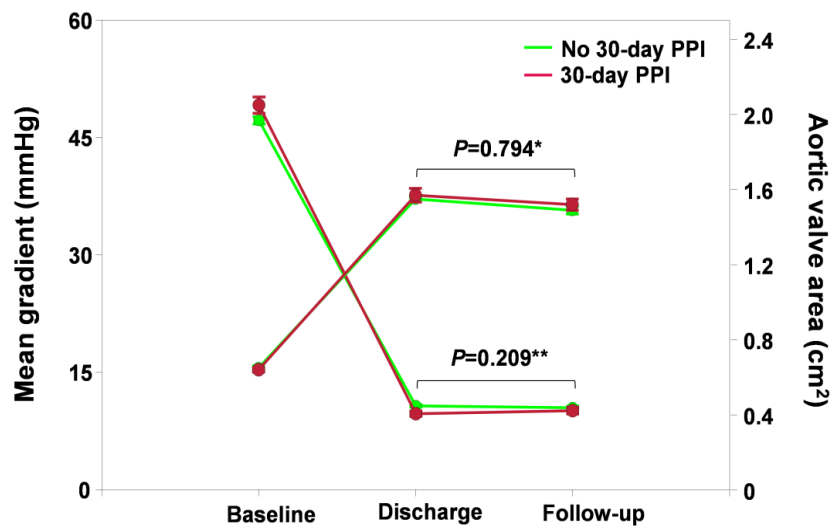
SUPPLEMENTAL FIGURE 8-1. Changes in valve hemodynamics (mean aortic valve gradient and aortic valve area) according to the need for permanent pacemaker implantation within 30-day following transcatheter aortic valve implantation
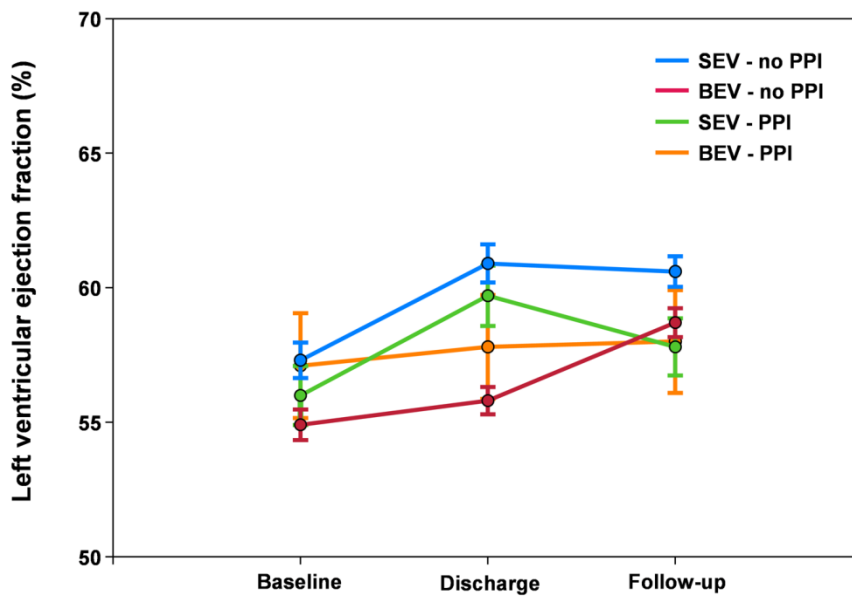
P<0.002, between baseline and follow-up for SEV–no PPI group
P<0.001, between baseline and follow-up for BEV–no PPI group
P=0.354, between discharge and follow-up for SEV–PPI group
P=0.996, between discharge and follow-up for BEV–PPI group
P=0.114, between SEV–no PPI and BEV–no PPI groups
P=0.688, between SEV–PPI and BEV–PPI groups

SUPPLEMENTAL FIGURE 8-2. LVEF changes between baseline and 6-to- 12 month follow-up according to the need for 30-day permanent pacemaker implantation and the type of valve implanted

CHAPTER 9-Article 5

Late Cardiac Death in Patients Undergoing Transcatheter Aortic Valve Replacement: Insights into the Incidence and Predictors of Advanced Heart Failure and Sudden Cardiac Death

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9.1. RESUME

Contexte: Peu de données existent sur la l'importance et les facteurs prédictifs de la mortalité cardiaque après remplacement valvulaire aortique transcathéter (TAVR).

Objectifs: Les objectifs de cette étude étaient d'évaluer l'incidence, le calendrier et les facteurs prédictifs de la mortalité par insuffisance cardiaque avancée (HF) et de la mort subite cardiaque (MSC) dans une grande cohorte de patients traités par TAVR.

Méthodes: Un total de 3726 patients traités par TAVR utilisant une valve déployée par ballon (57%) ou auto expansible (43%) ont été inclus. Les causes de décès ont été définies selon le Valve Academic Research Consortium-2.

Résultats: Au terme d'un suivi moyen de 22 ± 18 mois, 155 patients sont décédés en raison d'une HF évoluée (15.2% du total des décès, 46.1% des décès de causes cardiaques) et 57 patients de SCD (5.6% des décès, 16.9 % des décès cardiaques). Les comorbidités de base base (maladie pulmonaire chronique obstructive, fibrillation auriculaire, fraction d'éjection ventriculaire gauche [FEVG] $\leq$ 40%, faible gradient moyen transaortique, pression artérielle pulmonaire> 60 mmHg; p <0.05 pour tous) et 2 facteurs procéduraux (approche transapicale, HR: 2.38, IC à 95%: 1.60 à 3.54, *P* <0.001; présence d'une insuffisance aortique modérée ou sévère après TAVR, HR: 2,79, IC à 95%: 1.82 à 4.27, p <0,001) étaient des facteurs prédictifs indépendants de décès par IC sévère. Une FEVG$\leq$40% (HR: 1.89, IC à 95%: 1.05 à 3.55, P = 0.033) et l'apparition récente d'un bloc de branche gauche persistant (NOP-BBG) après TAVR (HR: 2.28, IC à 95%: 1.23 à 4.14, *P* = 0.008) étaient indépendamment associées à un risque accru de SCD. Parmi les patients ayant un NOP-BBG, le risque de SCD était supérieur chez les patients ayant un QRS> 160 ms (HR: 4.77, IC à 95%: 1.56 à 14.6, *P* = 0.006).

Conclusions: L'HF évoluée et la SCD ont représenté 2/3 des décès cardiaques chez les patients après TAVR. Des facteurs de risque accru de mortalité par HF et SCD potentiellement modifiables ou traitables ont été identifiés. De futures études devront confirmer si des stratégies ou des traitements ciblant ces facteurs permettront de réduire le risque de mort cardiaque chez ces patients.

9.2. ABSTRACT

Background: Little evidence exists on the burden and predictors of cardiac death after transcatheter aortic valve replacement (TAVR).

Objectives: The objectives of this study were to assess the incidence, timing and predictors of cardiac death from advanced heart failure (HF) and sudden cardiac death (SCD) in a large cohort of patients undergoing TAVR.

Methods: A total of 3,726 patients who underwent TAVR using balloon (57%) or self - expandable (43%) valves were included. The causes of death were defined according to the Valve Academic Research Consortium-2.

Results: At a mean follow-up of 22±18 months, 155 patients died due to advanced HF (15.2% of the total deaths, 46.1% of deaths from cardiac causes) and 57 patients due to SCD (5.6% of deaths, 16.9% of cardiac deaths). Baseline comorbidities (chronic obstructive pulmonary disease, AF, left ventricular ejection fraction [LVEF] $\leq$ 40%, lower mean transaortic gradient, pulmonary artery pressure >60mmHg; $P < 0.05$ for all) and 2 procedural factors (transapical approach, HR: 2.38, 95% CI: 1.60-3.54, $P < 0.001$; presence of moderate or severe aortic regurgitation after TAVR, HR: 2.79, 95% CI: 1.82-4.27, $P < 0.001$) were independent predictors of death from advanced HF. A LVEF $\leq$40% (HR: 1.93, 95% CI: 1.05-3.55, $P = 0.033$) and new-onset persistent left bundle branch block (NOP-LBBB) following TAVR (HR: 2.26, 95% CI: 1.23-4.14, $P = 0.009$) were independently associated with an increased risk of SCD. Among patients with NOP-LBBB, the risk of SCD was greater in those patients with a QRS duration >160 ms (HR: 4.78, 95% CI: 1.56-14.63, $P = 0.006$).

Conclusions: Advanced HF and SCD accounted for 2/3 of cardiac deaths in patients after TAVR. Potentially modifiable or treatable factors leading to an increased risk of mortality for HF and SCD were identified. Whether strategies or therapies targeting these factors might decrease the risk of cardiac death in such patients needs to be confirmed in future studies.

9.3. INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has been shown to improve survival in patients with symptomatic aortic stenosis deemed at high or prohibitive surgical risk [99]. However, initial studies showed that ~ 1 out 4 of patients undergoing TAVR died during the first year following the procedure despite relief of the valvular obstruction, highlighting the need for improving the patient-selection process. [286] Efforts made in this direction have resulted into a reduction in overall mortality after TAVR, [287] but this has been mainly at the The persistent risk of death from advanced heart failure (HF) and sudden cardiac death (SCD) in patients undergoing surgical aortic valve replacement (SAVR), the most common modes of death following SAVR, has been a matter of concern for a long time .[288-291] While the specific factors leading to advanced HF or SCD in such patients have yet to be clarified, some studies have suggested that potentially treatable factors such as the occurrence of new conduction disturbances increased the risk of cardiac death and SCD in such patients. [155, 288, 290, 292] Although little evidence exists on the burden of death from advanced HF and SCD in patients undergoing TAVR, both accounted for ~3/4 of cardiac deaths in some previous studies. [89, 293, 294] However, their predictors remain largely unknown and, more importantly, whether potentially treatable or modifiable factors might increase the risk of death from HF and SCD after TAVR has thus far not been elucidated. The objectives of this study were therefore to assess the incidence and predictors of death from advanced HF and SCD in patients undergoing TAVR.

expense of a decrease in the incidence of non-cardiac death without significant changes in the rate of death from cardiac causes.

9.4. METHODS

9.4.1. Study population

The study included a total of 3,726 patients who underwent TAVR in 18 Centers in North America, South America and Europe. Indications for TAVR and approach were based on the assessment of the heart team at each center, and TAVR procedures were performed as

described elsewhere. [99] Data were prospectively collected in a dedicated database in each center. Clinical outcomes for the purpose of this study were defined according to the Valve Academic Research Consortium (VARC)-2 criteria. [286]

9.4.2. Electrocardiography (ECG) and Echocardiography Data

A 12-lead ECG tracing was recorded at least at baseline, immediately after the procedure and at hospital discharge. ECGs at baseline and at hospital discharge were obtained in 95% of patients. The diagnosis of intraventricular conduction abnormalities was based on AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. [134] New-onset persistent left bundle branch block (NOP-LBBB) was defined as a new left bundle branch block (LBBB) in a patient without prior permanent pacemaker (PPM) which persisted at hospital discharge or death. In primary analyses, patients who developed a new-onset LBBB and required PPM implantation during the hospitalization period were excluded from this group. In a supplementary analysis, patients were classified in 3 groups: NOP-LBBB (no pacemaker), new-onset persistent LBBB and pacemaker during hospitalization (NOP-LBBB-PPM group), and patients with no NOP-LBBB. PPM was implanted if third-degree or advanced second-degree atrio-ventricular block (AVB) at any anatomical level occurred and was not expected to resolve, or in the presence of sinus node dysfunction and documented symptomatic bradycardia in agreement with current recommendations (19). Also, the indication of PPM in the presence of new-onset LBBB with PR prolongation (>200 ms) or very wide QRS (>150 ms) not expected to normalize was at the discretion of the physician.

Echocardiograms were analyzed by experienced echocardiographers at each center. The degree of aortic regurgitation (AR) was classified according to the VARC-2 criteria. Left ventricular ejection fraction (LVEF) was calculated using the Simpson's rule.

9.4.3. Follow-up

Follow-up was carried out by means of telephonic contacts and/or outpatient clinical visits at 1 month and 1 year after TAVR and yearly thereafter. Overall, a complete follow-up was achieved in 95.9% of patients (4.1% of the study population was lost at follow-up).

9.4.4. Definition of causes of death

Causes of death were obtained with the scrutiny of medical charts and telephone contacts or interviews with families and physicians. Also, civil registries were consulted when necessary. Cardiovascular death was defined according to the VARC-2 criteria. Any death attributable to a proximate cardiac was classified as cardiac death. SCD was defined according to the World Health Organization definition as a death occurring within 1 hour of symptom onset if witnessed, or within the previous 24 hours if unwitnessed. Patients with known terminal disease or an identifiable non-cardiac etiology of sudden death were not considered as SCD.[295] Death of unknown cause was also classified as cardiovascular.

9.4.5. Statistical analysis

Qualitative variables are expressed as n (percentage) and quantitative variables as mean ± standard deviation. Survival rates were summarized using Kaplan-Meier estimates and comparisons between groups were performed using the log-rank test. Predictors of death from HF and SCD were analyzed using univariate and multivariate proportional hazard models (cumulative outcomes). Hazard proportional assumption was evaluated by means of log-minus-log survival plots. A Fine-Gray Cox model was also constructed to account for death from other causes as a competing risk event for death from HF and SCD. Variables with a P value < 0.10 in the univariate analyses were included in the multivariate analysis. All univariate analyses were carried out on complete cases.

Overall, 3.4% of data were missing, and 23.4% of patients had missing data for at least one variable. Missing data were assumed to be missing at random and were dealt with through the multiple imputation procedure using the Markov Chain Monte Carlo method. Ten imputed data sets were created and results were pooled according to Rubin's protocol.[296] Multivariate models using complete-case analyses were also performed. Receiver operating characteristics (ROC) curves and the maximum Youden's index (sensitivity + especificity-1)[297] were used to define the optimal cut-off value for QRS duration to predict SCD in patients with NOP-LBBB. The results were considered significant with p-values <0.05. Analyses were conducted using the statistical packages SAS, version 9.2 (SAS Institute Inc., Cary, NC) and Statistical Package for Social Sciences, version 20 (SPSS Inc, SPSS Inc., IBM, New York, USA).

9.5. RESULTS

Table 9-1 shows the main clinical characteristics, echocardiographic and procedural findings and 30-day outcomes of the study population. The mean age of the study population was 81± 8 years and 50.2% of patients were males. The mean logistic EuroSCORE was 19.4 ± 13.0%. Balloon-expandable and self-expandable valves were used in 57% and 43% of patients, respectively and TAVR was performed through the transfemoral route in 79.7% of patients and the transapical route in 16.3%. After TAVR, moderate to severe AR was observed in 374 patients (11.0%) and NOP-LBBB occurred in 471 patients (13.3%). At 30 days after TAVR, the rates of mortality and stroke were 7.8% and 3.1%, respectively.

TABLE 9-1. Baseline Clinical Characteristics, Procedural Findings and 30-day Outcomes of the Study Population

	Study Population (n = 3726)
Clinical characteristics and electrocardiographic findings	
Age (years)	81 ± 8
Male	1,866/3,718 (50.2)
Body mass index (kg/m^2)	27 ± 5
NYHA class ≥3	2,740/3,668 (74.7)
Hypertension	2,854/3,704 (77.1)
Diabetes mellitus	1,118/3,706 (30.2)
COPD	955/3,685 (25.9)
eGFR <60 ml/min	1,864/3,638 (51.2)
Coronary artery disease	1,987/3,705 (53.6)
Complete or no need of revascularization	2,216/3,349/ (66.2)
Paroxysmal/chronic AF	1,093/3,628 (30.1)
Preexisting LBBB	330/3,540 (9.3)
Prior pacemaker	415/3,710 (11.2)
Logistic EuroSCORE (%)	19.4 ± 13.0
Echocardiographic findings	
LVEF ≤40%	682/3,657 (18.6)

Mean transaortic gradient (mm Hg)	47 ± 17
PASP >60 mm Hg	376/2,748 (13.7)
Procedural findings	
Approach	
Transfemoral	2,958/3,713 (79.7)
Transapical	607/3,713 (16.3)
Transaortic	69/3,713 (1.9)
Subclavian	79/3,713 (2.1)
Prosthesis type	
Self-expandable	1,559/3,717 (43.0)
Balloon-expandable	2,118/3,717 (57.0)
≥ Moderate AR	374/3,407 (11.0)
30-day outcomes	
Death	271 (7.3)
Stroke	114/3,666 (3.1)
Myocardial infarction	52/3,287 (1.6)
Major or life threatening bleeding	479/3,480 (13.8)
NOP-LBBB	471/3,539 (13.3)
PPM implantation	536/3,666 (14.6)

Values are expressed as n (%), mean (± SD).
AF = AF; AR = aortic regurgitation; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration ratio; LBBB = left bundle-branch block; LVEF = left ventricular ejection fraction; NOP-LBBB = new-onset persistent left bundle-branch block; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PPM = permanent pacemaker

9.5.1. Incidence of Death from Advanced HF and SCD

At a mean follow-up of 22 ± 18 months, 1,022 patients (27.4%) had died, 663 (17.8%) from cardiovascular causes. Cardiac death was confirmed in 336 patients (33.0% of deaths). Causes of cardiovascular death in the study population are shown in Table 9-2. Cumulative rates of overall mortality and cardiac mortality at 2-year follow-up were 26.6% (95% CI: 25.3 to 28.8) and 9.6 % (95% CI: 8.4 to 10.8), respectively (Figure 9-1). Death from advanced HF occurred in 155 patients (4.2%) and accounted for 15.2% of total deaths, and for 46.1% of cardiac deaths. Cumulative rates of death from advanced HF at 1-and 2-year follow-up were 2.9% (95% CI: 2.3-3.5) and 4.4% (95% CI: 3.7-5.2), respectively (Figure 9-2A). A total of 57 patients died from SCD (5.6%, 16.7% of cardiac deaths) and the cumulative rates of SCD at

1- and 2-year follow-up were 1.0% (95% CI: 0.6-1.4) and 1.8% (95%CI: 1.2 -2.4), respectively (Figure 9-2 B).

TABLE 9-2. Causes of Cardiovascular Death after Transcatheter Aortic Valve Replacement (n = 663)

	N (%)
Cardiac death	336 (50.7)
Advanced heart failure	155 (23.4)
Sudden cardiac death	57 (8.6)
Myocardial infarction	32 (4.8)
Endocarditis	17 (2.6)
Other procedure-related cardiac complications	75 (11.3)
Noncoronary vascular related death	69 (10.4)
Other procedure-related complications	163 (24.6)
Unknown	95 (14.3)
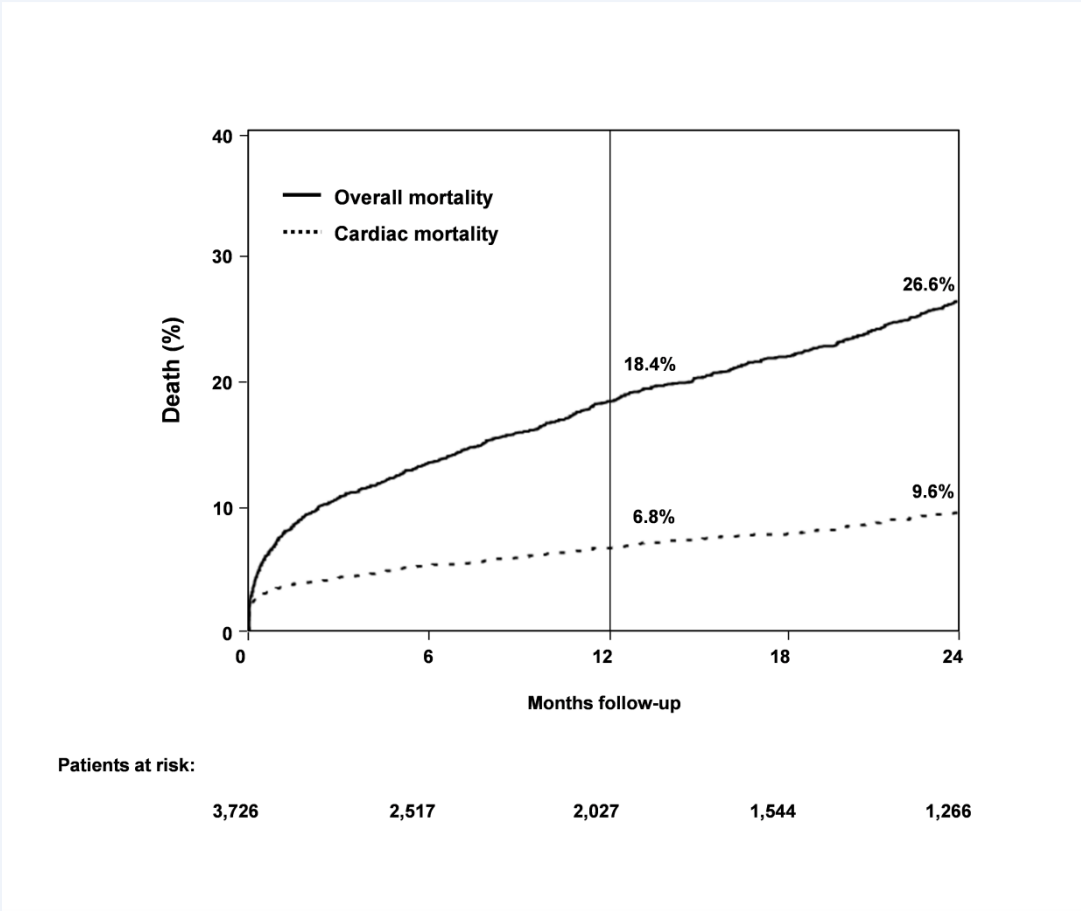
FIGURE 9-1. Rates of Overall and Cardiac Mortality

Kaplan-Meier curves at 2-year follow-up for overall and cardiac mortality in the study population.

181
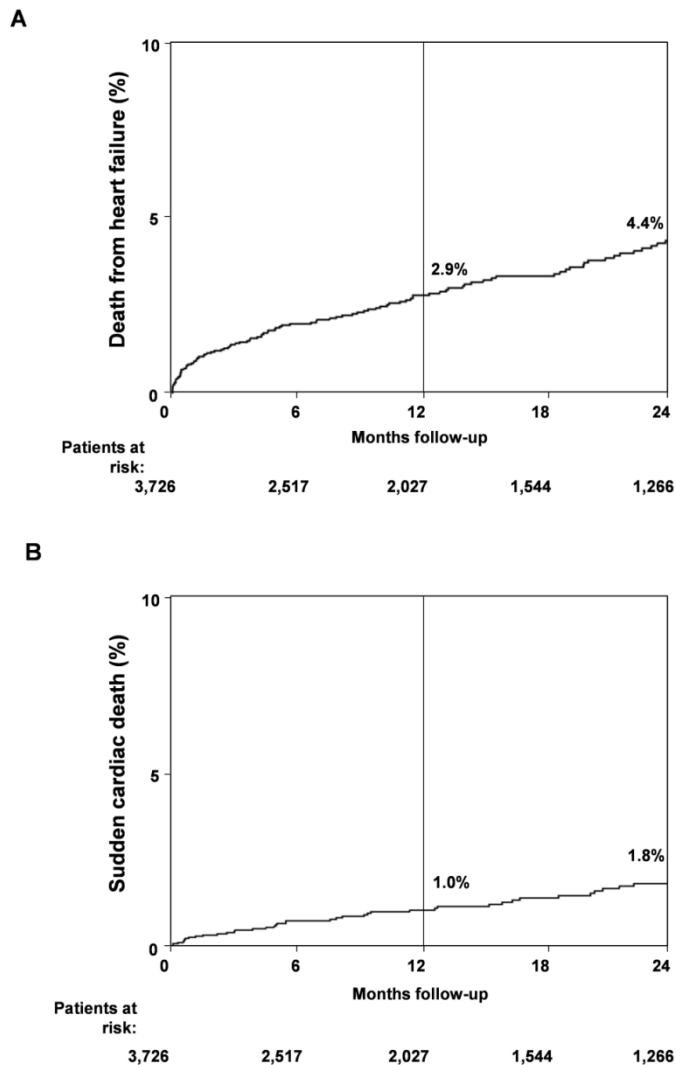
FIGURE 9-2. Rates of Death from Advanced Heart Failure and Sudden Cardiac Death

Kaplan-Meier curves at 2-year follow-up for death from advanced heart failure **(A)** and sudden cardiac death **(B)**

9.5.2. Predictors of Death from Advanced HF

Predictors of death from advanced HF are shown in Table 9-3.

182

TABLE 9-3. Univariate and Multivariate Predictors of Terminal Heart Failure Following TAVR

	Univariate HR (95% CI)	*P* Value	Multivariate HR* (95% CI)	*P* Value
Clinical characteristics and electrocardiographic findings				
Age (years)	1.02 (0.99-1.04)	0.162		
Male	1.22 (0.90-1.67)	0.225		
Body mass index (kg/m^2)	0.98 (0.94-1.01)	0.134		
NYHA class ≥III	1.75 (1.12-2.73)	0.014	1.19 (0.72-1.96)	0.502
Hypertension	1.33 (0.88-2.02)	0.176		
Diabetes mellitus	1.01 (0.71-1.44)	0.939		
COPD	1.54 (1.10-2.15)	0.011	1.59 (1.11-2.29)	0.012
eGFR <60 ml/min	1.36 (0.98-1.91)	0.058	0.64 (0.29-1.37)	0.248
Coronary artery disease	1.36 (0.98-1.87)	0.066	1.04 (0.61-1.77)	0.891
Complete or no need of revascularization	0.66 (0.47-0.92)	0.015	1.01 (0.59-1.71)	0.985
Paroxysmal/chronic AF	2.58 (1.87-3.56)	<0.001	2.33 (1.62-3.35)	<0.001
Preexisting LBBB	0.73 (0.38-1.38)	0.329		
Prior pacemaker	1.60 (1.04-2.46)	0.031	0.87 (0.54-1.40)	0.564
Echocardiographic findings				
LVEF ≤40%	1.87 (1.31-2.66)	0.001	1.68 (1.10-2.56)	0.017
Mean transaortic gradient (mm Hg)†	1.22 (1.11-1.35)	<0.001	1.11 (1.02-1.22)	0.040
PASP >60 mm Hg	1.85 (1.22-2.80)	0.004	1.99 (1.21-3.28)	0.007
Procedural findings				
Transapical approach	3.16 (2.29-4.38)	<0.001	2.38 (1.60-3.54)	<0.001
Balloon-expandable prosthesis type	2.72 (1.88-3.94)	<0.001	1.06 (0.55-2.06)	0.854
≥ Moderate AR	1.83 (1.19-2.84)	0.006	2.79 (1.82-4.27)	<0.001
30-day outcomes				
Stroke	1.97 (0.97-4.01)	0.063	1.89 (0.91-3.95)	0.090
Myocardial infarction	2.48 (0.92-6.71)	0.074	2.37 (0.86-6.54)	0.097
Major or life threatening bleeding	1.39 (0.91-2.14)	0.132		
NOP-LBBB	0.95 (0.60-1.51)	0.833		
PPM implantation	0.62 (0.37-1.04)	0.070	0.78 (0.42-1.44)	0.422

*For the multivariate analysis, patients with missing data were included through the use of multiple imputation; †per 10 mm Hg decrease

AF = AF; AR = aortic regurgitation; CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration ratio; HR = hazard ratio; LBBB = left bundle-branch block; LVEF = left ventricular ejection fraction; NOP-LBBB = new-onset persistent left bundle-branch block; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PPM = permanent pacemaker

In the multivariate analysis, baseline characteristics such as chronic obstructive pulmonary disease (HR: 1.59, 95% CI: 1.11-2.29, P = 0.012), pre-existing paroxysmal or chronic AF (HR: 2.33, 95% CI: 1.62-3.35, $P < 0.001$), LVEF $\leq 40\%$ (HR: 1.68, 95% CI:1.10-2.56, P=0.017), a lower mean transaortic gradient (HR: 1.11, 95% CI: 1.02-1.22, P = 0.040 per 10 mmHg decrease), pulmonary artery systolic pressure [PASP] >60mmHg (HR: 1.99, 95% CI: 1.21-3.54; P = 0.007), and 2 procedural factors such as the use of the transapical route (HR: 2.38, 95% CI: 1.60-3.54, $P < 0.001$) and the presence of moderate or severe AR after TAVR (HR: 2.79, 95% CI: 1.82-4.27, P <0.001) were associated with increased risk of death from advanced HF. The same predictors were found using complete-case analysis. When death from other causes was taking into account as a competing risk event, preexisting paroxysmal or chronic AF (HR: 1.88, 95% CI: 1.34-2.64, $P < 0.001$), LVEF $\leq$40% (HR: 1.49, 95% CI:1.00-2.26, P = 0.050), pulmonary artery systolic pressure [PASP] >60mmHg (HR: 1.90, 95% CI: 1.22-2.96; P = 0.005), the use of the transapical route (HR: 2.24, 95% CI: 1.54-3.26, P<0.001) and the presence of moderate or severe AR after TAVR (HR: 2.10, 95% CI: 1.42-3.14, $P < 0.001$) were also independent predictors of death from HF.

Figure 9-3 shows rates of death from HF at 2-year follow-up according to the use of transapical approach and the presence of moderate or severe AR after TAVR. Supplement table 9-1 displays differences between approach groups in baseline clinical characteristics, echocardiographic and procedural findings and 30-day outcomes. After adjusting for these differences, the use of TA approach remained an independent predictor of death from advanced HF (HR: 1.86, 95% CI: 1.20-2.86, P = 0.001).
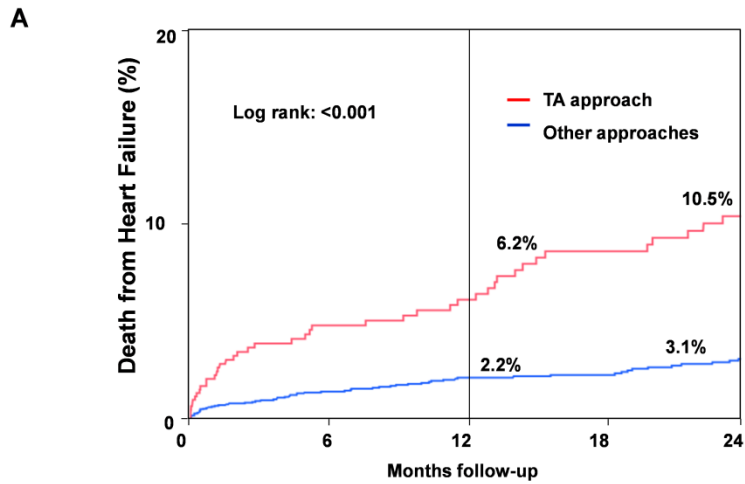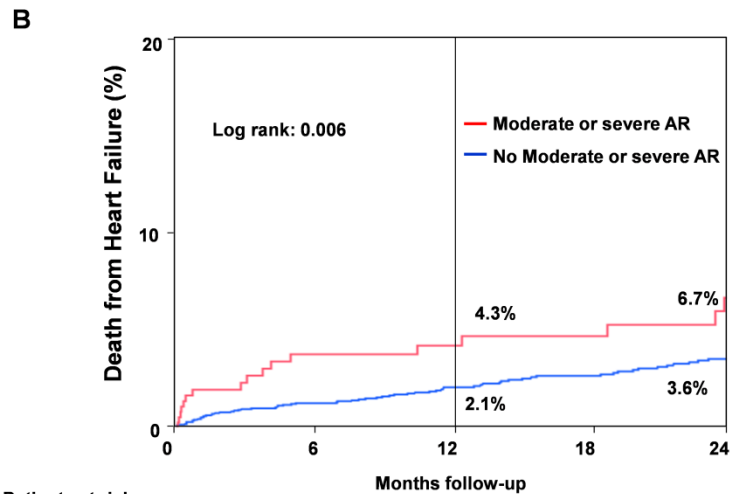
FIGURE 9-3. Rates of Mortality from Advanced Heart Failure According to the Use of Transapical Approach or Significant Aortic Regurgitation

Kaplan-Meier Curves at 2-year follow-up for death from heart failure according to the use of transapical approach **(A)** or the occurrence of moderate or severe aortic regurgitation **(B)**

TA: transapical; AR: aortic regurgitation

Among the 374 patients with moderate or severe AR after TAVR, 135 patients (36.1%) had died at last follow- up, 25 of them (6.7%) due to advanced HF. A lower mean transaortic gradient (HR: 1.35, 95% CI: 1.04-1.85, P = 0.040 per 10 mmHg decrease) and a PASP >60mmHg (HR: 3.06, 95% CI: 1.14-8.22, P = 0.027) were independent echocardiographic predictors of death from HF in these patients, whereas the presence of moderate or severe AR before TAVR (HR: 0.24, 95% CI: 0.07-0.83, P = 0.025) was an independent protective factor (Table 9-4).

TABLE 9-4. Echocardiographic Predictors of Death from Heart Failure in Patients with Moderate or Severe Aortic Regurgitation Following TAVR (n = 374)

	Univariate HR (95% CI)	*P* Value	Multivariate HR (95% CI)	*P* Value
Baseline				
LVEF (%)	0.99 (0.97-1.02)	0.591		
Mean transaortic gradient (mmHg)	0.74 (0.60-1.00)*	0.048	0.74 (0.54-1.00)*	0.040
PASP >60 mm Hg	2.38 (0.91-6.93)	0.079	3.06 (1.14-8.22)	0.027
Moderate or severe MR	1.55 (0.51-4.68)	0.439		
Moderate or severe AR	0.39 (0.14-1.03)	0.058	0.24 (0.07-0.83)	0.025
Discharge				
LVEF (%)	0.99 (0.96-1.01)	0.341		
Mean gradient	1.00 (0.91-1.10)	0.980		

*per 10 mm Hg increase

AR = aortic regurgitation; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure

In the subgroup of patients with LVEF ≤40% (n = 682), the presence of moderate or severe prosthesis-patient mismatch was not associated with an increased risk of death from HF (HR: 0.94, 95% CI: 0.42-2.09, P = 0.937).

9.5.3. Predictors of SCD

Table 9-5 shows the predictors of SCD. A LVEF ≤40% before TAVR (HR: 1.93, 95% CI: 1.05-3.55, P = 0.033) and the occurrence of NOP-LBBB (HR: 2.26, 95% CI: 1.23-4.14, P = 0.009) were independently associated with an increased risk of SCD. The same predictors were found using complete-case analysis. When considering death from other causes as a

competing risk event, LVEF ≤40% (HR: 2.13 [95% CI: 1.17-3.87; *P* = 0.011) and the occurrence of NOP-LBBB (HR: 2.20 [95% CI: 1.19-4.06, *P* = 0.010) remained as independent predictors of SCD. Figure 9-4 shows Kaplan-Meier curves for SCD according to the presence of LVEF ≤40% and/or NOP-LBBB. When both factors were present concomitantly, the risk of sudden death at 1-year follow-up increased up to 12.3% (95% CI: 7.1-22.5).

TABLE 9-5. Univariate and Multivariate Predictors of Sudden Cardiac Death Following TAVR

	Univariate HR (95% CI)	*P* Value	Multivariate HR* (95% CI)	*P* Value
Clinical characteristics and electrocardiographic findings				
Age (years)	1.00 (0.97-1.04)	0.862		
Male	1.30 (0.77-2.18)	0.329		
Body mass index (kg/m²)	1.00 (0.95-1.05)	0.918		
NYHA class ≥3	1.67 (0.82-3.40)	0.162		
Hypertension	1.32 (0.67-2.62)	0.421		
Diabetes mellitus	1.56 (0.91-2.67)	0.104		
COPD	1.34 (0.77-2.35)	0.305		
eGFR <60 ml/min	1.12 (0.65-1.94)	0.684		
Coronary artery disease	1.05 (0.62-1.77)	0.865		
Complete or no need of revascularization	0.70 (0.40-1.22)	0.206		
Paroxysmal/chronic AF	1.28 (0.73-2.26)	0.386		
Preexisting LBBB	0.56 (0.17-1.78)	0.321		
Prior pacemaker	0.47 (0.15-1.51)	0.205		
Echocardiographic findings				
LVEF ≤40%	2.07 (1.17-3.65)	0.013	1.93 (1.05-3.55)	0.033
Mean transaortic gradient (mm Hg)†	1.22 (1.35-1.00)	0.082	1.11 (0.90-1.34)	0.134
PASP >60 mm Hg	1.09 (0.49-2.43)	0.830		
Procedural findings				

Transapical approach	0.46 (0.18-1.16)	0.101		
Balloon-expandable prosthesis type	0.85 (0.51-1.44)	0.550		
≥ Moderate AR	1.97 (1.02-3.81)	0.044	1.40 (0.64-3.05)	0.395
30-day outcomes				
Stroke	2.94 (1.06-8.14)	0.038	1.85 (0.43-7.89)	0.405
Myocardial infarction	-	-		
Major or life threatening bleeding	1.24 (0.58-2.62)	0.581		
NOP-LBBB	2.00 (1.11-3.61)	0.021	2.26 (1.23-4.14)	0.009
PPM implantation	0.94 (0.44-2.00)	0.871		

*For the multivariate analysis, patients with missing data were included through the use of multiple imputation; †per 10 mm Hg decrease

AF = AF; AR = aortic regurgitation,; CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration ratio; HR = hazard ratio; LBBB = left bundle-branch block; LVEF = left ventricular ejection fraction; NOP-LBBB = new-onset persistent left bundle-branch block; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PPM = permanent pacemaker

A total of 15 patients with NOP-LBBB (3.2% of patients with NOP-LBBB) died of SCD at last follow up. Table 9-6 shows the electrocardiographic predictors of the occurrence of SCD in patients with NOP-LBBB. The receiver-operating characteristic curve showed that the best QRS duration cut-off for predicting SCD in patients with NOP-LBBB was >160 ms, with a sensitivity of 38.5% and specificity of 87.8% (area under the curve: 0.64, standard error: 0.09). A QRS duration>160 ms at hospital discharge in patients with NOP-LBBB was associated with an increased risk of SCD (HR: 4.78, 95% CI: 1.56-14.63, *P*=0.006). Cumulative rates of SCD at 2-year follow-up in patients with NOP-LBBB according to QRS duration (> or <160 ms) are shown in Figure 9-5. In patients with QRS duration>160 ms, the rate of SCD was 9.9% at 1-year follow-up.

TABLE 9-6. Electrocardiographic Predictors of Sudden Cardiac Death in Patients with New-Onset Persistent Left Bundle-Branch Block Following TAVR (n = 471)

	Univariate HR (95% CI)	*P* Value
Baseline		
QRS duration	1.01 (0.98-1.04)	0.551
PR >200 ms	-	-
Discharge		
QRS duration	1.02 (0.99-1.05)	0.162
QRS >160 (ms)	4.78 (1.56-14.63)	0.006
PR >200 ms	0.26 (0.03-2.20)	0.218

CI: confidence interval, HR: hazard ratio

In a further analysis, patients were classified in 3 groups according to the occurrence of new-onset LBBB and PPM during the hospitalization period: NOP-LBBB (n = 471 patients [12.6%]), NOP-LBBB-PPM (n = 92 patients [2.5%]) and no NOP-LBBB (n = 2976 patients [79.9%]). Reasons for PPM in patients with NOP-LBBB were: paroxysmal or transient advanced degree AVB in 58 patients (63.0%) and prophylactic in 34 patients (37.0%). Whereas those patients with NOP-LBBB-PPM had no increased risk of SCD compared to those with no NOP-LBBB (HR: 0.71, 95% CI: 0.09-5.48, *P* = 0.740) (Supplemental data table 2), those with NOP-LBBB (with no PPM) had an increased risk of SCD compared to those with no NOP-LBBB (HR: 2.21, 95% CI: 1.20-4.09, *P* = 0.011). No significant differences in SCD were observed between NOP-LBBB and NOP-LBBB-PPM groups (HR: 3.13, 95% CI: 0.38-25.63, *P* = 0.287). Supplemental Figure 9-1 displays Kaplan-Meier curves for SCD according to the occurrence of NOP-LBBB (with no PPM), NOP-LBBB and PPM or no NOP-LBBB.
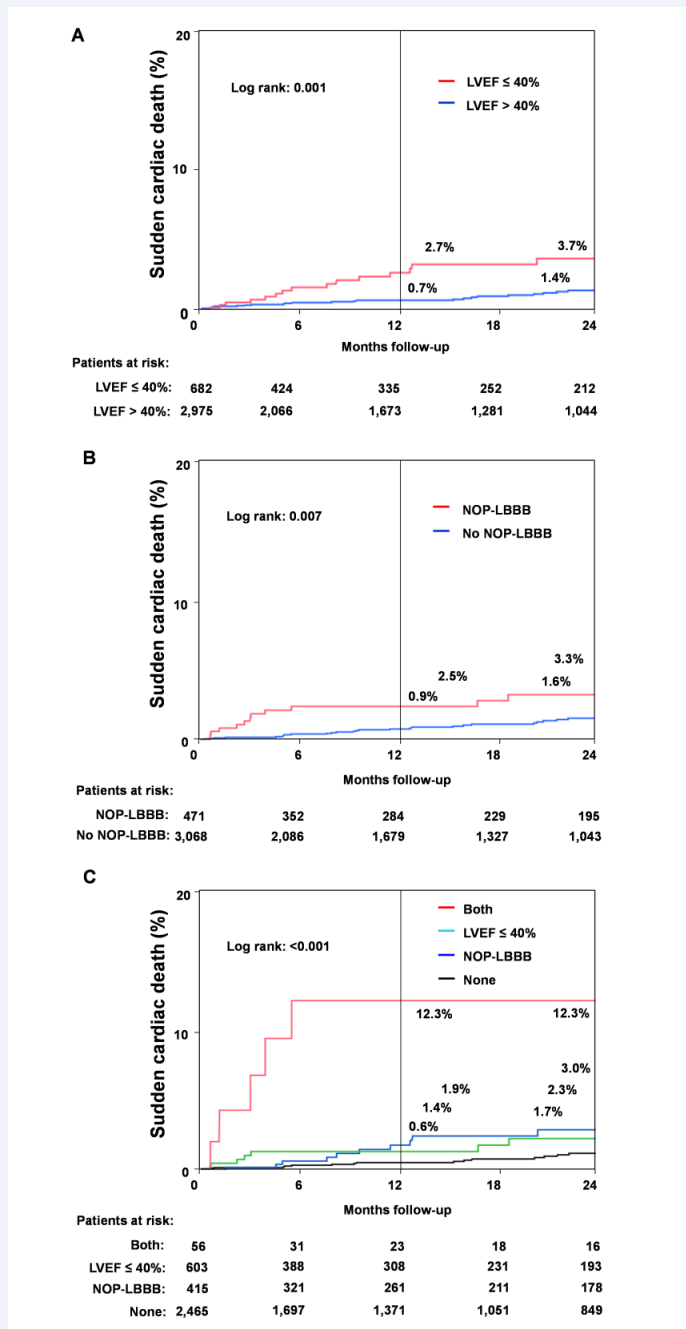
FIGURE 9-4. Rates of Sudden Cardiac Death According to the Presence of a Left Ventricular Ejection Fraction ≤40% and/or the Occurrence of New-Onset Persistent Left Bundle-Branch Block

Kaplan-Meier curves at 2-year follow-up for sudden cardiac death according to the presence of a left ventricular ejection fraction (LVEF) ≤40% **(A)**, new-onset persistent left bundle-branch block (NOP-LBBB) **(B)**, or both **(C)**.
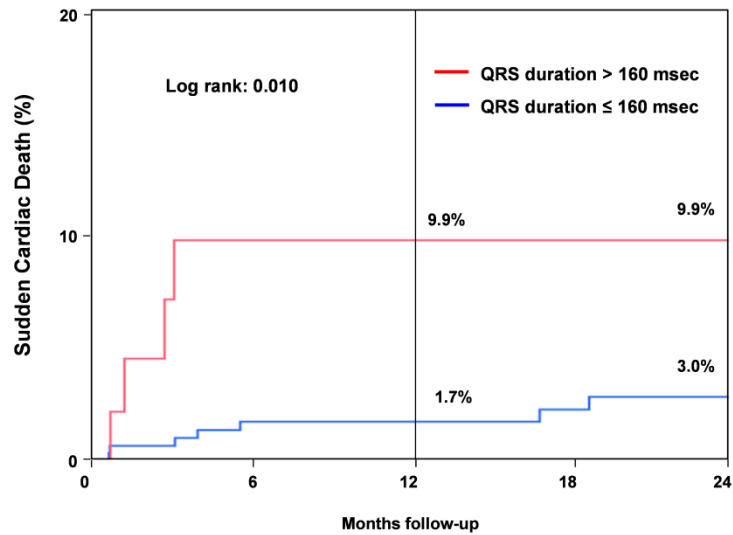
FIGURE 9-5. Rate of Sudden Cardiac Death in Patients with New-Onset Left Bundle-Branch Block

Kaplan-Meier curves at 2-year follow-up for sudden cardiac death in patients with new-onset left bundle-branch block, defined by the presence of a QRS duration >160 ms.

9.6. DISCUSSION

Advanced HF and SCD have been reported to be the most common causes of death after SAVR, accounting for >50% of total deaths in most of surgical series [288-291]. The percentage of both modes of death out of total deaths was much lower (~20%) in our study. This was in accordance with prior observations in patients undergoing TAVR,[89, 294] and may be attributable to the high prevalence of severe non-cardiac comorbidities in this population, leading to a high incidence of death from non-cardiac causes.

9.6.1. Death from Advanced HF after TAVR

The interplay between chronic obstructive pulmonary disease, AF, left ventricular dysfunction, severe pulmonary hypertension, and overt heart failure is well known [298], and it is therefore not surprising that these baseline comorbidites predicted the occurrence of death from advance HF after TAVR in our study. All these factors had already been identified as predictors of poorer outcomes in patients undergoing TAVR, [99, 298] and were also associated with an increased risk of mortality due to HF after cardiac surgery. [289-291] Likewise, a lower mean transaortic gradient, another baseline factor associated with death from advanced HF following TAVR in our study, had been associated with higher rate of HF recurrence, a poorer NYHA class, a higher rate of death from HF in patients with aortic stenosis undergoing SAVR, regardless of the presence or absence of left ventricular dysfunction. [299]

Interestingly, 2 potentially modifiable factors were identified as independent predictors of death from HF in this study: the use of the transapical approach and the presence of moderate or severe AR after TAVR (**Central Illustration**).
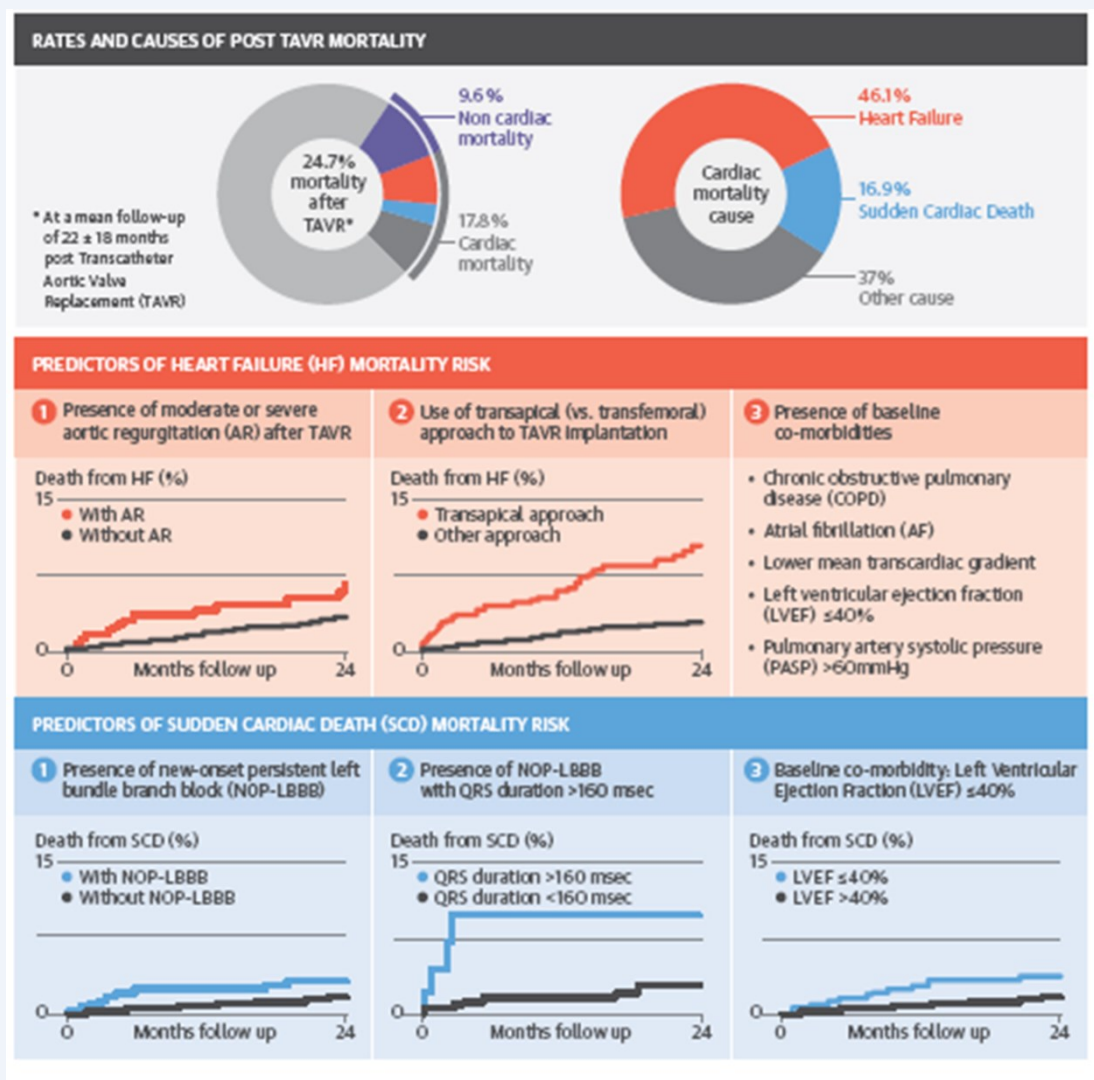
CENTRAL ILLUSTRATION. Baseline comorbidities and procedural factors leading to an increased rate of death from heart failure and sudden cardiac death. Kaplan-Meier curves for potentially modifiable or treatable factors are shown.

TAVR = transcatheter aortic valve replacement.

Growing evidence suggests that the use of the transapical (vs. transfemoral) approach may increase the risk of mortality after TAVR.[293, 300, 301] Nonetheless, the causes of this excess mortality remain largely unknown. The present study showed, for the first time, a ~2-fold increased risk of death from HF associated with the use of the transapical access. This suggests that the increased mortality associated with the transapical approach is driven, at

least in part, by a higher rate of progression to advanced HF. Accordingly, several studies have reported a poorer evolution of LVEF in patients undergoing transapical (vs. transfemoral) procedures,[302, 303] attributable to the occurrence of a higher degree of myocardial injury and an impairment in left ventricular apical function.[304, 305] This may also explain the early rise in NT-ProBNP levels following transapical but not transfemoral TAVR [104]. The results of the present study suggest that in patients at high risk of advanced HF not-suitable for the transfemoral approach, other alternative approaches to the transapical route such as subclavian, transaortic or carotid approaches, may be considered.

While the presence of residual moderate or severe AR is a well-established predictor of both overall and cardiovascular mortality after TAVR,[99, 306] the specific mechanisms leading to this increased mortality have not yet been elucidated. An increased risk of death from HF was observed in patients with residual moderate or severe AR in this study, suggesting that the progression to advanced HF may partially explain the excess of death in such patients. It has been reported that this increased risk of mortality occurs particularly in patients with a significant increment in the degree of AR following TAVR compared to baseline, due to a sudden increase in end-diastolic ventricular pressure which prevents the development of compensatory mechanisms like those present in patients with chronic AR[307]. Accordingly, a protective effect of the presence of significant AR before TAVR on the risk of death from HF in patients with residual moderate or severe AR was observed in this study. On the other hand, both the presence of severe pulmonary hypertension and a lower transaortic gradient before TAVR were associated with an increased risk of mortality due to HF. The development of pulmonary hypertension in patients with aortic stenosis has been mainly attributed to diastolic dysfunction,[308, 309] which markedly reduces the tolerance to acute AR, and in fact, higher pulmonary pressure levels have been associated with increased mortality in patients with significant AR after TAVR.[310] Also, the presence of lower transaortic gradients may reflect a more advanced stage of myocardial disease even in the absence of left ventricular dysfunction.[311] Whether the implementation of therapies directed at reducing the degree of AR after TAVR, such as balloon post-dilatation, valve-in-valve procedures, percutaneous closure of paravalvular leaks, or high pacing rates may be associated with a reduction in the rates of mortality from advanced HF after TAVR should be further evaluated.

9.6.2. SCD following TAVR

The impact of NOP-LBBB on mortality after aortic valve replacement has been the subject of great deal of controversy in both surgical and transcatheter fields.[155, 169, 252, 288, 312, 313] Several studies have reported an increased risk of SCD, complete atrio-ventricular block (AVB) or syncope in patients with NOP-LBBB following SAVR.[155] In the TAVR field, although NOP-LBBB has been associated with increased risk of complete AVB or PPM implantation during the follow-up period, [312, 313] no increased rates of SCD had been observed in such patients in previous studies assessing the impact of NOP-LBBB.[169, 252] However, differences in the definition of both SCD and LBBB (e.g. persistent at hospital discharge vs. all), in addition to underpowered sample sizes (all previous studies included <1,200 patients) may partially explain such differences. Although the specific causes of SCD in patients with NOP-LBBB (ventricular arrhythmia vs. advanced AVB) have not yet been elucidated, autopsy data has shown the presence of necrosis of the bundle of His and left bundle branch due to a mechanical compression of the transcatheter prosthesis,[314] supporting the progression to advanced AVB as a possible mechanism of SCD in such patients. Also, the facts that most of patients with NOP-LBBB and wide QRS died early within the first 6 months after TAVR and that no increased risk of SCD was observed in patients with NOP-LBBB and PPM implanted before hospital discharge, might suggest the occurrence of advanced AVB as the main cause of SCD in these patients. Nonetheless, no significant differences were observed between NOP-LBBB and NOP-LBBB-PPM in the risk of sudden cardiac death. The ongoing MARE study (clinicaltrials.gov $\neq$ NCT02153307) with continuous ECG recording (up to 3 years) in patients with NOP-LBBB following TAVR should help to clarify this issue.

The results of our study also highlighted the importance of measuring the QRS duration, in patients with NOP-LBBB following TAVR. In fact, 1 out of 10 patients who had TAVR and left the hospital with NOP-LBBB and a QRS duration >160 ms had died because of SCD within the first months following the procedure (vs. <3% in patients with NOP-LBBB and QRS<160 ms) (Central Illustration). A higher rate of progression to advanced AVB may be responsible for the high rate of SCD in such patients and, while waiting for the results of further studies, the implantation of a preventive pacemaker before hospital discharge may be justified in this situation. This might be particularly important in lower risk populations and younger patients with longer expected survival and lower risk of death from non-cardiac causes, in whom TAVR is being currently evaluated.

A large body of evidence supports the association between left ventricular dysfunction and sudden cardiac death,[315] and it is therefore not surprising that patients with a LVEF ≤40% were found to be at higher risk of SCD in this study (Central Illustration). Of note, the group of patients with both NOP-LBBB and a LVEF ≤40% exhibited the highest rate of SCD (>12%) within the year following TAVR, much higher than the rates of SCD in the presence of only one of these factors (<5%). This may be secondary to the occurrence ventricular arrhythmias, bradyarrhythmias and/or even advanced heart failure due to LBBB-related mechanical dyssynchrony in such patients. A longer QRS duration has been reported to be a predictor of SCD in patients with heart failure,[316] and the impairment or lack of improvement in LVEF in patients with NOP-LBBB after TAVR[253, 258] may also contribute to the very high risk of SCD observed in patients with both factors. While the effectiveness of implantable cardioverter defibrillator devices in patients aged >80 years, particularly in those with associated comorbidities such as renal failure and chronic pulmonary diseases (who in fact represent a high proportion of the TAVR population), has not been confirmed,[315] future studies are needed to evaluate the usefulness (and cost-effectiveness) of implanting such devices in this high risk group of patients. Also, the use of cardiac resynchronization in patients with left ventricular dysfunction requiring ventricular pacing or implantable cardioverter defibrillators has been associated with a lower risk of death or re-hospitalization for heart failure.[285] However, whether biventricular pacing might be associated with an increase in survival in patients with reduced LVEF and NOP-LBBB or PPM after TAVR should be further studied.

Limitations

Although the causes of death were defined according to the VARC-2 in each center, no event adjudication committee was available in this study. ECG and echocardiographic findings were interpreted in each center, with no ECG or echocardiography core lab evaluation. No contractile reserve data was available in patients with low-flow low-gradient aortic stenosis. The occurrence of advanced AVB in patients with NOP-LBBB during the follow-up period was not prospectively collected in all participating centers and was not analyzed in order to major bias leading to misleading results. Also, the number of patients in the NOP-LBBB - PPM group was limited, and the potential protective effect of PPM in patients with NOP-LBBB should be interpreted with caution and needs further investigation. Finally, while data

was prospectively collected in each center, data analysis for this study was of a retrospective nature.

Conclusions

Advanced HF and SCD accounted for ~2/3 of cardiac deaths following TAVR and occurred most frequently during the first 6 months after the procedure. Apart from baseline co-morbidities, some potentially modifiable or treatable factors leading to an increased risk of mortality from HF and SCD were identified. Whether specific therapeutic strategies targeting these factors, such as alternative approaches to the transapical approach in patients not-suitable for transfemoral access, further treatment of residual moderate or severe AR (especially if acute increase vs. baseline), pacemaker implantation in patients with NOP-LBBB (particularly in the presence of QRS duration >160 ms), or implantable cardiac defibrillator implantation in patients with left ventricular dysfunction, would decrease the risk of cardiac death in these patients should be evaluated in future studies. Meanwhile, the results of this study would allow us to identify the patients at the highest risk of dying of HF or SCD within the first months following TAVR and should contribute to improving the case-by-case clinical decision-making process in such a challenging group of patients.

9.7. DISCLOSURES

9.8. ACKNOWLEDGMENTS

SUPPLEMENTAL TABLE 9-1. Baseline Clinical Characteristics, Procedural Findings and 30-day Outcomes of the Study Population According to Approach Groups

	Other approaches (n=3106)	TA approach (n=607)	*P* value
Clinical characteristics and electrocardiographic findings			
Age (years)	82 ± 8	80 ± 8	<0.001
Male	1561/3105 (50.3)	301/607 (49.6)	0.757
Body mass index (kg/m^2)	27 ± 5	26 ± 5	<0.001
NYHA class ≥3	2239/3056 (73.3)	497/605 (82.1)	<0.001
Hypertension	2324/3091 (75.2)	525/607 (86.5)	<0.001
Diabetes mellitus	927/3094 (30.0)	189/606 (31.2)	0.547
COPD	781/3083 (25.3)	174/606 (28.7)	0.082
eGFR <60 ml/min	1521/3029 (50.2)	341/603 (56.6)	0.004
Coronary artery disease	1552/3092 (50.2)	430/607 (70.8)	<0.001
Complete or no need of revascularization	240/506 (47.4)	1973/2838 (69.5)	<0.001
Peripheral vascular disease	377/2762	307/587	<0.001
Paroxysmal/chronic AF	893/3016 (29.6)	198/606 (32.7)	0.133
Preexisting LBBB	282/2951 (9.6)	47/580 (8.1)	0.271
Prior pacemaker	324/3097 (10.5)	91/606 (15.0)	0.001
Logistic EuroSCORE (%)	18.5 ± 12.2	24.4 ± 15.8	<0.001
Echocardiographic findings			
LVEF≤40%	546/3044 (17.9)	134/602 (22.3)	0.013
Mean transaortic gradient (mmHg)	47 ± 17	43 ± 16	<0.001
PASP>60 mmHg	61/512 (11.9)	313/2232 (14.0)	0.210
Procedural findings			
Prosthesis type			
Self-expandable	1519/3103 (49.0)	10/607 (1.6)	<0.001
Balloon-expandable	1584/3103(51.0)	507/607 (98.4)	
≥Moderate AR	330/2846 (11.6)	43/553 (7.8)	0.009
30-day outcomes			
Stroke	100/3058 (3.3)	14/604 (2.3)	0.218

Myocardial infarction	36/2685 (1.3)	16/598 (2.7)	0.018
Major or life threatening bleeding	349/2876 (12.1)	130/598 (21.7)	<0.001
NOP-LBBB	414/2952 (14.0)	57/579 (9.8)	0.005
PPM implantation	492/3063 (16.1)	43/598 (7.2)	<0.001

AF: AF, AR: aortic regurgitation, COPD: chronic obstructive, ECG: electrocardiogram, eGFR: estimated glomerular filtration ratio, LBBB: left bundle branch block, LVEF: left ventricular ejection fraction NOP-LBBB: new-onset persistent left bundle branch block, NYHA: New York Heart Association, pulmonary disease, PASP: pulmonary artery systolic pressure, PPM: permanent pacemaker

SUPPLEMENTAL TABLE 9-2. Impact of the Occurrence of New-Onset Persistent Left Bundle Branch Block with or without Permanent Pacemaker Implantation during the Hospitalization Period on Sudden Cardiac Death

	Others (n=2976)	NOP-LBBB-PPM (n=92)	NOP-LBBB (with no PPM) (n=471)	*P* value NOP-LBBB-PPM vs. others	*P* value NOP-LBBB (with no PPM) vs. others	*P* value NOP-LBBB (with no PPM) vs. NOP-LBBB-PPM
Sudden cardiac death						
Number of patients (%)	41 (1.4)	1 (1.1)	15 (3.2)			
HR for NOP-LBBB without PPM and NOP-LBBB with PPM (95% CI)						
Univariate HR	1.00 (ref.)	0.60 (0.08-4.66)	1.90 (1.04-3.48)	0.627	0.036	
Multivariate HR*,**	1.00 (ref.)	0.71 (0.09-5.48)	2.21 (1.20-4.09)	0.740	0.011	
HR for NOP-LBBB without PPM vs. NOP-LBBB with PPM (95% CI)						
Univariate HR		1.00 (ref.)	3.16 (0.39-25.90)			0.283
Multivariate HR*,**		1.00 (ref.)	3.13 (0.38-25.63)			0.287

*Adjusted for univariate risk factors of SCD: LVEF≤40%, moderate or severe AR, mean transaortic gradient and 30-day stroke; ** For the multivariate analysis, patients with missing data were included through the use of multiple imputation

CI: confidence interval, HR: hazard ratio, NOP-LBBB: new-onset persistent left bundle branch block, PPM: permanent pacemaker

SUPPLEMENTAL FIGURE 9-1. Rates of Sudden Cardiac Death According to the Occurrence of New-Onset Persistent Left Bundle Branch Block and the Need of Permanent Pacemaker during the Hospitalization Period Groups
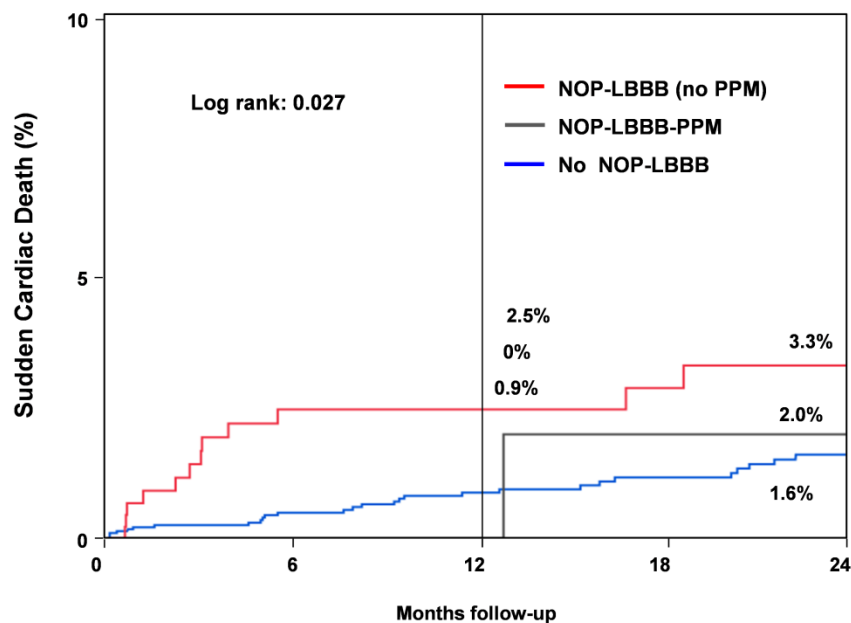
Kaplan-Meier curves at 2-year follow-up comparing rates of sudden cardiac death in new-onset persistent left bundle branch block (with no permanent pacemaker), new-onset persistent left bundle branch block and permanent pacemaker implanted before hospital discharge and no new-onset persistent left bundle branch block groups.

CHAPTER 10-Article 6

Managing Heart Block after Transcatheter Aortic Valve Implantation – from Monitoring to Device Selection and Pacemaker Indications

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10.1. RESUME

L'introduction de dispositifs de nouvelle génération a entraîné une réduction spectaculaire de l'incidence de complications associées à l'implantation valvulaire aortique par cathéter (TAVI). Toutefois, les données préliminaires suggèrent que la survenue de troubles de la conduction, en particulier de blocs auriculo-ventriculaires et blocs de branche gauche, non seulement n'a pas diminué, mais plutôt augmenté avec l'utilisation de tels dispositifs et reste la complication la plus fréquente du TAVI. Bien qu'il existe des discordances entre les études, un effet négatif potentiel des troubles conductifs post TAVI sur la mortalité globale, la mort subite cardiaque et la fonction ventriculaire gauche a été rapporté. Des stratégies destinées à la fois à réduire le risque et à améliorer la gestion de ces complications sont donc nécessaires. En pratique, l'indication et le moment d'implantation d'un stimulateur cardiaque permanent sont souvent déterminées par les préférences des centres/opérateurs. Des études évaluant l'impact de ces complications et les indications optimales d'une stimulation cardiaque permanente chez ces patients sont actuellement en cours. Cet article examine les données disponibles sur l'incidence et l'impact des troubles de la conduction post-TAVI et propose une stratégie de gestion de ces complications.

10.2. ABSTRACT

The introduction of the so-called newer generation devices has led a dramatic reduction in the incidence of complications associated with transcatheter aortic valve implantation (TAVI). However, preliminary data suggest that the occurrence of conduction abnormalities, particularly new atrio-ventricular block and left bundle branch block, has not decreased - rather increased - with the use of such devices and remains the most frequent complications of TAVI. Although inconsistencies across studies exist, a potential negative effect of new conduction abnormalities post-TAVI on overall mortality, sudden cardiac death and left ventricular function has been reported. Strategies intended to both reduce the risk and improve the management of such complications are therefore mandatory. In fact, the indication and timing of permanent pacemaker implantation is frequently individualized according to the centers/operators' preferences. Currently, studies assessing the impact of these complications and the optimal indications for permanent cardiac pacing in these patients are underway. This article reviews the data available on the incidence and impact of conduction disturbances following TAVI and proposes a strategy for the management of such complications.

10.3. INTRODUCTION

The aortic valve has a close spatial proximity with the conduction system, in particular the bundle of His and the left bundle branch. [246, 317] As a result of this anatomical interaction, conduction abnormalities are frequently observed in patients with calcified aortic stenosis and an increased rate has been reported following aortic valve interventions, in particular transcatheter aortic valve implantation (TAVI). The stent frame of the valve prosthesis, in addition to the delivery system and stiff guide-wires used during these procedures may exert a mechanical stress on the ventricular wall bounding the aortic valve, including the ventricular septum and the conduction system. The location, magnitude and duration of these mechanical forces and patients' anatomical and pathological conditions may determine the type, mostly, atrio-ventricular (AV) block or left bundle branch block (LBBB), and duration of these conduction abnormalities (transient or persistent).

10.4. INCIDENCE AND PREDICTORS OF CONDUCTION DISTURBANCES POST-TAVI

Overall, the rate of new-onset LBBB after TAVI is ~27%, ranging from 4 to 57% [317] and the rate of permanent pacemaker (PPM) implantation is ~17 % (from 2 to 51%). [318] Wide variations have been reported across studies and according to the type of valve prosthesis (Table 10-1). Overall, the incidence of both new-onset LBBB and PPM implantation is higher with the use of the self-expanding CoreValve system (~48 and 28%, respectively) than with the balloon-expandable Edwards SAPIEN/SAPIEN XT valve (~14 and 6%, respectively).[246, 317, 318] Indeed, the increased risk of PPM associated with the CoreValve prosthesis compared to the Edwards SAPIEN/SAPIEN XT valve has been confirmed in a randomized trial (37.6 vs. 17.3%, P <0.001).[319] A slow but significant reduction in the rate of conduction abnormalities and PPM associated with both transcatheter valve types has been observed over time.[317, 320] This may be related to the improvements in delivery systems, an increased experience and a better knowledge of the factors associated with conduction

disturbances post-TAVR, in addition to the use of more restrictive indications for PPM implantation.[320]

In the last years, many novel generations of transcatheter valve devices intended to improve the results of TAVI have been introduced. The preliminary results associated with such new devices have shown a dramatic decrease in the incidence of some major peri-procedural complications but not in the occurrence of conduction abnormalities. Data on the risk of new-onset LBBB associated with these devices is scarce or lacking (Table 10-1). However, these early results show a lack of reduction or even an increase in the rate of PPM implantation associated with newer transcatheter valves (~13%, range from 8 to 30%) (Table 10-1), suggesting that the retrievability/repositionability capabilities of most of these prostheses failed to reduce the occurrence of conduction abnormalities post-TAVI. Also, no additional features have been developed in order to reduce the risk of these complications and, therefore, no significant decrease in the rate of new conduction disturbances post-TAVR is therefore anticipated in the near future.

Both patient clinical characteristics and procedural features have been reported as predictors of new-onset LBBB and PPM requirement. Clinical predictors associated with an increased risk of new-onset LBBB include the presence of pre-existing conduction abnormalities (longer baseline QRS duration) and TAVI within the native aortic valve (as opposed to valve-in-valve).[246, 317] Valve prosthesis type (self-expandable) and the depth of implantation are the only modifiable procedural factors predicting the occurrence of new-onset LBBB.[317] Likewise, clinical factors such as male gender, absence of prior valve surgery, the presence of porcelain aorta and pre-existing conduction abnormalities (mainly pre-existing right bundle branch block, but also pre-existing left anterior hemi-block and first degree AV block) are independent predictors of PPM after TAVI.[317] Similarly, intraprocedural AV block, and modifiable factors such as the implantation depth, the use of the CoreValve system, and the use of balloon predilatation, have been independently associated with an increased risk of PPM implantation.[246, 317, 318] Nonetheless, up to now only a more aortic position of the prosthesis (≤ 6mm below the aortic annulus) and the use of the Edwards SAPIEN/SAPIEN XT valves (compared to the Corevalve System) have demonstrated to reduce the risk of PPM after TAVI.[320]

TABLE 10-1. Incidence of Left Bundle Branch Block and Permanent Pacemaker Implantation in Newer Generation Transcatheter Valve Devices

Author, year, no. of patients	Valve Type	30-day new-onset LBBB %*	30-day PPM %*
Bax et al.,[317] 2014, n=4305 Siontis et al.,[318] 2014, n=11,210	Overall	27.1 (4.4-57)	17.1 (2.3-51.1)
Bax et al.,[317] 2014, n=4305 Siontis et al.,[318] 2014, n=11,210	CoreValve® Revalving System (Medtronic Inc, Minneapolis, MN, USA)	47.6 (38.0-56.8)	28 (16.4-51.1)
Bax et al.,[317] 2014, n=4305 Siontis et al.,[318] 2014, n=11,210	Edwards® SAPIEN/ SAPIEN XT™ valve (Edwards Lifesciences Corp., Irvine, CA, USA)	14.1 (4.4-28.2)	6 (2.3-14.4)
Kempfer et al.,[321] 2013, n=40 Seiffert et al.,[322] 2014, n=62 Möllmann et al.• 2014, n=250	ACURATE TA™ (Symetis SA, Ecublens, Switzerland)	NA	11.7 (7.5-21.0)
Maeda et al.[323], 2015, n=15 Möllmann et al.,• 2014, n=89	ACURATE neo™ (Symetis SA, Ecublens, Switzerland)	NA	7.7 (0-9.0)
‡Meredith, 2015, n=60	Corevalve® Evolute R™ System (Medtronic Inc, Minneapolis, MN, USA)	NA	11.7
Schofer et al.,[324] 2014, n=100 Treede et al.,[325] 2010, n=22	Direct Flow Medical Valve System™ (Direct Flow Medical Inc., Santa Rosa, CA, USA)	NA	16.4 (13.6-17.0)
Kodali, 2014§, n=1659 Webb et al., 2014, n=150	Edwards® SAPIEN 3™ valve (Edwards Lifesciences Corp., Irvine, CA, USA)	18.0	11.5 (11.3-13.3)
Wendler et al.□, 2014, n=115 Treede et al., 2012, n=67 Seiffert et al.,[322] 2015, n=88	JenaValve™ (JenaValve Technology GmbH, Munich, Germany)	NA	12.6 (9.1-14.8)
Meredith et al.,[326] 2014 , n=11 Meredith et al.,[327] 2014, n=120 Gooley et al.,[328] 2015, n=50 Whöhrle et al.,[329] 2015, n=26	Lotus™ Valve System (Boston Scientific Corp., Natick, MA, USA USA)	NA	28.7 (26.9-36.4)
Seiffert et al.,[322] 2014, n=50	Medtronic Engager™ (Medtronic Inc, Minneapolis, MN, USA)	NA	30.0
¶Monoharan, 2015, n=102 Wilson et al.,[330] 2012, n=10	Portico™ Valve (St Jude Medical Inc., Minneapolis, MN, USA)	22.2	8.9 (0-9.8)

*Most of the studies included patients with pre-existing LBBB or PPM in the denominator. •Presented at: Transcatheter Cardiovascular Therapies (TCT); September 15, 2014; Washington, D.C., USA. ‡Presented at: EuroPCR Congress; May 20, 2015. Paris, France; § Presented at: American College of Cardiology/i2 Scientific Session; March 15, 2015; San Diego, CA, USA. □Presented at: EuroPCR Congress, May 21, 2014. Paris, France;¶Presented at: Transcatheter Valve Therapies; June 4, 2015. Chicago, IL, USA.

10.5. MANAGEMENT OF CONDUCTION DISTURBANCES POST-TAVI

It has been shown that the strict adherence to current guidelines regarding the indication of PPM after TAVI may be associated with a decrease in the rate of this complication. [320] The main reason for PPM implantation following TAVI relates to the occurrence of complete or high degree AV block, [318] with about 33% and 50% of PPMs being implanted within the first 24 and 48 hrs post-TAVI, respectively.[331, 332] This contrasts with current European recommendations suggesting a period of clinical observation and ECG monitoring for up to 7 days before implanting a PPM in patients with high degree or complete AV block after TAVI in order to assess the temporary (vs. permanent) nature of rhythm disturbances post-TAVI (recommendation class I, level of evidence C).[333] This observation period is recommended to be shortened only in cases of complete AV block with low rate of escape rhythm.[333] Such as strategy of a more prolonged ECG monitoring post-TAVI prior to PPM implantation is supported by the results of studies showing that (i) a significant proportion of these conduction abnormalities resolves early within the post-TAVI period, and (ii) there is increased risk of late mortality or repeated hospitalisations for heart failure associated with cardiac pacing, particularly in patients with low LVEF and higher rates of PPM dependency. [246]

Although early TAVI studies failed to demonstrate an association between PPM implantation and mortality or MACE over a mean follow-up of ~3 years, recent results have suggested a negative impact of PPM implantation the evolution of left ventricular ejection fraction after TAVI.[334, 335] Also, PPM implantation post TAVI may lack clinical benefit in a significant proportion of patients due to recovery of AV conduction during the follow-up period. [317] Nonetheless, the risk/benefit and cost/benefit ratio of continuous ECG monitoring (often with associated temporary pacing) for a period of seven days following TAVR to allow possible rhythm recovery before implantation of a PPM required confirmation in future studies. In fact, this strategy competes with current trends towards reducing the length of hospital stays post TAVI in order to limit costs and complications. Interestingly, the adoption of early discharge (24-72 hours) strategies post-TAVR has not been associated with an increased risk of re-hospitalisation or sudden cardiac death,[336, 337] suggesting that 24 hours of

ECG monitoring (instead of the 72 hours recommended in ESC guidelines) may be sufficient in patients with no conduction abnormalities immediately after TAVI procedures.

Interestingly, conduction abnormalities post TAVI often seem to be present pre-procedure and remain undetected until post-procedural ECG monitoring is performed. Therefore, ECG monitoring for at least 24 hours pre TAVI could allow prompt identification and treatment of the conduction abnormalities which are not expected to resolve and could lead to an overall reduction in length of hospital stay.[338]

In addition to complete or high degree AVB, sick sinus syndrome or severe bradycardia and the occurrence of new-onset persistent LBBB are other reasons to consider PPM implantation post TAVI.[318] No evidence exists on a causal relationship between TAVI and the occurrence of sinus node disease or severe bradycardia due to causes other than AV blocks and there are no current specific indications for PPM (other than general recommendations for PPM implantation) in these patients. However, the indications for PPM implantation in patients with new LBBB post TAVR are more controversial. Several studies have shown an increased risk (>3-fold) of late advanced AVB and need for PPM implantation in patients with new-onset persistent LBBB post TAVI (**Table 10-2**). In addition, although results have been discordant across studies, the occurrence of new-onset persistent LBBB has been associated with an increased risk of overall mortality and sudden cardiac death, particularly in patients with prolonged QRS duration (>160 ms).[169, 252, 313, 338, 339]

The ongoing MARE (Ambulatory Electrocardiographic Monitoring for the Detection of High-Degree Atrio-Ventricular Block in Patients With New-onset PeRsistent LEft Bundle Branch Block After Transcatheter Aortic Valve Implantation) study (NCT02153307), and the recently commenced "Assessment of the Prognosis of Persistent Left Bundle Branch Block (LBBB) After Transcatheter Aortic Valve Implantation (TAVI) by an Electrophysiological and Remote Monitoring Risk-adapted Algorithm (LBBB-TAVI)" study (NCT02482844) will provide insight into the complications associated with this conduction abnormality as well as its optimal therapy. Meanwhile, current indications for PPM implantation appears to be reasonable in some groups of patients with new persistent LBBB (ex. those with QRS >160 ms) post TAVI.

TABLE 10-2. Main Studies Assessing the Incidence of Permanent Pacemaker Implantation in Patients with New-Onset Left Bundle Branch Block after Transcatheter Aortic Valve Replacement

Study	n	Type of valve	Results (PPM vs. no PPM)
Urena et al. [253](2012)	202	ESV	Adjusted HR: 5.99 (2.93 to 15.61), $P<0.001$
Franzoni et al. [340](2013)	238	ESV CV	$P = 0.74$
Mouillet et al.[341] (2013)	79	CV	32.1% vs. 13.3%, $P = 0.004$
Nazif et al.[313] (2013)	1151	ESV	Adjusted HR: 3.18 (1.76 to 5.76), $P < 0.001$
Testa et al. [169](2013)	818	CV	5% vs. 2%, $P = 0.02$ 18.2% vs. 17%, $P = 0.09$
Urena et al. [312](2014)	668	ESV	Adjusted HR: 3.88 (1.86 to 8.05), $P < 0.001$

CV: CoreValve, ESV: Edwards SAPIEN/SAPIEN XT, HR: hazard ratio, PPM: permanent pacemaker

10.6. CONCLUSIONS

The occurrence of new conduction disturbances and of the need for PPM post TAVI remains a major concern due to its high incidence (which is unlikely to decrease in the near future) and potentially negative impact on mid- and long-term outcomes. Use of balloon-expandable valve systems and a high (more aortic) implantation site have been associated with significant reductions of such complications. Limiting the indications for PPM to those strictly recommended in guidelines, with more prolonged periods of ECG monitoring prior to PPM

implant, may ultimately reduce implantation rates. The group of patients with new-onset LBBB post-TAVI is particularly challenging, and the indications for PPM in such patients remain controversial. Ongoing studies will provide further insights into the risks associated with this complication and its optimal therapy.

CHAPTER 11. DISCUSSION, FUTURE

PERSPECTIVES AND CONCLUSIONS

11.1. INCIDENCE OF ARRHYTHMIAS AND CONDUCTION DISORDERS IN TAVR CANDIDATES

The high prevalence of conduction disturbances in TAVR candidates confirmed in the first study of this thesis was first suggested by the results of the Cohort B of the PARTNER trial:[80] no differences were observed in the rate of new-onset AF or PPM implantation between TAVR and medical treatment group. Indeed, the rate of 1-year PPM implantation and new-onset AF were numerically higher in the medical treatment group (PPM: 7.8 vs. 4.5%; AF: 1.7 vs. 0.6%), although such differences were not significant. A proportion of these arrhythmias might be a complication of percutaneous balloon valvuloplasty, performed in almost 70% of patients. However, balloon valvuloplasty does not to explain the persistent high-risk of conduction abnormalities up to 1 year follow-up.

Accordingly, the association between aortic valve disease and rhythm and conduction disorders have been widely reported.[143, 233, 234] In addition, patients undergoing TAVR nowadays have advanced age and comorbidities such as hypertension, chronic obstructive pulmonary disease, diabetes, which are known predictors of the occurrence of AF and conduction disorders in the overall population.[143, 219-223, 227, 235] Such high-risk patients' profile, might be responsible, at least in part, for the great differences observed in the rate of conduction disturbances between patients undergoing TAVR and surgery in registries, much higher than that observed in randomized trials comparing both therapies. According to this observation, the inclusion of lower risk patients in TAVR studies might be associated with a reduction in the risk of such complications. However, last series including patients at intermediate-risk did not report a reduction in the risk of conduction disturbances as showed in the sixth article included in this thesis. The use of new-generation devices, with longer stent frames and an increased radial force, may compensate the potential decrease in the rate of such complications related to the lower-risk conditions of patients.[102]

In addition, younger and lower profile risk patients have a lower rate of baseline conduction disorders and therefore, they might be at higher risk for the occurrence of new disorders during interventions. In fact, in the second study of this thesis including patients with no baseline conduction disorders, the rate of new-onset LBBB was higher than that previously reported in patients undergoing TAVR with a balloon-expandable valve.

During the last years, the technique of TAVR has evolved to minimally invasive interventions, using percutaneous closure devices (vs. surgical cut downs) and local (vs. general) anesthesia. These strategies have allowed the shortening of hospital stays and, consequently thecosts. In fact, it has been claim that shortening the hospital stay to 72 hours is feasible and safe in such patients.[336, 337] However, the occurrence of rhythm and conduction disorders after TAVR precludes the implementation of such strategies, increasing costs and risks. The first article of this thesis shows that a proportion of such disorders are already present before TAVR. This is of major clinical interest, since the detection of such conduction disorders before TAVR might allow early therapy indication, reduction in risks and shortening in hospitalisation periods.

11.2.   CLINICAL IMPACT OF NEW-LBBB AFTER TAVR

From the beginning of this thesis, several articles evaluating the clinical impact of new-onset LBBB after TAVR have been published. Main characteristics of such articles are resumed in Table 10-1. Major differences were observed across studies regarding the sample size, the type of prosthesis, the definition of new-onset LBBB and the profile of patients included. Likewise, results regarding the impact of new-onset LBBB differed across studies. While Houthuizen et al.[252] found an increased risk in mortality associated with the occurrence of new-onset LBBB, no differences in mortality were observed between LBBB and no LBBB groups in all other studies. Some characteristics are different in this study: first, the global risk of patients included in the Houthuizen et al. study was lower than that of the rest of studies (Logistic EuroSCORE of 16% vs. >20% in all other studies), and the weight of NOP-LBBB in clinical outcomes may vary according the presence of comorbidities. Second, this study considered all new LBBB observed within the first 7 days after TAVR, while several studies considered only patients with LBBB persistent a hospital discharge, and the rest any LBBB observed immediately after the procedure. In addition, Houthuizen et al [252] included patients undergoing both balloon and self-expandable valves, with most of patients receiving a self-expandable prosthesis. All other studies included patients undergoing TAVR using mostly one type of prosthesis. The incidence and evolution over time of conduction disturbances differ between the 2 -balloon- and self-expandable - valve systems,[181, 253] and therefore, the impact of this conduction disorder might be different according to the type of prosthesis used.

Table 11-1. Main Studies Assessing the Incidence of Permanent Pacemaker Implantation and Mortality in Patients with New-Onset Left Bundle Branch Block after Transcatheter Aortic Valve Replacement

Study	n	Type of valve	STS/ Euroscore	Risk of 1-year PPM	Risk of 1-year all-cause mortality
Urena et al. (2012)[253]	202	ESV	7.5±3.7/-	Adjusted HR: 5.99 (2.93 to 15.61), p<0.001	13 % vs. 16%, *P*=0.610
Houthuizen et al. (2012)[252]	679	ESV / CV	-/ 16 (10-25)	-	1.54 (1.12-2.10), *P*=0.007
Franzoni et al. (2013)[340]	238	ESV / CV	8± 8/ 22±15	*P*=0.74	*P*=0.42
Mouillet et al. (2013)[341]	79	CV	-/ 23±10	32.1% vs. 13.3%, *P*=0.004	-
Nazif et al. (2013)[313]	1151	ESV	11± 4 25±16	Adjusted HR: 3.18 (1.76 to 5.76), *P*<0.001	17.1% vs. 18.4%, *P*=0.067
Testa et al. (2013)[169]	818	CV	-/ 23±11	18.2% vs. 17%,*P*=0.09	18.7% vs. 19.8%, *P*=0.100
Urena et al. (2014)[312]	668	ESV	8±5 21±14	Adjusted HR: 3.88 (1.86 to 8.05), *P*<0.001	11.0 vs. 19.9% Adjusted HR: 0.73 (0.44–1.23), *P*=0.240

CV: CoreValve, ESV: Edwards SAPIEN/SAPIEN XT, HR: hazard ratio, PPM: permanent pacemaker
Adapted from Urena M, Rodes-Cabau R. Permanent pacemaker implantation following transcatheter aortic valve replacement. still a concern? JACC Interv 2015; 8: 71-73

The association between new-onset LBBB and the need of PPM was first reported in the second article included in this work, and later confirmed by several studies, including the PARTNER trial[313] (Table 10-1). In all these studies, the main cause of PPM was the

occurrence of advanced degree or complete AVB. Testa et al.[169] found a higher risk of 30-day PPM implantation in patients with new-onset persistent LBBB (5% vs. 2%, $P = 0.02$), although these differences were no longer significant at 1-year follow-up. Such discordance might be explained by the different definition used for persistent LBBB (defined as a LBBB persisting at least 48h by Testa et al, and as a LBBB persisting at hospital discharge in this study), and mainly, the high rate of rate of PPI at 1-year follow-up in the NOP-LBBB group in the Testa study (17% vs. 3% observed in the results of this thesis).

That the progression of NOP-LBBB to AVB described above might translate into an increased risk of sudden cardiac death if it is not diagnosed and treated early, might be plausible, and might explain the findings observed in the fifth study included in this thesis: NOP-LBBB was an independent predictor of sudden cardiac death along with the presence of LV dysfunction. This might be further supported by anatomical-pathological studies showing the presence of necrosis of the bundle of His and left bundle branch due to a mechanical compression of the transcatheter prosthesis in patients having a sudden cardiac death[314] and the results of the fourth study of this thesis showing a reduced risk of death from unknown causes in patients with a PPM implanted post TAVR compared to those without PPM.

Although appealing, these studies are hypothesis-generating studies and such hypothesis needs to be confirmed. Indeed, new conduction disorders post TAVR have been associated with a poorer evolution of LV ejection fraction and the presence of LV dysfunction was the other predictor of sudden cardiac death in this study. Therefore, the occurrence of ventricular arrhythmias cannot be ruled out. The ongoing MARE study (clinicaltrials.gov ≠ NCT02153307) will add insight into the impact of new-onset LBBB.

Conversely to that observed in the fifth study of this thesis, other studies assessing the clinical impact of new conduction disorders after TAVR failed to find any increased risk in sudden cardiac death in patients with new-onset LBBB. Although there was a tendency towards a higher rate of sudden death among patients with new-onset LBBB (6.4% vs. 4.0% at 1-year follow-up) in the Houthuizen et al. study, [252] such differences were not significant. As aforementioned, the differences in the definition of sudden cardiac death and new-onset (vs. new onset persistent) LBBB and the limited simple size of previous studies, might explain such discordances. Nonetheless, results showing the increased risk of AVB and sudden cardiac death in patients with NOP-LBBB are in agreement with that which is currently performed in the clinical practice. Although no uniform strategy exists, a prophylactic PPM is

frequently implanted in patients with NOP-LBBB post TAVR, mainly in those with long PR interval or large QRS duration. [342]

11.3. IMPACT OF PPM ON LATE CLINICAL OUTCOMES

Such preventive strategy has been favoured by the findings reporting the absence of increased risk of mortality observed in patients undergoing post TAVR PPM implantation, such as was observed in the fourth article included in this thesis. Main studies published from the beginning of this thesis assessing the impact of PPM implantation after TAVR are shown in Table 10-2. Most studies did not observed an increased risk of mortality or MACE in patients requiring PPM. On the contrary, a PARTNER sub-study showed poorer clinical outcomes in patients needing PPM implantation after TAVR, with an increased rate of the combined endpoint of 1-year all-cause mortality or repeat hospitalization for any cause (42.0% vs. 32.6%, $P = 0.007$) and a trend towards a higher risk of 1-year all-cause mortality (26.3% vs. 20.8%, $P = 0.08$) in patients requiring PPM implantation. However, this excess mortality was attributable to non-cardiovascular causes and no differences were observed in cardiovascular deaths (7.6% vs. 9.0% in the PPM vs. no PPM groups, respectively, $P = 0.52$) and, furthermore, the need for cardiac pacing had not impact on the LV ejection fraction evolution after TAVR. Although this finding is poorly understood, no multivariate adjustment was made and patients requiring PPM had a higher rate of renal failure requiring dialysis and the need for hemodynamic support during the TAVR procedures, which might have had an impact on the increased risk of late mortality.[331] Despite such limitations, these results confirm the need of avoid unnecessary pacemakers and to establish clear recommendations for permanent pacing in patients undergoing TAVR. The sixth article of this thesis proposes a strategy for the management conduction abnormalities after TAVR according to available evidence.

11.4. IMPACT OF LBBB AND PPM ON LVEF

Articles 2, 3 and 4 included in this thesis confirmed the poorer evolution of LV ejection fraction after TAVR in patients with both NOP-LBBB and PPM implantation during the hospitalization period. Of note, this detrimental impact was greater in those patients with no conduction abnormalities at baseline. Several studies have confirmed such results later. [197,]

[258, 335, 343] However, 2 studies failed to find differences in the evolution of LV ejection fraction after TAVR: the aforementioned subanalysis of the PARTNER trial by Nazif et al[332] and the Testa et al study.[169] As mentioned above, the high rate of PPM implantation in the group of patients without LBBB and tendency towards a high rate of paravalvular leaks in

TABLE 11-2. Main Studies Assessing the Impact of Permanent Pacemaker Implantation after Transcatheter Aortic Valve Replacement

Author, year (Ref. #)	N	Intervention	Age (years)	LVEF (%)	Incidence PPM (%)	Mean/median follow‑up (years)	Endpoints	Results	Long-term pacing
D'Ancona et al, 2011[202]	322	TAVR (ES)	79 ± 8	51 ± 15	6.2	1	Mortality	16 vs. 19%, P = 0.30	NA
Buellesfeld et al, 2012[264]	352	TAVR (ES, CV)	83 ± 6	51 ± 15	32.1	1	Mortality Death, stroke and myocardial infarction	adjusted HR:1.06, P = 0.90 adjusted HR: 0.98, P = 0.98	NA
De Carlo et al, 2012[263]	275	TAVR (CV)	82 ± 6	52 ± 12	26.9	1.8	Mortality	12.5 vs. 11.8%, P = 0.90	NA
Urena et al, 2014[334]	1,516	TAVR (ES, CV)	80 ± 8	55 ± 14	15.4	1.9 ± 1.4	Mortality Death or re-hospitalisation for heart failure	adjusted HR: 0.98, P = 0.87 adjusted HR: 1.0, P = 0.98	66.9% (on ECG)
Nazif et al, 2014[332]	1,763	TAVR (ES)	84 ± 7	54	8.8	1	Mortality Death and any re-hospitalization	26 vs. 18%, P = 0.08 42 vs. 33%, P = 0.007	50.5% (on ECG)

Values are % or mean ± standard deviation.

CV: CoreValve, ECG: electrocardiogram, ES: Edwards SAPIEN, HR: hazard ratio, LVEF: left ventricular ejection fraction, NA: not available, PPM: permanent pacemaker, SAVR: surgical aortic valve replacement, TAVR: transcatheter aortic valve replacement.

the LBBB group in the Testa's study might explain the lack of differences. In the PARTNER substudy, such lack of effect might be attributed to a high rate of recovery of the AV conduction and low rate of pacing-dependency, as suggested by the finding that less than 50% of patients exhibited pacing on ECG performed during the follow-up period, despite most PPMs were implanted due to advanced AVB.[331]

11.5. FUTURE PERSPECTIVES

This thesis provided important insight into the real incidence and impact of rhythm and conduction disorders after TAVR. However, several questions remain. Firstly, if clinical or electrocardiographic factors accurately predict the progression of NOP-LBBB to AVB is stillunknown. The identification of such predictors is of utmost importance and might prevent the implantation of unnecessary PPMs reducing risks and costs. Secondly, the predictors and mechanisms leading to an increased risk of sudden cardiac death in patients with LBBB needs to be elucidated. The knowledge of these mechanisms will answer the question of whether a PPM implantation might prevent the occurrence of sudden cardiac death in such patients, or if a defibrillator is required. In addition, rates of pacing dependency after AVB post TAVR and the optimal delay to PPM implantation after TAVR procedure remain unknown. Although small studies have suggested that conservative strategies in patients with AVB post TAVR are safe, such data have not been confirmed yet. Finally, the clinical benefit of resynchronization therapies in patients with conduction abnormalities needs to be determined.

The ongoing MARE study (NCT02153307) will provide important information regarding the rate and potential predictors of AVB in patients with LBBB after TAVR, as well as the potential risk for sudden cardiac death in such patients. This is a multicenter, interventional study which will include 80 patients undergoing TAVR. The main objective of this study is to determine the incidence and predictors of high degree or complete AVB (paroxysmal or persistent) in patients with NOP-LBBB following TAVR. Patients with NOP-LBBB after TAVR and no PPM implantation who consent to participate will undergo the implantation of the cardiac monitor REVEAL Linq (Medtronic, Minneapolis, Minnesota) and then followed for a 3-year period. Stored data by the monitor will be transmitted daily through the CareLink® Network System to the CareLink website and patients will be followed in

outpatient clinic visits at 1, 12, 24 and 36 months after TAVI. A summary of the study protocol and study design is shown in the ANEXE I.

11.6. CONCLUSIONS

One third of rhythm and conduction disorders post-TAVR are already present before TAVR but remain undiagnosed unless an ECG monitoring is performed. Such undiagnosed arrhythmias may have a negative impact and being associated with an increased rate of post TAVR cerebrovascular events. New-onset LBBB occurs in up to 30% of the patients with no prior conduction disturbances post TAVR and it is transient in more than one half of them. Longer baseline QRS duration and a more ventricular positioning of the prosthesis independent predictors of the development of post TAVR LBBB. When persistent, new-onset LBBB is associated with a higher risk of complete AVB and PPM implantation, a lack of improvement in LV ejection fraction and a poorer functional status. No increased rate of overall or cardiac mortality at 1-year follow-up is observed in patients with this conduction disorder. Nonetheless, NOP-LBBB, in particular in those patients with a QRS duration >160 ms, may increase the risk of sudden cardiac death. The need for PPM implantation remains a frequent complication of TAVR. Although, it is associated with a poor evolution of LV ejection fraction, no increased late overall or cardiovascular death or rehospitalization due to heart failure are observed in patients requiring PPM implantation after TAVR. Finally, the use of the balloon expandable valve system, in particular the SAPIEN XT device, a more aortic implantation of the transcatheter valve and limiting the indications of PPM to those strictly recommended, with more prolonged periods of ECG monitoring before PPM implants, may reduce the rate of PPM.

Several questions remain such as the predictors of the progression of LBBB to AVB and sudden cardiac death, the optimal strategies to avoid the deleterious effect of conduction disorders on LV ejection fraction, late pacing requirements and the optimal timing for PPM implantation after TAVR. The ongoing MARE study will provide insight information into these TAVR complications.

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ANNEXE I.

Ambulatory Electrocardiographic <u>M</u>onitoring for the Detection of High-Degree <u>A</u>trio-Ventricular Block in Patients with New-onset Pe<u>R</u>sistent L<u>E</u>ft Bundle Branch Block after Transcatheter Aortic Valve Implantation. The "MARE" Study

Principal Investigator: Josep Rodés-Cabau

PROTOCOL SYNOPSIS

TITLE	Ambulatory electrocardiographic monitoring for the detection of high-degree atrio-ventricular block in patients with new-onset persistent left bundle branch block after transcatheter aortic valve implantation. The "MARE" study
SITES	15-20 centers in Canada and Europe
STUDY OBJECTIVES	To determine the incidence and predictors of high degree or complete atrioventricular block (AVB) (paroxysmal or persistent) in patients with new-onset persistent left bundle branch block (NOP-LBBB) following transcatheter aortic valve implantation (TAVI) and to evaluate the *Reveal LINQ® Insertable Cardiac Monitor (ICM)* (Medtronic, Inc., Minneapolis, Minnesota, USA) for the detection of significant arrhythmias in patients with NOP-LBBB following TAVI.
STUDY DESIGN	Consecutive patients with NOP-LBBB at hospital discharge, at least 3 days after the procedure, will receive a *Reveal LINQ®ICM*
PRIMARY OUTCOMES	- Rate and time onset of high degree or complete AVB within the first 1 year following TAVI procedure - Incidence of arrhythmic events identified by the *Reveal ICM* leading to a change in treatment or major adverse event.
STUDY POPULATION	Patients with NOP-LBBB after TAVI that persists at hospital discharge
MAIN INCLUSION CRITERIA	Patients undergoing TAVI with either balloon or self-expandable valves, who develop new-onset LBBB persistent at hospital discharge, at least 3 days after the procedure
MAIN EXCLUSION CRITERIA	- Failure to provide informed consent - Baseline pacemaker or pacemaker implanted during the hospitalization period following the TAVI procedure - Pre-existing complete LBBB
NUMBER OF PATIENTS	80 patients
ASSESSMENT SCHEDULE	Patients with NOP-LBBB after TAVI will receive a *Reveal ICM* and will be followed in outpatient clinic visits at 1, 12, 24 and 36 months after TAVI. Transmissions of stored data will be scheduled daily through the CareLink® Network System to the CareLink website. Phone contacts will be also carried out every 3 months (excluding months 12, 24 and 36 after device implantation, when a clinical visit will be carried out) up to 3 years follow-up.

PRINCIPAL INVESTIGATOR   Josep Rodés-Cabau
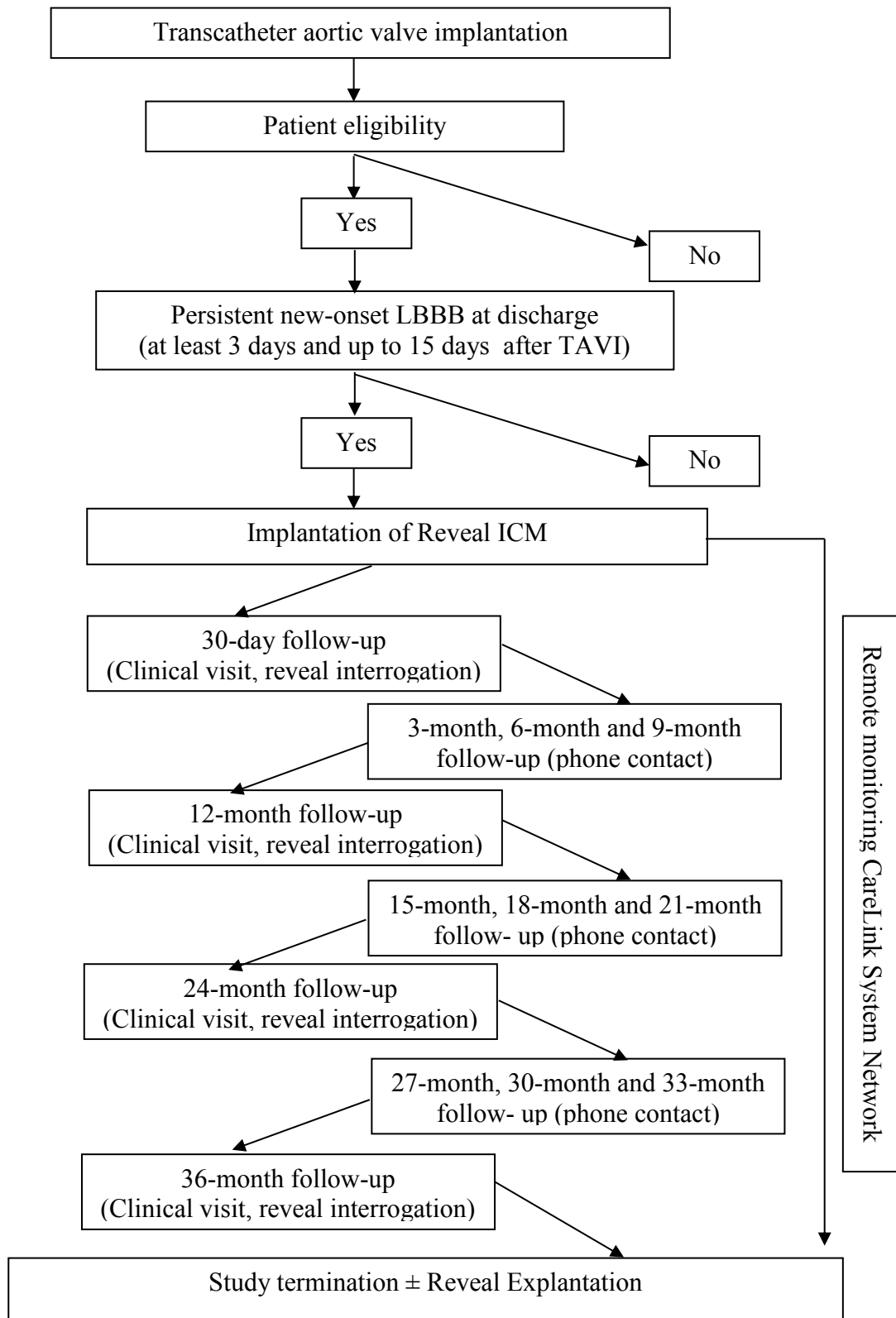Quebec Heart and Lung Institute

CO-PRINCIPAL INVESTIGATOR   François Philippon
Quebec Heart and Lung Institute

STUDY COORDINATOR   Emilie Pelletier Beaumont
Quebec Heart and Lung Institute
Phone: 418-656-8711 ext: 3929
Fax: 418-656-4911

Study design

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┌─────────────────────────────────────────────────────┐
│        Transcatheter aortic valve implantation       │
└─────────────────────────────────────────────────────┘
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                          ▼
        ┌─────────────────────────────────┐
        │        Patient eligibility       │
        └─────────────────────────────────┘
                 │              ╲
                 ▼               ╲──────────►  ┌──────────┐
           ┌──────────┐                        │    No    │
           │   Yes    │                        └──────────┘
           └──────────┘
                 │
                 ▼
   ┌──────────────────────────────────────────────────┐
   │     Persistent new-onset LBBB at discharge        │
   │ (at least 3 days and up to 15 days  after TAVI)   │
   └──────────────────────────────────────────────────┘
                 │              ╲
                 ▼               ╲──────────►  ┌──────────┐
           ┌──────────┐                        │    No    │
           │   Yes    │                        └──────────┘
           └──────────┘
                 │
                 ▼
   ┌──────────────────────────────────────────────────┐
   │            Implantation of Reveal ICM             │
   └──────────────────────────────────────────────────┘
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30-day follow-up
(Clinical visit, reveal interrogation)

3-month, 6-month and 9-month
follow-up (phone contact)

12-month follow-up
(Clinical visit, reveal interrogation)

15-month, 18-month and 21-month
follow- up (phone contact)

24-month follow-up
(Clinical visit, reveal interrogation)

27-month, 30-month and 33-month
follow- up (phone contact)

36-month follow-up
(Clinical visit, reveal interrogation)

Remote monitoring CareLink System Network

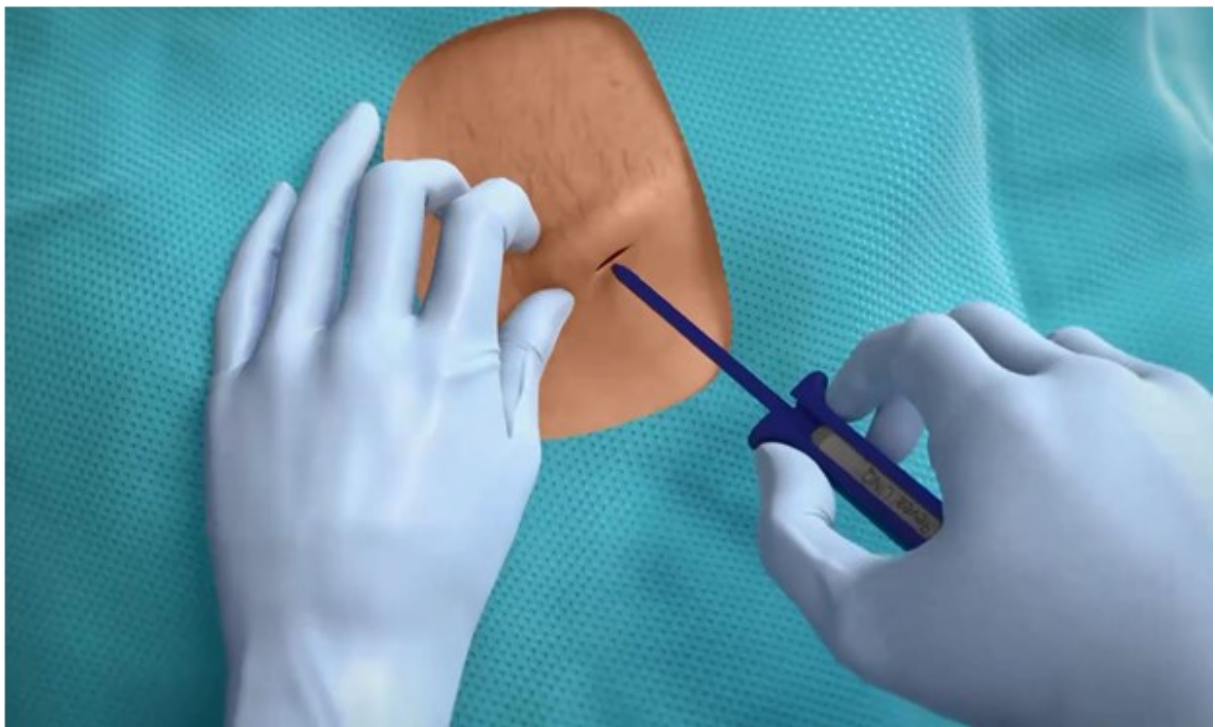Study termination ± Reveal Explantation

FIGURE 1. Image showing the reveal Linq device and a sequence of the implantation procedure