Late arrhythmic disorders after transcatheter aortic valve implantation

Thèse

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RÉSUMÉ

L'avènement du remplacement de la valve aortique par cathéter (TAVI) a entraîné un changement de pratique dans le traitement de la sténose aortique. Le TAVI est devenu le traitement de choix pour les patients à risque chirurgical moyen à élevé et son expansion vers le traitement des patients à faible risque est déjà à l'étude.

Au cours des dernières années, les améliorations successives apportées aux systèmes de valvules cardiaques par cathéter ont permis de réduire progressivement le nombre de complications péri-procédurales et de décès. Cependant, certains problèmes restent à résoudre. Les troubles de la conduction tels que le bloc de branche gauche nouvellement apparu ou le bloc auriculo-ventriculaire de haut degré nécessitant une implantation permanente de stimulateur cardiaque n'ont pas diminué avec le temps et restent la complication la plus fréquente de la procédure. Alors que les études précédentes se sont concentrées sur l'apparition des troubles de la conduction dans la période péri-procédurale, il existe peu de données sur les épisodes tardifs (après la sortie de l'hôpital). D'autre part, la prévalence et l'impact clinique des tachyarythmies chez les patients après un TAVI ont été moins étudiés, en particulier après la sortie de l'hôpital.

Différents inconvénients restent non résolus dans ce contexte (par exemple, l'évolution à long terme de l'ECG chez des patients sans troubles de la conduction, la prise en charge des patients avec nouveau bloc de branche gauche, les prédicteurs de la régression des anomalies à l'ECG chez des patients avec bloc de branche gauche). En outre, la surveillance électrocardiographique continue est apparue comme un outil utile pour diagnostiquer les troubles arythmiques (brady- et tachyarythmies) après le départ de l'hôpital, mais les données disponibles dans le cadre du TAVI sont rares. Leur sécurité et leur utilité clinique restent donc à élucider.

Les principaux objectifs de ce projet de recherche doctoral sont les suivants: (i) évaluer l'incidence et l'impact clinique des troubles arythmiques tardifs (après le départ de l'hôpital) chez les patients avec TAVI, et (ii) démontrer la sécurité et l'utilité de la surveillance continue non invasive de l'ECG après une procédure TAVI.

ABSTRACT

The advent of transcatheter aortic valve implantation (TAVI) has meant a paradigm shift in the treatment of aortic stenosis. TAVI has become the preferred treatment for patients at intermediate to high surgical risk and its expansion towards the treatment of low-risk patients is under study.

During the last years, the successive improvements in transcatheter heart valve systems have led to a progressive reduction of periprocedural complications and death. However, some issues remain to be resolved. Conduction disturbances (CDs) such as new-onset left bundle branch block (LBBB) or high-degree atrioventricular block requiring permanent pacemaker (PPM) implantation have not decreased over time and remains the most frequent complication of the procedure. Whereas previous studies focused on the occurrence of CDs in the periprocedural period, scarce data exist on late (after discharge) episodes. On the other hand, the prevalence and clinical impact of new-onset tachyarrhythmias in patients following TAVI have been less studied, especially after the hospital discharge.

Different drawbacks remain unsolved in this context (e.g. long-term ECG evolution in patients without ECG-CDs, management of new-onset LBBB, predictors of ECG regression in new-onset LBBB patients). Furthermore, continuous electrocardiographic monitoring has emerged as a useful tool to unravel arrhythmic disorders (either brady and tachyarrhythmias) in the early phase post-discharge, but data in the TAVI setting is scarce. Thus, their safety and clinical usefulness remain to be elucidated.

The main objectives of this PhD research project are: (i) to assess the incidence and clinical impact of late arrhythmic disorders (post discharge) in TAVI recipients (ii) to demonstrate the safety and usefulness of non-invasive continuous ECG monitoring post-TAVI.

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1-AVB: First-degree atrioventricular block.
ACC/AHA: American College of Cardiology/American Heart Association.
ACC/AHA/HRS = American College of Cardiology/American Heart Association/Heart Rhythm Society.
AECG monitoring: Ambulatory ECG monitoring.
AF: Atrial fibrillation.
AFL = atrial flutter.
AS: Aortic stenosis.
AVA: Aortic valve area.
AVB: Atrioventricular block.
AVR: Aortic valve replacement.
BAV: Balloon Aortic Valvuloplasty.
BBB: Bundle branch block.
CAD: Coronary artery disease.
CI: Confidence Interval.
CDs: Conduction disturbances.
CT: Computed tomography.
CRT: Cardiac resynchronization therapy.
CVEs: Cerebrovascular events.
FDA: Food and drug administration.
ECG: Electrocardiogram.
ECG-CDs: ECG conduction disturbances.
ESC: European Society of Cardiology.
HAVB/CHB: High degree or complete atrioventricular heart block.
HF: Heart failure.
ICD = implantable cardioverter-defibrillator.
NIVCD: nonspecific intraventricular conduction disturbance.
IQR: Interquartile range.
LCVEs = Late cerebrovascular events.
LBBB: Left bundle branch block.
LV: left ventricle.
LVEF: Left ventricular ejection fraction.
MCT: Mobile cardiovascular telemetry.
mRS: modified Rankin Score.
NOAF = New-onset atrial fibrillation.
NOP: new-onset persistent left bundle branch block.
PPM: Permanent pacemaker.
PPI: Permanent pacemaker implantation.
PVL: Paravalvular leak.
RBBB: Right bundle branch block.
SAVR: Surgical aortic valve replacement.

STS: Society of Thoracic Surgeons.
STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality.
SVD: Structural valve degeneration.
TAVI: Transcatheter aortic valve implantation.
THV: Transcatheter heart valve.
TAVR: Transcatheter aortic valve replacement.
TA: Transapical.
TAo: Transaortic.
TC: Transcarotid.
TCv: Transcaval.
TIA: Transient ischemic attack.
TS: Trans-subclavian.
TF: Transfemoral.
TVT: Transcatheter valve therapy.
VARC: Valve Academic Research Consortium.
VT: Ventricular tachycardia.

ACKNOWLEDGMENTS

"Tot està per fer i tot és possible"
Miquel Martí i Pol, catalan poet (1929-2003)

The expressions of gratitude in a project of the magnitude of a thesis are enormous. First, this work would not have been possible without the guidance and mentorship of the director of this PhD project, Dr. Josep Rodés-Cabau. He gave me the wonderful opportunity to work in his research team in Quebec, a time in my life that I will never forget and that I remember with great affection. Dr. Rodés-Cabau's teachings in the field of research are priceless, and his rigour and tenacity in his work are values that will undoubtedly mark my professional career. I hope to continue working with him in the future.

On the other hand, this work would not be the same without the help of Dr. François Philippon, co-director of the project and a key player in the presented research work. Thank you for your advice. I would also like to thank Dr. Isabelle Nault, whose work was also fundamental to the success of the project.

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The fellowship in Quebec was a time of intense work. Beyond this, I was able to meet fantastic colleagues and friends, people who made that the experience transcend the professional aspect. I would like to share this work with all my fellowship friends: Lluís Asmarats, Leonardo Guimarães, Alfredo Ferreira, Jerôme Wintzer, Lucía Junquera, David del Val, Laurent Faroux, and Alberto Alperi.

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FOREWORD

The research works embedded in this PhD thesis were carried out in the research group of Structural Heart Disease Interventions at the Quebec Heart and Lung Institute (IUCPQ, Laval University, Québec City, Québec), led by Dr Josep Rodés-Cabau.

Throughout the research project, the student received a research grant from the Fundación Alfonso Martin Escudero (Madrid, Spain), effective between July 2018 and June 2020; and Dr Rodés-Cabau held the Research Chair "Fondation Famille Jacques Larivière" for the Development of Structural Heart Disease Interventions.

This thesis is composed by 5 research articles, which have been published in high-impact peer-review cardiovascular journals.

The first article included in this thesis is entitled "**Long-term electrocardiographic changes and clinical outcomes of transcatheter aortic valve implantation recipients without new post-procedural conduction disturbances**", which was the first work focusing on this subset of patients. This work was published in the **American Journal of Cardiology** and evaluated the clinical evolution and permanent pacemaker implantation rates at long-term follow-up in TAVI patients without new post-procedural significant ECG changes. The student was the first author of this article and participated, under the supervision of Josep Rodés-Cabau, in the conception and design of the article, data collection, analyses and interpretation, 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 "**Late electrocardiographic changes in patients with new-onset left bundle branch block following transcatheter aortic valve implantation.**". The student is the first co-author (equally contribution) of this project and participated in the conception, design, data collection, drafting, and Dr Josep Rodés-Cabau is the senior author. The article explores the predictors of left bundle branch block (LBBB) regression at follow-up in patients with new-onset LBBB, the most frequent de

novo TAVI-related complication. This work was published in the **American Journal of Cardiology.**

The third article, which is entitled "**Arrhythmic burden in patients with new-onset persistent left bundle branch block after transcatheter aortic valve implantation: Two-year results of the MARE study"** was published in the **EP Europace** journal**.** The student is the first author of the study, and participated in the analysis of the study, interpretation of the data, statistical analysis, and drafting of the manuscript, under the supervision of Dr Josep Rodés-Cabau. All other authors approved and revised the manuscript. This article reported the arrhythmic burden at 2 years of follow-up using continuous ECG monitoring in patients with new-onset LBBB after TAVI.

The fourth article, which is entitled "**Late cerebrovascular events following transcatheter aortic valve implantation",** was published in the **JACC: Cardiovascular Interventions** journal. This article was the first that reported late stroke in TAVI patients, and the student, which is the first author, participated in data collection, statistical analysis, interpretation of the data, and drafting of the manuscript, under the supervision of Dr. Josep Rodés-Cabau. All other authors approved and revised the manuscript.

The fifth and last article, which is entitled **"Ambulatory electrocardiographic monitoring following minimalist transcatheter aortic valve implantation",** is the largest experience using ambulatory ECG monitoring immediately after discharge in consecutive TAVI patients. The work is published in **JACC: Cardiovascular Interventions**. The student, first author of the article, was responsible for the design of the study, collection and interpretation of the data, performing the statistical analysis, and drafting and revision of the manuscript. All steps were supervised by the senior author, Dr. Josep Rodés-Cabau. All other authors approved the manuscript and revised it for relevant intellectual content.

INTRODUCTION

1.1 THE HEART. VALVULAR HEART DISEASE AND AORTIC STENOSIS

The heart is a four-chambered fibromuscular organ that is the keystone of the human cardiovascular apparatus, acting as a pump that ejects blood through the vessels of the circulatory system (~ 5 liters/minute). It is roughly the size of a fist, and it is situated between the two lungs and slightly to the left, behind the breastbone, resting on the diaphragm (1). The lower tip of the heart (called the apex) lies to the left of the sternum, between the union of the fourth and fifth ribs near their articulation with the costal cartilages (2). The great veins like the vena cava, the aorta, and the pulmonary arteries are attached to the upper part of the heart (called the base). The heart is cone-shaped, with the base positioned upwards and tapering down to the apex (**Figure 1**) (2,3).

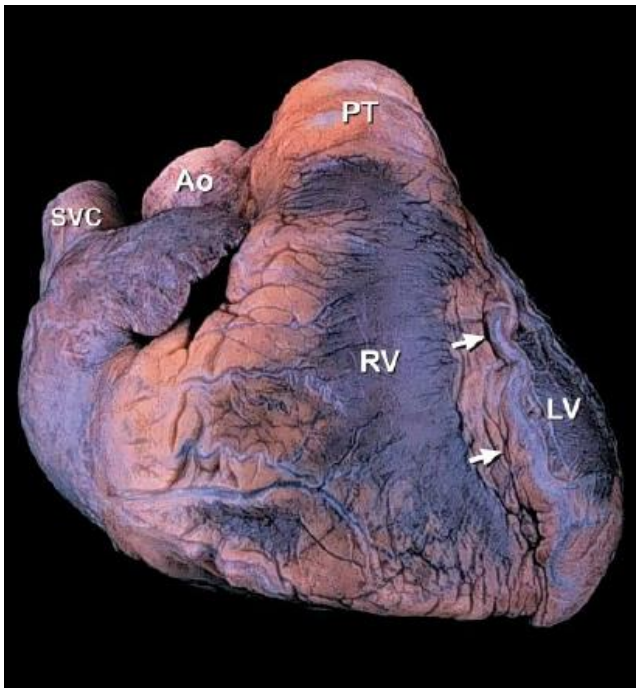

Figure 1. Anterior view of the heart in its usual anatomic position with its apex directed from right to left. Arrows point to the anterior interventricular sulcus, which delimitates the left and right ventricle. Ao: ascending aorta. LV: left ventricle; P: Pulmonary trunk; R: Right ventricle; SVC: Superior vena cava. From Hurst's The Heart, 13th edition *(3)*.

The heart is surrounded by a thin fibrous sac called the pericardium, which has a small amount of liquid that lubricates its surface and allows it to move freely during systole (contraction) and diastole (relaxation). The heart is composed of four chambers,

called the atria (right and left), the receiving chambers, and the lower right and left ventricles, the discharging chambers. (**Figure 2**) (3) .

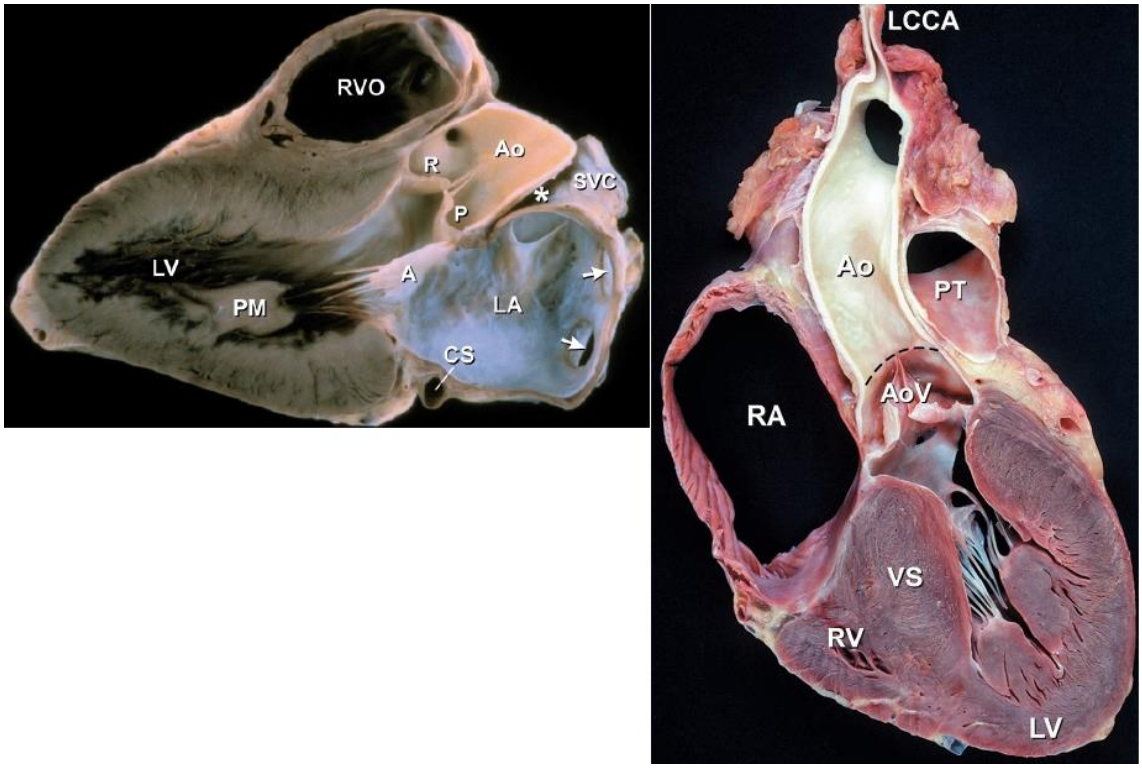

Figure 2.
A. Left ventricular long-axis view. *Transverse sinus. The arrows point to the right upper and lower pulmonary veins. A, anterior mitral leaflet; Ao, ascending aorta; CS, coronary sinus; LA, left atrium; LV, left ventricle; P, posterior aortic cusp; PM, posteromedial mitral papillary muscle; R, right aortic cusp; RVO, right ventricular outflow; SVC, superior vena cava.
B. Frontal plane view. The dashed line indicates the aortic sinotubular junction.
A: anterior mitral leaflet; Ao: ascending aorta; AoV: aortic valve; CS: coronary sinus; LA: left atrium; LCCA: left common carotid artery; LV: left ventricle; P: posterior aortic cusp; PM: posteromedial mitral papillary muscle; PT: pulmonary trunk; R: right aortic cusp; RVO: right ventricular outflow; SVC, superior vena cava; VS, ventricular septum. From Hurst's The Heart, 13th edition *(3)* .

The right and left atrium open into the ventricles through the tricuspid and mitral atrioventricular valves, respectively. The right and left ventricle eject blood through the pulmonary and aortic valves, respectively. They are separated from each other by the interventricular septum, visible on the surface of the heart as the anterior and posterior longitudinal sulcus (**Figure 1**). The four cardiac valves are anchored to their annuli, or valve rings. These fibrous rings, at the base of the heart, join to form the fibrous skeleton of the heart. The aortic valve is located centrally, and it forms the cornerstone of this cardiac skeleton, and its fibrous extensions are adjacent with each of the other three valves. The cardiac skeleton also contains the membranous septum and the aortic

intervalvular, right, and left fibrous trigones. The fibrous trigones form the anatomic substrate for direct mitral-aortic continuity. The right fibrous trigone, called the central fibrous body, attaches together the aortic, mitral, and tricuspid valves, and forms the largest and strongest component of the cardiac skeleton. On the other hand, it is through the right fibrous trigone that the cardiac electrical system (more specifically, the bundle of His) passes. The fibrous cardiac skeleton serves to electrically isolate the atria from the ventricles.

The heart's wall is composed of three layers: epicardium, myocardium, and endocardium (2). The deepest layer of the heart is the endocardium, and it covers the heart chambers and valves. The middle layer is called the myocardium and is constituted of a layer of involuntary striated muscle tissue surrounded by a skeleton of collagen. Furthermore, there are two types of cardiac cells. First, the muscular cells, which compound most cardiac cells and have the ability to contract. Second, the pacemaker cells, which are 1% of cells and form the conduction system of the heart. The pacemaker cells initiate the electrical impulses known as action potentials and set the pace for blood pumping, controlling the heart rate.

The heart receives blood flow from the systemic circulation (the venous system), which is low in oxygen and enters the right atrium and passes to the right ventricle. Afterwards, it is pumped into the pulmonary circulation, where it receives oxygen and gives off carbon dioxide. The oxygenated blood then returns to the left atrium, passes through the left ventricle, and is pumped out through the aorta to the systemic circulation, where the oxygen is used and metabolized to carbon dioxide (4). The cardiac cycle is the sequence of events in which the heart contracts (systole) and relaxes (diastole) with every heartbeat (4). At the beginning of the cardiac cycle, the ventricles are filled by blood that passes passively through the open mitral and tricuspid valves. Afterwards, the atria contract, forcing more blood into the ventricles. Next, the ventricles contract and the pressure within the ventricles rises, exceeding the pressure within the aorta and pulmonary artery, forcing the aortic and pulmonary valves to open. At that point the blood is ejected from the heart, causing the pressure in the ventricles to fall. When the pressure within the ventricles falls below the pressure within the aorta and

pulmonary arteries, the aortic and pulmonary valves close. Then, the ventricles start to relax, the mitral and tricuspid valves open, and the cycle starts again (4) .

Heart valves consist of thin, mobile, and flexible leaflets which ensure unidirectional circulation of blood. Driven by mechanical forces exerted by blood and surrounding structures, the heart valves are composed of endothelial and valvular interstitial cells and extracellular matrix. The valves between the atria and ventricles are called the atrioventricular valves. The valve located between the right atrium and the right ventricle is called the tricuspid valve, which has three cusps. The mitral valve lies between the left atrium and left ventricle. It has two cusps (anterior and posterior), which are attached via chordae tendinae to two papillary muscles projecting from the ventricular wall. As the heart chambers contract, the papillary muscles also do so. Finally, two semilunar valves are located at the exit of each ventricle. First, the pulmonary valve, which has three cusps and opens through the pulmonary artery. The semilunar aortic valve is at the base of the aorta, and it usually has three cusps that close with the pressure of the blood flowing back from the aorta (**Figure 3**) (2,3). However, a congenitally bicuspid (two leaflets) aortic valve is common, present in 0.5-0.8% of the general population (5) .

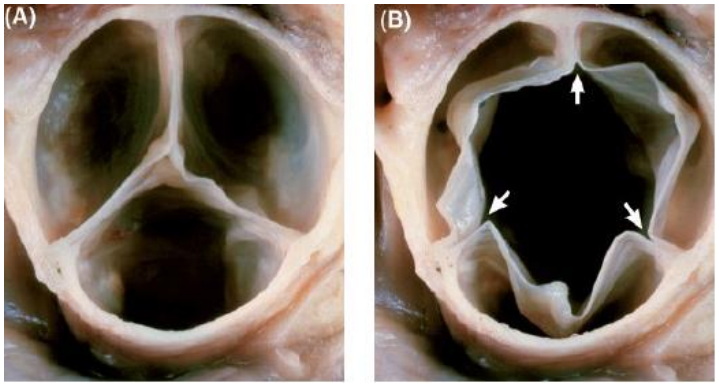

Figure 3. The aortic valve viewed from above in simulated closed (**A**) and open (**B**) positions. The normal aortic valve has 3 leaflets. The arrows show the three commissures. From Hurst's The Heart, 13th edition (3).

Cardiovascular diseases (CVD) are the most common cause of death globally as of 2008, accounting for 30% of deaths (6). More precisely, degenerative aortic stenosis (AS) is the most common primary valve disease leading to surgery or catheter intervention in Europe and North America (7,8), and its burden will increase further as the population ages.

1.2 HISTORICAL PERSPECTIVE OF AORTIC STENOSIS

The foundations for anatomy in the Western world started with Aristotle (384 BCE-322 BCE). Afterwards and during the early centuries of the Christian era, Galen was among the first to describe the valves of the heart. Among other demonstrations, he stated that arteries carry blood instead of air, challenging what was believed during his time and centuries before (9). However, the first accurate drawing of the aortic valve was by Leonardo da Vinci in 1512 (**Figure 4**).

Figure 4. The aortic valve, picture from Leonardo Da Vinci.

Later, the anatomist Andreas Vesalius (1514-1564) performed autopsies on humans. His key work was written in 1543, "De Humani Corporis Fabrica", and it is considered as the largest single contribution to medical science (10). AS was first described in 1663 in "Opera Medica Universa" by Lazare Riviere (1589-1655). AS was also described by Giovanni Battista Morgagni, the founder of pathological anatomy. Finally, investigations focusing on the causes of AS were performed in the first half of the 20th century (11).

1.3 PATHOGENESIS AND RISK FACTORS OF AORTIC STENOSIS

Degenerative AS is the most prevalent form of AS, and represents 84% of the AS patients. Other causes of AS include congenital AS (5%), rheumatic disease (11%), endocarditis (1%), and other causes (<1%), such as inflammatory or drug-induced AS (12). Degenerative aortic stenosis is usually caused by aortic valve leaflet thickening and calcification. Although the pathogenesis of AS has been classically considered an age-related process (13), recent studies have shown that it is also an active and progressive syndrome. Two phases have been described regarding the evolution of AS. First, the initiation phase or early phase, which seems to be caused by endothelial damage due to mechanical factors and reduced shear stress (the early damage is located in regions with low shear stress in the aortic side of the valve). Second, a progression period leads to severe calcific AS. Several factors play a role in both the initiation and progression of AS, such as anatomic, genetic, and clinical factors that are mediated by cellular and molecular pathways (14,15).

The presence of a bicuspid aortic valve, genetic mutations, old age, male sex, hypertension, diabetes, metabolic syndrome, smoking, and hypercholesterolemia have been associated with AS (**Figure 5**) (15).

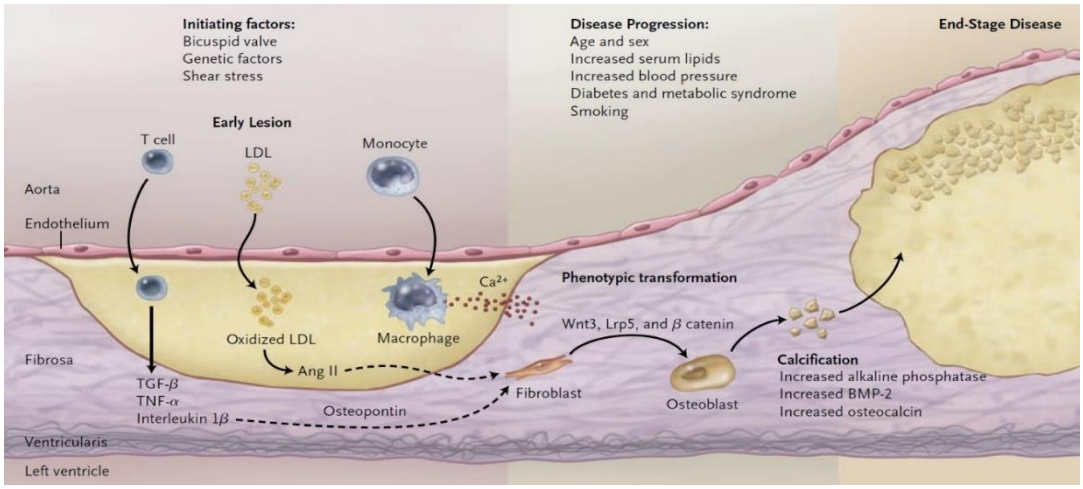

Figure 5. Changes in histologic features in the aortic valve leaflets. From Otto et al (14).

As previously stated, the initiation of the disease is caused by mechanical factors and changes in the aortic wall shear stress (16) , which causes endothelial damage at the level of the aortic valve leaflets. More specifically, the bicuspid valve (present in ~0.5-0.8% of the population) is the underlying anatomy in a significant proportion of patients. Then, subendothelial accumulation of lipid and lipoproteins triggers progressive endothelial injury and lipid oxidization, which leads to an inflammatory response characterized by infiltration of macrophages and T-lymphocytes. Afterwards, a fibrotic process with deposition of matrix collagen and a subsequent progressive calcification occurs.

In conclusion, the pathophysiology of AS is an active process comparable to atherosclerosis, including three major elements: lipid accumulation, inflammation, and calcification. A summary of the factors implied in the physiopathology of AS is shown in **Table 1** (17–29).

Table 1: Main factors involved in the physiopathology of degenerative aortic valve stenosis

Lipid accumulation	Focal areas of accumulation of low density lipoprotein (LDL) and lipoprotein(a) with evidence of lipoprotein oxidation (20,23).
Inflammation	Inflammation evidenced by macrophage and T lymphocyte infiltration, inflammatory mediators (interleukin-1-beta), transforming growth factor beta-1, and increased fluorodeoxyglucose uptake on positron emission tomography scanning (18–20,24,25).
Calcification	Upregulation of adhesion molecules and alterations in matrix metalloproteinase activity (28,29). Local production of proteins that promote tissue calcification (17,21,26,27).

1.4 EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS OF AORTIC STENOSIS

As previously mentioned, degenerative AS is the most common primary valve disease leading to surgery or catheter intervention in western countries (7,8). Epidemiological studies have shown that AS is present in 2-7% of the population > 65 years (**Table 2**) (8,30).

	Aortic Valve Abnormality			
	None	Sclerosis	Stenosis	Valve Replacement
All subjects	3,736 (72%)	1,329 (26%)	88 (2%)	23 (0.4%)
Women	2,249 (76%)	641 (22%)	43 (1.5%)	12 (0.4%)
Men	1,487 (67%)	688 (31%)	45 (2%)	11 (0.5%)
65–74 years old	2,684 (78%)	697 (20%)	43 (1.3%)	16 (0.5%)
Women	1,654 (82%)	344 (17%)	20 (1.0%)	9 (0.4%)
Men	1,030 (73%)	353 (25%)	23 (1.6%)	7 (0.5%)
75–84 years old	962 (62%)	542 (35%)	37 (2.4%)	7 (0.5%)
Women	546 (66%)	259 (31%)	22 (2.7%)	3 (0.4%)
Men	416 (58%)	283 (39%)	15 (2.1%)	4 (0.6%)
85+ years old	90 (48%)	90 (48%)	8 (4%)	0 (0%)
Women	49 (56%)	38 (43%)	1 (1%)	0
Men	41 (41%)	52 (52%)	7 (7%)	0

Data are expressed as number (%) of subjects.

Table 2. Prevalence of aortic valve abnormalities by echocardiography. From Stewart et al (7)

A meta-analysis conducted in occidental countries found a population prevalence of AS of 12.4%, and a prevalence of 3.4% of severe AS in those aged 75 years and older (31). In addition, a more recent study has shown relatively comparable rates of aortic valve disease, with a 4.3% rate of severe AS in an Icelandic cohort aged ≥70 years old (32). There is an exponential escalation in AS prevalence with age, with 0.2% in the 50–59-year group, 1.3% in the 60–69-year group, 3.9% in of the 70–79-year group, and 9.8% in those aged 80–89 years. In this line, the number of patients with an indication for aortic valve replacement is projected to more than double by 2050 in both the USA and Europe (31). On the other hand, the presence of a bicuspid aortic valve is the most common form of congenital heart disease and is found in 0.5–0.8% of the population (5). The presence

of a bicuspid aortic valve leads to a requirement for treatment related to severe AS at a younger age compared to tricuspid valves (mean age at surgery around 50 years).

Finally, epidemiologic studies showed similar rates of AS in women compared to men. However, women tend to present later in the disease history, with older age, more higher rates of frailty, renal insufficiency, symptomatic heart failure, and more frequent concomitant significant mitral regurgitation (33).

The progressive nature of degenerative AS will result in a gradual obstruction to the ventricular outflow of the left ventricle, which in turn will increase the left ventricular pressure. The latter will translate into a proportional increase in the left ventricle afterload and finally an impaired left ventricular function. Initially, the left ventricular afterload may be compensated by left ventricular hypertrophy, which might maintain the cardiac output (34). However, the occurrence of left ventricular hypertrophy is considered a maladaptive process, as it has been linked to the occurrence of ischemia, diastolic dysfunction, an increased risk of mortality, and the development of left ventricular systolic dysfunction (35–37).

Patients with AS are, in general, asymptomatic for a long period despite the obstruction and increased pressure load on the left ventricle. Mostly, symptoms in patients will rarely occur until stenosis is severe. When severe AS is present, even mild symptomatology should prompt for intervention, since survival will be reduced if left untreated, with average survival after the onset of symptoms of only two to three years, and a high risk of sudden cardiac death (**Figure 6**) (38). As depicted in **Figure 6**, the classic symptoms due to severe AS are heart failure, syncope, and angina. The most typical symptom of AS is dyspnea, usually associated with a decreased exercise tolerance. Besides, the presence of systolic left ventricular dysfunction is uncommon, and overt heart failure may entail an end-stage finding.

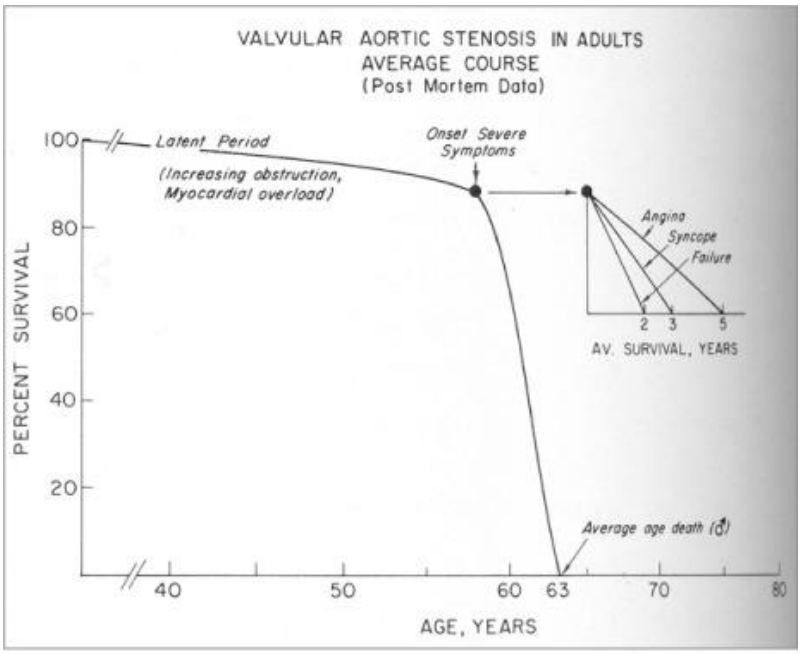

Figure 6. Survival in patients with aortic stenosis. From Ross et al (38)

Effort angina is also a typical symptom in patients with severe AS, and it may be present in half of the patients without significant coronary artery disease (CAD)(39,40). However, it should be highlighted that about 50% of the patients have underlying coronary artery disease, and the absence of angina does not reliably exclude the presence of severe CAD (39). The presence of angina in this context has been attributed to left ventricular hypertrophy, which can cause myocardial ischemia in relation to several mechanisms: increased left ventricle oxygen demand, compression of intramyocardial coronary arteries, reduced diastolic coronary perfusion time during tachycardia and reduced coronary flow reserve (41).

Finally, exertional dizziness (presyncope) or even syncope may reflect an abrupt reduction in cerebral perfusion, which may be caused by different mechanisms: exercise-induced vasodilation in patients with almost fixed cardiac output due to the aortic obstruction, abnormalities in the baroreceptor response, transient bradyarrhythmia, and supraventricular and ventricular arrhythmias.

1.5 DIAGNOSIS OF AORTIC STENOSIS

Overall, patients with AS may be referred to the cardiologist due to a heart murmur, the presence of symptoms, or because of incidental findings on non-invasive tests. Classically, severe AS may have a loud heart murmur, it may peak later in systole, and the aortic valve closure component of the second heart sound may be reduced or absent. Apart from a scrupulous physical examination, an electrocardiogram (ECG), blood analysis, and an X-ray, transthoracic echocardiography will be the key diagnostic tool. Echocardiography confirms the presence of aortic stenosis and assesses its severity, valve calcification, presence of bicuspid morphology, aortic dilatation and left ventricular function and thickness. It also can diagnose the presence of other associated valve diseases. Doppler echocardiography is the preferred technique for assessing the severity of aortic stenosis (42).

The recently published American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on valvular heart disease divided the patients with AS into 4 stages: patients at risk of AS (Stage A), patients with progressive hemodynamic obstruction (Stage B), patients with severe asymptomatic AS (Stage C), and those with symptomatic AS (Stage D) (43) (**Figure 7**).

The severity of AS is defined by transaortic maximum velocity (or mean pressure gradient) when the transaortic volume flow rate is normal. However, some patients can present with a low transaortic volume flow rate, related to left ventricular systolic dysfunction with a low left ventricular ejection fraction (LVEF) or because of a small, hypertrophied left ventricle with a low stroke volume. Severe AS with low flow is designated D2 (with a low LVEF) or D3 (with a normal LVEF) (43).

The diagnosis of AS using transthoracic echocardiography may be considered as a continuum, ranging from aortic sclerosis to very severe flow obstruction. In routine clinical practice, the peak transaortic jet velocity along with mean gradients and valve area are commonly used to grade the severity of AS. The current recommendations for AS gradation are depicted in **Table 3** (44,45).

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of AS	BAV (or other congenital valve anomaly) Aortic valve sclerosis	Aortic V_{max} <2 m/s with normal leaflet motion	None	None
B	Progressive AS	Mild to moderate leaflet calcification/fibrosis of a bicuspid or trileaflet valve with some reduction in systolic motion or Rheumatic valve changes with commissural fusion	Mild AS: aortic V_{max} 2.0–2.9 m/s or mean ΔP <20 mm Hg Moderate AS: aortic V_{max} 3.0–3.9 m/s or mean ΔP 20–39 mm Hg	Early LV diastolic dysfunction may be present Normal LVEF	None
C: Asymptomatic severe AS					
C1	Asymptomatic severe AS	Severe leaflet calcification/ fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA typically is ≤1.0 cm² (or AVAi 0.6 cm²/m²) but not required to define severe AS Very severe AS is an aortic V_{max} ≥5 m/s or mean P ≥60 mm Hg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None Exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV systolic dysfunction	Severe leaflet calcification/ fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA typically ≤1.0 cm² (or AVAi 0.6 cm²/m²) but not required to define severe AS	LVEF <50%	None
D: Symptomatic severe AS					
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification/ fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA typically ≤1.0 cm² (or AVAi ≤0.6 cm²/m²) but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present	Exertional dyspnea, decreased exercise tolerance, or HF Exertional angina Exertional syncope or presyncope
D2	Symptomatic severe low-flow, low-gradient AS with reduced LVEF	Severe leaflet calcification/ fibrosis with severely reduced leaflet motion	AVA ≤1.0 cm² with resting aortic V_{max} <4 m/s or mean ΔP <40 mm Hg Dobutamine stress echocardiography shows AVA <1.0 cm² with V_{max} ≥4 m/s at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF <50%	HF Angina Syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification/ fibrosis with severely reduced leaflet motion	AVA ≤1.0 cm² (indexed AVA ≤0.6 cm²/m²) with an aortic V_{max} <4 m/s or mean ΔP <40 mm Hg AND Stroke volume index <35 mL/m² Measured when patient is normotensive (systolic blood pressure <140 mm Hg)	Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling LVEF ≥50%	HF Angina Syncope or presyncope

Figure 7. Stages of aortic stenosis. From Otto et al (43)

Table 3. Grading aortic stenosis severity by transthoracic echocardiography

	Aortic sclerosis	Mild AS	Moderate AS	Severe AS
Peak 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 (cm2)	-	>1.5		<1.0
Indexed AVA (cm2/m2)	-	>0.85	0.60-0.85	<0.6
Velocity ratio	-	>0.50	0.25-0.50	<0.25

AS: Aortic stenosis; AVA: aortic valve area.

Of note, the presence of concomitant left ventricular dysfunction may lead to low-flow and therefore lower mean transaortic gradients, even in the presence of a severe AS. This is characterized as "low-flow low-gradient AS", which is defined by an aortic valve area (AVA) of < 1cm2, left ventricular dysfunction (LVEF <40%), and a mean gradient <40mmHg (46,47). In these cases, the use of low-dose dobutamine stress testing may be useful to differentiate true stenosis from a "pseudo-severe" AS, and also to determine the presence of left ventricular reserve. In patients with "true" AS, the increase in cardiac output with dobutamine will translate into an increase in transaortic gradients and AVA will remain unchanged. In pseudo-severe stenosis, an increase in the AVA (≥1.0 cm2) may be observed (48). Alternatively, an important proportion of patients with preserved LVEF and severe AS regarding AVA (<1cm2) can also present with a low-flow state (indexed stroke volume of 35 ml/ m2), together with low transvalvular gradients (<40 mmHg). This entity is known as "paradoxical low-flow low-gradient" AS and is associated with adverse outcomes (49,50). This state is typically found in hypertensive elderly patients with small left ventricular size and marked hypertrophy (51,52), and may be associated with conditions associated with low stroke volume (e.g. significant mitral valve disease, severe tricuspid regurgitation, large ventricular septal defect, and severe right ventricular dysfunction).

Beyond echocardiography, cardiac catheterization, cardiac magnetic resonance (53), and computed tomography (CT) may provide alternative information. In the case of CT, an aortic valve calcification score can accurately identify a severely stenotic valve, interestingly, independently of flow. In patients with AS, the cut-offs of 3000 Agatston Units in men and 1600 Agatston Units in women have been proposed as the most accurate to reveal the presence of severe AS (54). On the other hand, brain natriuretic peptides (BNP) and NT-proBNP are liberated when left ventricular afterload is increased, and this has been associated with symptoms in patients with normal left ventricular function and severe AS (55,56). Alternatively, natriuretic peptides may be used to elucidate the source of symptoms in patients with several potential causes of dyspnea and to identify those asymptomatic patients that may benefit from early intervention (54).

To summarize, the recently published European Society of Cardiology Guidelines divide the patients with AS into four broad Categories (54):

- High-gradient AS (mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, valve area ≤1 cm2 [or ≤0.6 cm2/m2]). In this subset of patients, severe AS can be assumed irrespective of LVEF and flow conditions.

- Low-flow, low-gradient aortic stenosis with reduced ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm2, LVEF <50%, Stroke volume index ≤35 mL/m2). As previously mentioned, low-dose dobutamine stress echocardiography is recommended (48).

- Low-flow, low-gradient aortic stenosis with preserved ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm2, LVEF >_50%, Stroke volume index ≤35 mL/m2). As previously cited, CT assessment of the degree of valve calcification provides important additional information in this context.

- Normal-flow, low-gradient aortic stenosis with preserved ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm2, LVEF>_50%, Stroke volume index >35 mL/m2). These patients usually have only moderate aortic stenosis.

1.6 MANAGEMENT OF AORTIC STENOSIS

The dreadful natural history of AS without intervention described by Ross and Braunwald (38) has been confirmed in subsequent studies, reporting survival of around 50% at 3-5 years of follow-up (57,58). In this context, no medical therapy has been demonstrated to be effective in terms of outcomes or to slow the progression of the degenerative, calcific AS. However, diuretic treatment may relieve the symptoms and signs of heart failure (pulmonary and systemic congestion). Furthermore, it has been proposed that the administration of statins may slow the progression of AS (59). However, randomized trials failed to prove any clinical benefit (60). On the other hand, the use of inhibitors of the renin-angiotensin system is safe in patients with AS that are carefully monitored and may have beneficial myocardial effects before the onset of symptoms and after intervention (61–64). Finally, those patients with clinical heart failure who are suitable for aortic valve intervention should be medically treated according to the recent European Society of cardiology (ESC) heart failure Guidelines (65).

In line with the latter, the dismal prognosis of symptomatic patients with AS warrants intervention as soon as the symptoms appear, as recommended by current guidelines (43,54). Aortic intervention includes percutaneous balloon aortic valvuloplasty (BAV), surgical aortic valve replacement (SAVR), and transcatheter aortic valve implantation (TAVI) or replacement (TAVR)*. **Figure 8** shows the aortic stenosis management algorithm proposed by the recent European guidelines on the management of valvular heart disease (54).

*Transcatheter aortic valve implantation (TAVI) will be used through the thesis to keep the same term along all the manuscript.

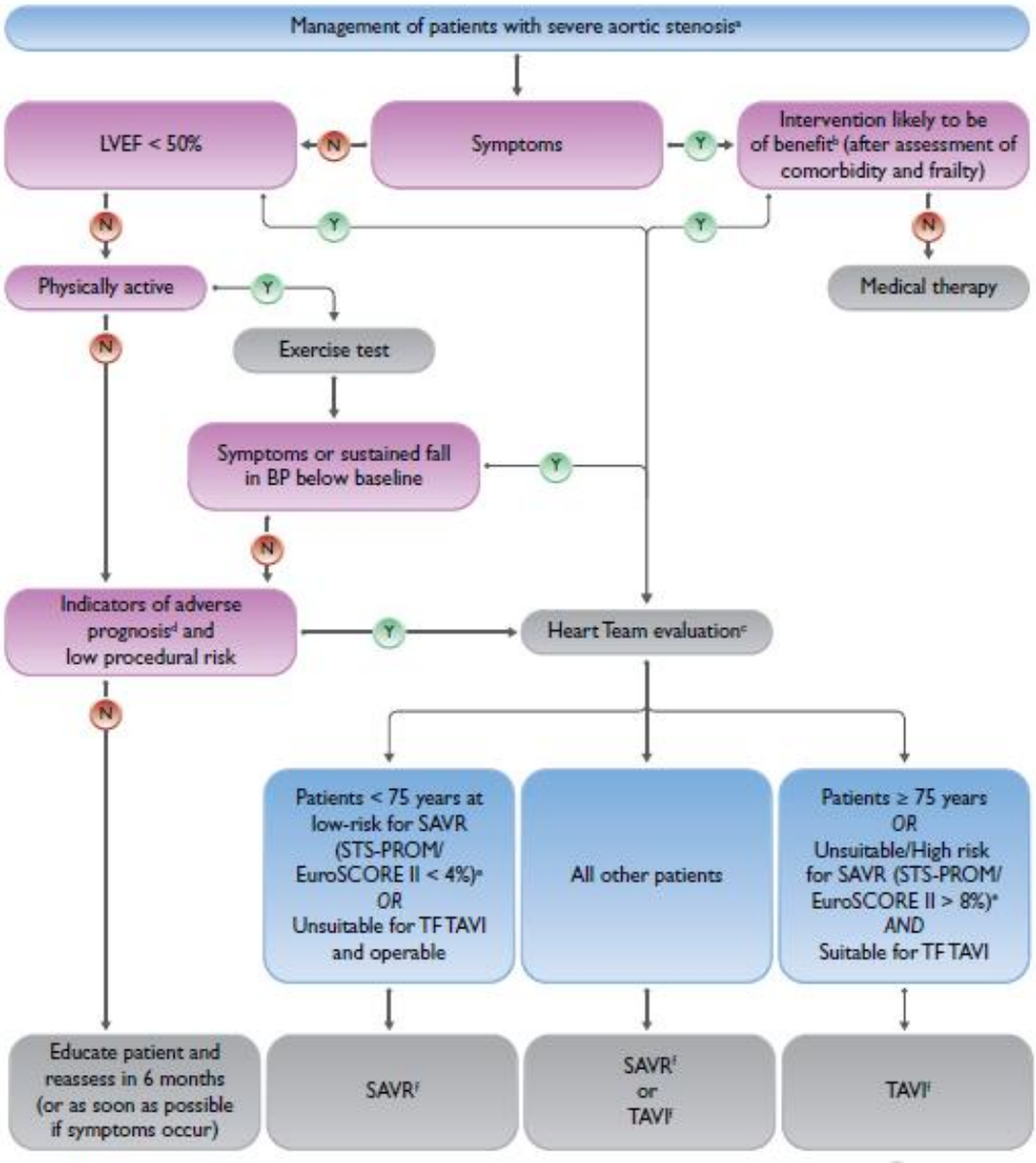

Figure 8. Management of aortic stenosis. From Vahanian et al (54)

1.6.1 Balloon aortic valvuloplasty (BAV)

BAV is a transcatheter technique that was first used by Cribier and colleagues in 1986 and it consists in the mechanical dilatation of the aortic valve using a balloon (66). The balloon inflation results in fractures of calcified nodules at the leaflet hinge points, leaflet microfractures, and separation of fused leaflets (67,68). This may lead to improved

leaflet mobility, a reduction in aortic valve gradients, and a modest improvement in the AVA. However, subsequent clinical studies demonstrated that its benefit was generally limited to a few months after the procedure, and restenosis of the valve occurred again after 6-12 months (69–72).

The limited efficacy of BAV in the long-term results in an absence of benefit regarding mortality at follow-up (72,73). However, there is still room for this therapy in specific subsets (74). First, BAV can be used as a palliative treatment in patients who cannot undergo SAVR or TAVI. Second, current European guidelines state that BAV may be considered as a bridge to TAVI or SAVR in patients with decompensated aortic stenosis (severe heart failure, cardiogenic shock) and in those with severe aortic stenosis who require urgent high-risk non-cardiac surgery (54)

1.6.2 Surgical aortic valve replacement

The first SAVR procedure was performed in the early 1960s and has transformed the treatment of aortic stenosis, improving the survival of patients with valvular heart disease (75). This treatment is nowadays the most frequently performed procedure in valve surgery (represents half of all operations for valvular heart disease), as approximately 90 000 SAVR procedures are performed in the United States and 280 000 worldwide each year (76,77). Isolated SAVR can be performed with a mini-sternotomy. The SAVR procedure may be performed using either mechanical or biological prostheses (78), and each type implies associated benefits and risks. Whereas mechanical valves require lifelong anticoagulation and therefore this increases the risk of hemorrhage and thromboembolism (**Figure 9**), biologic prosthetic valves are associated with a higher risk of reoperation due to structural valve deterioration (77,79).

Figure 9. Examples of mechanical aortic valve prostheses. From Pibarot et al (77)

Biological surgical valves include homografts, pulmonary autografts, and porcine (assembled aortic valve leaflets or complete aortic valves) or pericardial bovine bioprostheses. Biological prostheses are divided into stented or stentless valves (**Figure 10**). Stented valves are composed of valve leaflets reinforced with a stent frame, which is composed of polymeric material or alloys, and a circular or scallop-shaped external sewing ring located outside of the stent frame (80). Stentless valves were designed to optimize the effective orifice area and do not have a base ring or a frame to support the leaflets (81). More recently, sutureless valves have emerged as an option to reduce cardiopulmonary bypass times and facilitate minimally invasive approaches (82).

The choice of the proper prosthesis in each patient is determined by balancing the risks of anticoagulation and reoperation. However, recent reports of improved durability of biologic prostheses have led to a substantial increase in their use, and nowadays biological prostheses are the preferred SAVR option in most cases (76,83). Current ACC/AHA guidelines recommend mechanical prostheses in patients under 50 years of age, mechanical or bioprosthetic SAVR in patients between 50 and 65 years (the decision should be individualized in such cases), and bioprostheses in patients ≥65 years (43).

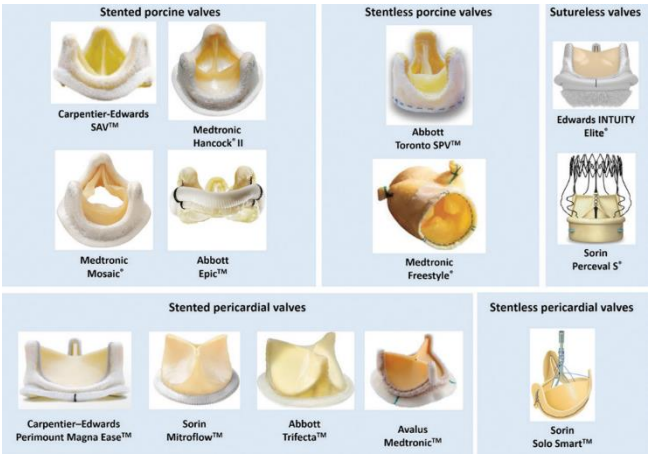

Figure 10. Examples of biological aortic valve prostheses. From Rodríguez-Gabella et al (79)

Overall, the isolated SAVR procedure mortality is around 1-3% (76). However, those patients with comorbidities or those > 80 years of age may have in-hospital mortality rates up to 5-10% (76,84). At 30-days, comorbidities such as left ventricular dysfunction, concomitant coronary artery disease, renal insufficiency, and chronic pulmonary disease have been associated with increased mortality (85), which remained stable around 4-5% according to a recent retrospective analysis (86) (**Figure 11**).

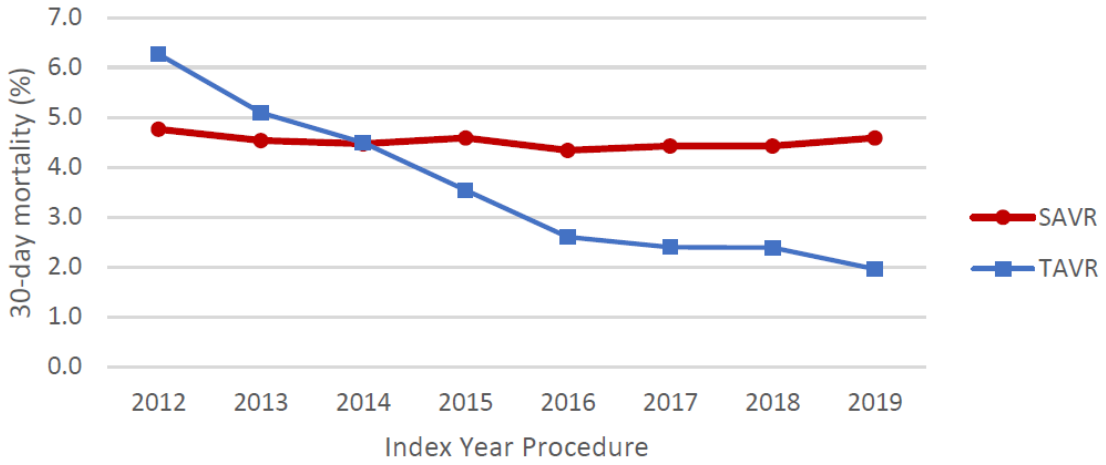

Figure 11. Temporal trends in unadjusted 30-day mortality for SAVR and TAVI (86).

The assessment of preoperative risk is of paramount importance. Nowadays, several risk scores are available, including the EuroSCORE and the Society of Thoracic Surgeons (STS) risk calculator (87,88). Of note, none of these scores include important variables such as frailty and cognitive status, which have demonstrated to significantly impact survival at follow-up (89).

Although the clinical benefit of the aortic valve replacement is well-established, more than half of the patients may not undergo SAVR due to high operative risk (58,90,91). More precisely, up to one-third of patients ≥75 years are deemed unsuitable for SAVR due to high procedural risk (90). The lack of alternative therapeutic options in patients with high surgical risk led to the development of a minimally invasive definitive intervention: the TAVI therapy.

1.7 TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)

1.7.1 Introduction

The initial TAVI concept was made by Andersen *et al* back in 1992, who developed a porcine aortic valve sutured to a metal stent, which could be inflated using a balloon to expand the valve in the native aortic annulus (analogous to a coronary stent) (92). Later on, the first human balloon-expandable TAVI was performed in Rouen in 2002 by Alain Cribier, in a 57-year-old patient with critical AS and cardiogenic shock (93). The valve was successfully delivered via a transseptal approach. The success of this procedure confirmed the feasibility of TAVI in humans, with a good hemodynamic profile and absence of the most feared periprocedural complications (no significant paravalvular aortic regurgitation, no coronary obstruction, and no associated atrioventricular block). Afterwards, the early Cribier-Edwards 23-mm valve was redesigned and the TAVI procedure began the transition to a mainstream clinical and commercial reality (94). Thereafter, Webb and colleagues reported the transfemoral retrograde trans-arterial implantation technique issuing a deflectable pusher sheath along with the first transapical implantations (95–97). Beyond the cited balloon-expandable system, Grube et al reported the first human implants of a self-expanding transfemoral transcatheter heart valve (THV) system in 2005 (98,99).

1.7.2 TAVI procedure: devices, approaches, and complications

The TAVI procedure is the deployment of a biological prosthesis at the level of the aortic valve, performed in a beating heart without the need for cardio-pulmonary bypass (**Figure 12**).

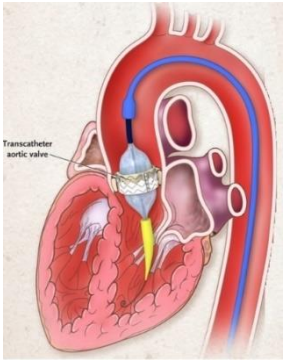

Figure 1.12. Schematic illustration of transfemoral aortic valve implantation.

The valve is advanced using a catheter or delivery system that is usually introduced through a large-bore sheath placed in the common femoral artery (transfemoral [TF] approach) (100). The procedure is usually performed in a cardiac catheterization laboratory room or hybrid (interventional/surgical) suite. In contemporary practice, the TAVI technique is commonly performed under conscious sedation (101). However, the technique is different depending on the type of device. Among others, two main THVs systems exist: balloon-expandable and self-expanding valves (100). **Table 4** summarizes the older and current generation of main THVs.

1.7.2.1. TAVI procedure: devices

The current United States Food and Drug Administration (FDA) approved balloon-expandable TAVI devices are the SAPIEN 3 and SAPIEN 3 Ultra, which are the new-generation Edwards Lifesciences valves (former Cribier-Edwards, SAPIEN, and SAPIEN XT valves). The SAPIEN 3 valve is composed of a trileaflet bovine pericardial valve mounted in a cobalt-chromium frame with an outer seal cuff to reduce paravalvular leak (PVL) (102). In this line, the recently released SAPIEN 3 Ultra incorporated an increased outer skirt to reduce residual PVL (**Figure 13**) (103).

Figure 13. Edwards Lifesciences balloon-expandable SAPIEN valves family (104).

The SAPIEN 3 Ultra valve has four different sizes: 20-mm, 23-mm, 26-mm, and 29-mm, which covers aortic annulus diameters from 16 to 28 mm. The size of the prosthesis should be selected according to the measurements of the native aortic annulus, which are measured by computed tomography images (105). The prosthesis is crimped into a balloon and, after placing a stiff guidewire in the left ventricle, is advanced through this wire and deployed by means of a balloon inflation. The balloon inflation is performed during rapid pacing (to minimize cardiac output and avoid valve embolization during the deployment) through a right ventricular temporary lead or through the left ventricular

wire (106). A dedicated, deflectable delivery system is used to advance and facilitate the valve alignment and position (**Figure 14**) (102).

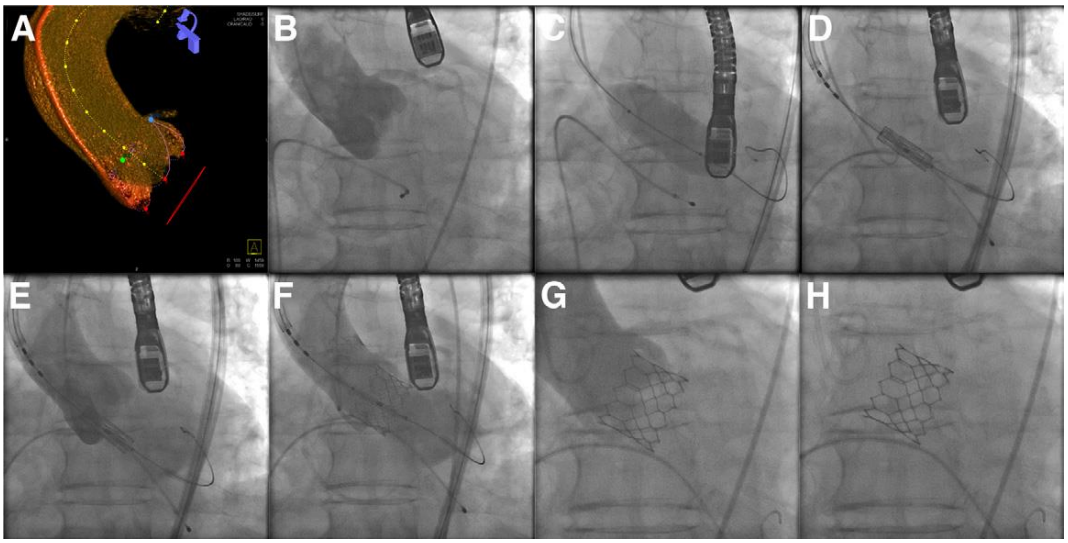

Figure 14. Implantation sequence. **A-B**. Optimal implant angle with the three Valsalva sinus alienated in the same plane. **C.** After crossing the valve, balloon aortic valvuloplasty was performed (not mandatory). **D-E**. Positioning of the SAPIEN valve and deployment under rapid ventricular pacing. **F-H**. Delivery system withdrawal and assessment of the final position. From Binder et al (102).

Several self-expanding THVs are nowadays in commercial use or under clinical investigation (**Figure 15** and **Table 4**). Currently, the more implanted self-expanding valve worldwide is the Evolut PRO + (Medtronic), the last generation of the CoreValve family (the former THV systems are the CoreValve, the Evolut R, and the Evolut PRO valves) (107).

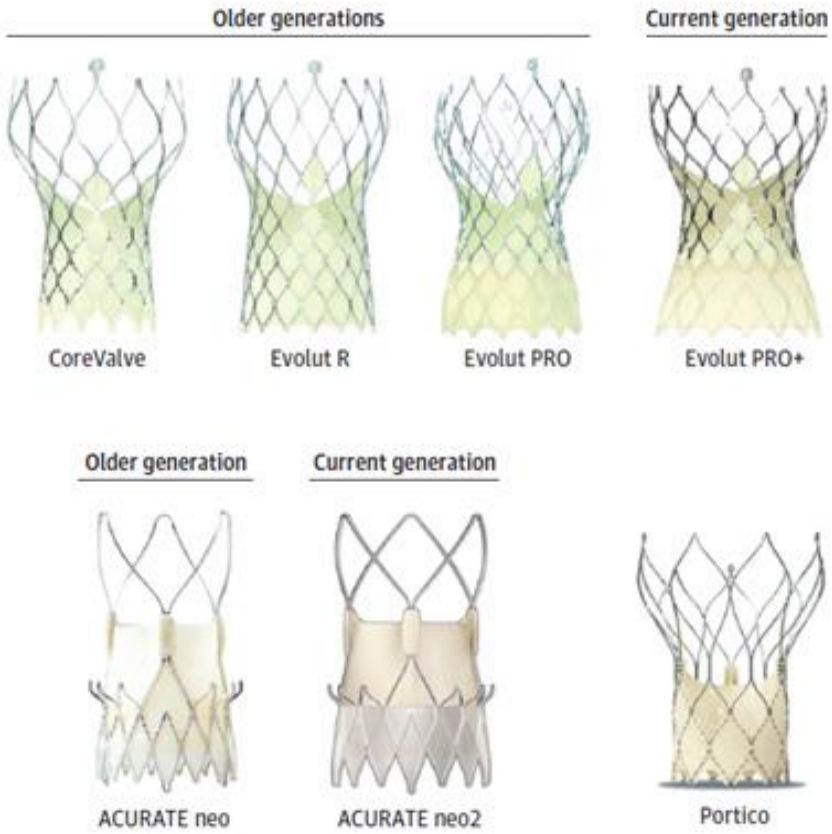

Figure 15. Older and current generations of self-expandable THV systems (104).

The Evolut PRO + THV consists of a self-expanding nitinol frame with a porcine trileaflet supra-annular pericardial valve. The valve is available in four sizes: 23, 26, 29, and 34 mm, which cover aortic annular sizes from 18 to 29 mm. The Evolut PRO + is recapturable and repositionable and has a skirt in the inflow tract and an external tissue wrap, which reduces the risk of significant PVL. The prosthesis is deployed by retrieving the delivery system and no rapid pacing is mandatory (**Figure 16**) (107).

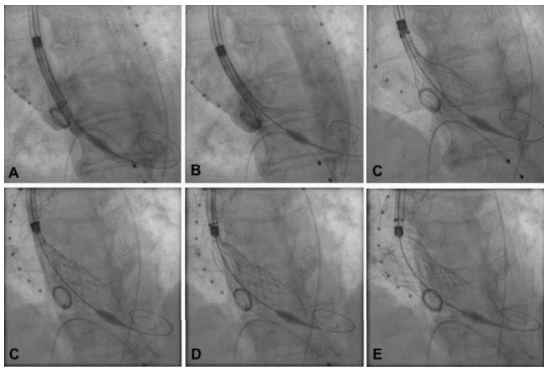

Figure 16.
A-**B**. Initial phase of the deployment.
C. The valve is functional at this point (2/3 of the deployment) and can be recaptured and repositioned.
D-**E**. Completion of deployment.

Compared with balloon-expandable THVs, the supra-annular design of the CoreValve family may lead to lower gradients. On the other hand, the increased frame height compared to the SAPIEN THV family make the coronary access after the procedure more challenging (108–111).

Other self-expandable valves include the ACURATE neo2 valve (Boston Scientific) and the Portico valve (Abbott Structural Heart) (112,113). Finally, the mechanically expandable LOTUS valve (Boston Scientific) was approved for non-operable patients (114), but is not currently available due to issues related to the delivery system. **Table 4** summarizes the main features of THV systems.

Table 4. Main features of old and current transcatheter heart valve systems

Prosthesis	Frame	Valve	Valve sizes, mm	Sheath sizes	Position	Reposi-tionable
Balloon-Expandable						
SAPIEN	Stainless steel	Bovine pericardial	23, 26	22 Fr (23 mm); 24 Fr (26 mm)	Intra-annular	No
SAPIEN XT	Cobalt-Chromium	Bovine pericardial	23, 26, 29	16 Fr (23 mm); 18 Fr (26 mm); 20 Fr (29 mm)	Intra-annular	No
SAPIEN 3	Cobalt-Chromium	Bovine pericardial	20, 23, 26, 29	14 Fr (20, 23, 26 mm); 16 Fr (29 mm)	Intra-annular	No
SAPIEN 3 Ultra	Cobalt-Chromium	Bovine pericardial	20, 23, 26, 29	14 Fr	Intra-annular	No
Self-Expandable						
CoreValve	Nitinol	Porcine pericardial	26, 29, 31	18 Fr	Supra-annular	Yes
CoreValve Evolut R	Nitinol	Porcine pericardial	23, 26, 29, 34	14 Fr equivalent (23, 26, and 29 mm); 16 Fr equivalent (34 mm)	Supra-annular	Yes
CoreValve Evolut Pro	Nitinol	Porcine pericardial	23, 26, 29	16 Fr equivalent	Supra-annular	Yes
CoreValve Evolut Pro+	Nitinol	Porcine pericardial	23, 26, 29, 34	14 Fr equivalent (23, 26, and 29 mm); 16 Fr equivalent (34 mm)	Supra-annular	Yes
ACURATE neo	Nitinol	Porcine pericardial	23, 25, 27	18 Fr	Supra-annular	No
ACURATE neo2	Nitinol	Porcine pericardial	23, 25, 27	14 Fr	Supra-annular	No
Portico	Nitinol	Bovine pericardial	23, 25, 27, 29	18 Fr (23, 25 mm); 19 Fr (27, 29 mm)	Intra-annular	Yes

Fr: French.

1.7.2.2. TAVI procedure: approaches

TAVI is nowadays performed using the TF approach in about 95% of cases (**Figure 17**) (115,116). This high percentage has been achieved due to the improvements in THV delivery systems (reduction of the catheter profile to 14-16 French diameter), and undoubtedly ranks the TF approach as the preferred route for TAVI. The TF approach represents the less invasive access, allowing the possibility of conscious sedation without the need for general anesthesia. Consequently, it is favored by international guidelines because of its reported superiority to alternative transthoracic approaches (transapical [TA], transaortic [TAo]) (43,54,117).

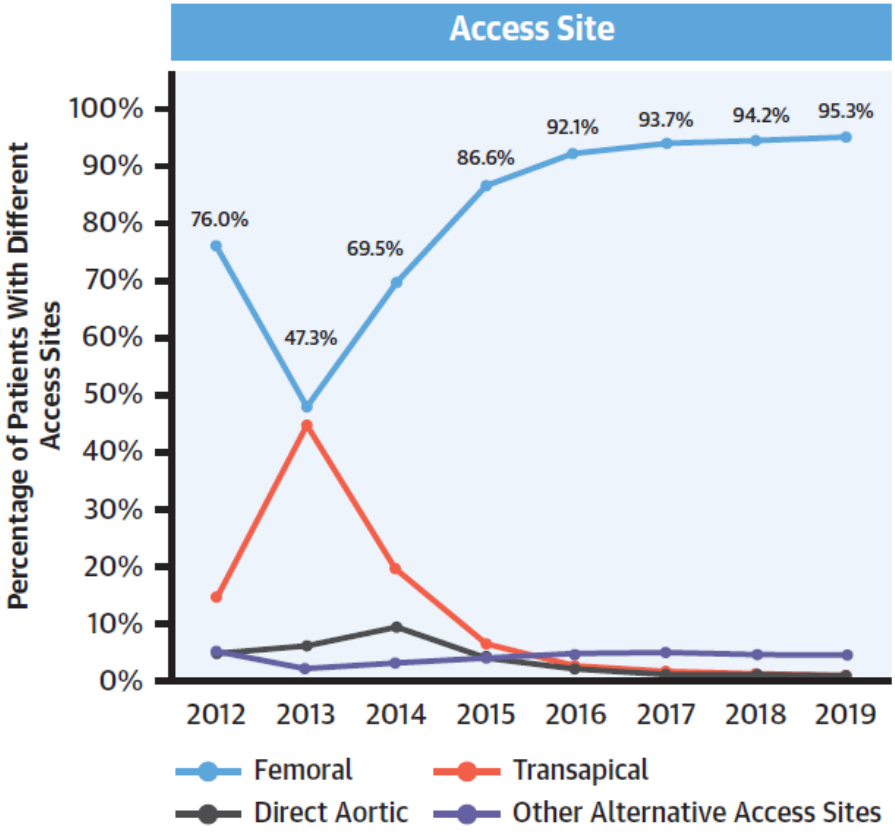

Figure 17. Percentage of patients with different approaches in the STS-ACC TVT Registry **(**Society of Thoracic Surgeons–American College of Cardiology Transcatheter Valve Therapy Registry)**.**

However, the progressive increase in TAVI indications (discussed later) will mean that a significant number of patients would require a non-transfemoral approach, even if it represents a relatively small percentage of TAVI recipients. At the beginning of the TAVI therapy, the transapical (TA) approach was the first to be introduced (118). Later,

newer and less-invasive approaches have been developed, including transcarotid (TC), transaortic (TAo), trans-axillary/subclavian (TS), transiliac, and transcaval (TCv) (**Figure 18 and Table 5**) (119).

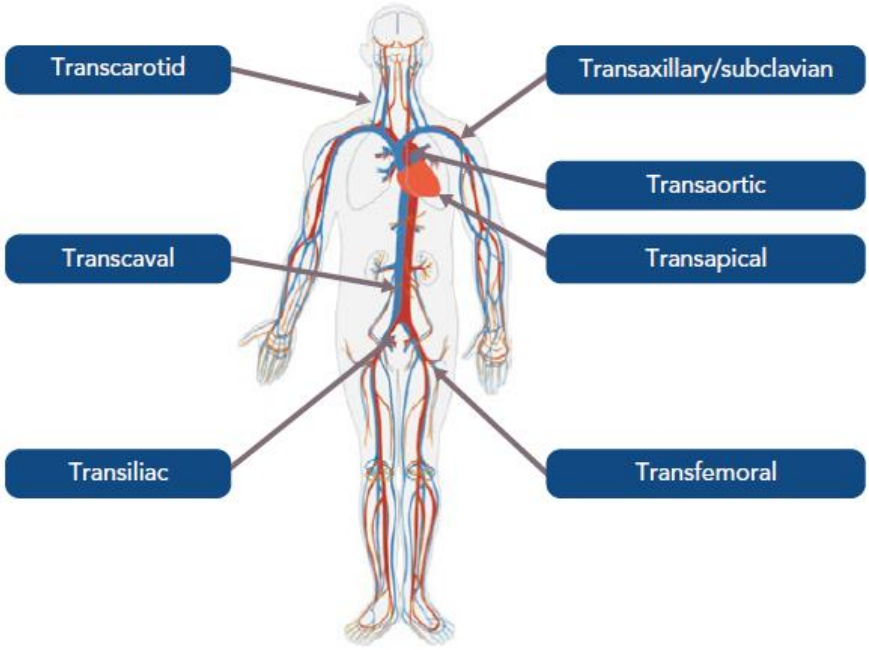

Figure 18. Schematic illustration of contemporary TAVI access options.

Therefore, patients with a non-suitable TF approach (iliofemoral artery diameter < 5-6mm and/or significant tortuosity, calcification, or angulation) may undergo TAVI through an alternative, non-transfemoral access. Among them, current recommendations discourage the use of a transthoracic approach (TA, TAo) according to the less invasive nature of non-transthoracic alternative approaches (TC, TS, TCv) (119). However, little data exist comparing alternative TAVI approaches (119). Whereas a fully percutaneous alternative access under conscious sedation and local anesthesia may be preferred, the final decision will usually be based on local experience at each cardiovascular institution. **Table 4** summarizes the main pros and cons of alternative TAVI approaches.

Table 5. Advantages and disadvantages of alternative TAVI approaches		
	Advantages	**Disadvantages**
Transapical (TA)	- Easy aortic valve crossing - Excellent THV maneuverability - Not limited by peripheral vascular anatomy and size	- General anesthesia and ventilation needed. - Mini-thoracotomy - Damage to left ventricular apex - Longer in-hospital stay
Transaortic (TAo)	- Excellent THV maneuverability - No guidewire manipulation in aortic arch and supra-aortic vessels. - Not limited by peripheral vascular anatomy and size	- General anesthesia and mechanical ventilation needed. - Partial sternotomy (unless suprasternal access) - Longer in-hospital stay.
Transcarotid (TC)	- Atherosclerotic disease is usually less frequent in common carotid artery compared with femoral arteries. - No guidewire manipulation of aortic arch.	- Surgical cut-down is necessary - Need for common carotid artery minimal lumen diameter >6mm. - Need for absence of contralateral significant carotid artery disease.
Trans-subclavian (TS)	- Possibility of local anesthesia and conscious sedation. - Atherosclerotic disease is usually less frequent in the subclavian artery compared with femoral arteries.	- Difficult alignment with the aortic annulus. - Deep location and proximity of the brachial plexus
Transcaval (TCv)	- Fully percutaneous venous access with possibility of local anesthesia and conscious sedation.	- Extensive preoperative planning (computed tomography). - Challenging technique involving an arterial puncture in the abdominal aorta from the inferior venous cava to allow the passage of the TAVI sheath.
TAVI: Transcatheter aortic valve implantation; THV: Transcatheter heart valve.		

1.7.2.3. TAVI procedure: complications

The TAVI field has progressively evolved to lower surgical-risk patients (120). Also, the improvements in THV systems and the operators' experience in TAVI have led to a reduction of most major complications related to the procedure (115,121–123). In order to standardize definitions and to allow proper comparison between studies, the Valve Academic Research Consortium (VARC) proposed consensus definitions for important clinical endpoints (124), including major complications (e.g. all-cause mortality, major stroke, vascular complications and bleeding, acute kidney injury), that has recently been updated as the VARC-3 criteria (125). As previously mentioned, the rate of mortality and major complications has decreased during recent years. As an example, the United Kingdom registry reported a dramatic reduction in in-hospital

mortality and major complications (tamponade, dialysis post-TAVI, stroke) following TAVI (mortality rate of 9.09% in 2008 and 1.84% in 2016) (120) (**Figure 19**).

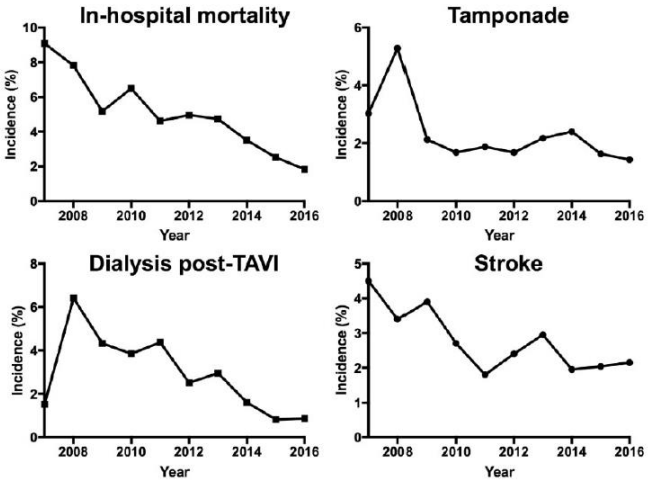

Figure 19. In-hospital mortality and major complication rates from 2008 to 2016 according to the United Kingdom registry (120).

In concordance, the STS-ACC transcatheter valve therapy (TVT) registry reported a major reduction in in-hospital, 30-days, and 1-year mortality from 2012 to 2019 (115) (**Figure 20**). Consequently, these improvements in the TAVI outcomes implied a progressive evolution to a "minimalist" approach with a short post-procedural length of stay (24-48h after the procedure or even same-day discharge in selected cases) (126,127).

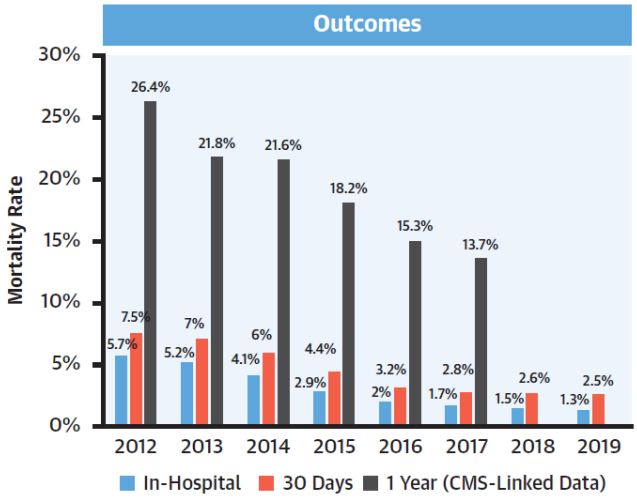

Figure 20. Mortality rates from 2012 to 2019 in the STS-ACC TVT registry.

On the other hand, vascular complications at the access site (i.e. bleeding, dissection, thrombosis) are common in patients undergoing TAVI, especially using the transfemoral approach. In the early TAVI era, the rate of vascular complications using first-generation 18-22 Fr devices was around 15% (128,129). Also, its occurrence has been classically associated with poorer outcomes (130,131). In contemporary cohorts, the use of smaller sheaths has translated to a reduction in bleeding and vascular complications (132), which are around 5% in current practice (133). Again, both bleeding and vascular complications are linked with adverse cardiovascular outcomes (133), which underlines the need to improve this complication and make the TAVI procedure safer.

Cerebrovascular events after TAVI may be devastating and are clearly associated with short-term mortality (134,135). TAVI recipients are at risk of embolic stroke during the procedure (positioning and deployment of the valve) and at follow-up (134,136,137). Data from the large STS-ACC TVT analysis reported a rate of clinically significant stroke of 2.3% at 30 days and 4.1% at 1 year (115,138). During the last years, the strategies to reduce peri-procedural and post-discharge stroke have focused on embolic protection during the procedure (139) and post TAVI antithrombotic treatment (140,141), respectively.

Residual paravalvular leak (PVL) has been one of the main drawbacks of the TAVI procedure, being more frequent compared to SAVR. When significant PVL is seen during the procedure (just after valve implantation), the overinflation of a balloon may reduce or even abolish residual PVL. In balloon-expandable valves, the same delivery balloon is commonly used. For self-expanding valves, a balloon usually sized to the mean diameter of the annulus is advanced through the THV to perform post-dilatation. To date, the known predictive factors for PVL have been asymmetric calcification, valve under-sizing, and device mispositioning (142,143). Furthermore, moderate or greater PVL has been associated with mortality and heart failure rehospitalization at one year of follow-up (144). As previously stated, newer THV generations have focused on anti-paravalvular leak strategies (capacity to reposition the THV during the procedure, outer seal cuff to minimize PVL).

Finally, arrhythmic disorders (especially conduction disturbances [CDs] including new-onset left bundle branch block [LBBB] and/or high-degree atrioventricular block

leading to PPM implantation) are a frequent complication of the TAVI procedure and its occurrence has not decreased over time (121,145).

1.7.3 Clinical evidence for TAVI

The clinical evidence concerning TAVI procedures came from studies performed over the last 15 years, ranging from clinical trials including inoperable aortic valve replacement (AVR) candidates to the expansion of the therapy to patients at low surgical risk. The clinical efficacy of TAVI translated in a significant uptake, with >800,000 procedures performed in >65 countries over the last 15 years (125). The initial evidence came from the first two pivotal trials, the PARTNER (Placement of Aortic Transcatheter Valve) trial and the US CoreValve Pivotal Trial (146–148).

The PARTNER trial was a randomized, multicenter trial that included 2 arms. The Cohort A compared TAVI using the SAPIEN device (Edwards Lifesciences, Irvine, CA, USA) to SAVR in patients considered at high surgical risk. The Cohort B compared TAVI to medical treatment, which included balloon aortic valvuloplasty, in patients considered inoperable. For the inclusion in PARTNER A, a minimal STS score of 10% was required. In the cohort 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%. Finally, a total of 1057 patients were enrolled: 358 patients were included in the cohort B and 699 in the cohort A.

The PARTNER B cohort demonstrated a 20% survival benefit of TAVI in inoperable patients compared to medical treatment, with a 1-year mortality of 30.7% in the TAVI group and a 50.7% in the medical therapy group (146). In the high-risk surgical cohort, TAVI and SAVR were equivalent for both 30-day mortality (TAVI: 3.4%, surgical AVR 6.7%, $P = 0.07$) and 1-year mortality (TAVI, 24.2%; surgical AVR, 26.8%, $P = 0.44$). A higher incidence of neurologic events was observed in the TAVI cohort compared to surgery (5.1 vs. 2.4%, $P=0.04$), along with a higher rate of vascular complications (18 vs. 4.8%, $P = 0.04$) and significant aortic regurgitation (6.8 vs. 1.9%, $P < 0.001$). Patients undergoing TAVI had a lower rate of bleeding (14.7 vs. 25.7%, $P < 0.001$) than surgery (147). The results led to approval by the FDA of the device for commercial use in inoperable and high-risk surgical patients.

The CoreValve US pivotal trial also included 2 arms. First, an extreme-risk that included 489 non-randomized patients which were compared with a pre-specified goal for all-cause mortality or stroke at 1 year of 43% using a non-inferiority with superiority test (149). Second, a randomized high-risk cohort where TAVI using the CoreValve system (Medtronic, Minnesota, USA) was compared to SAVR (148). Like the PARTNER trial, the patients were included if they had severe AS and a high-surgical risk judged by interventional cardiologists and cardiac surgeons. The extreme risk cohort confirmed that the system was safe and led to the FDA approval. In the high-risk cohort, the primary endpoint of all-cause mortality was observed in 14.2% of the TAVI patients and 19.1% of the surgical AVR group (P <0.001 for non-inferiority and P=0.04 for superiority) (148).

Following the pivotal trials focusing on patients at high surgical risk, two landmark randomized clinical trials reported outcomes in patients at intermediate risk (150,151). The PARTNER 2A randomized 2032 patients with an STS mortality risk of 4–10% to TAVI (Sapien XT valve) or SAVR. The mean STS score of the population was 5.8%, clearly under the previously cited PARTNER I and CoreValve US Pivotal trials (147,149). At 2 years of follow-up, there were no significant differences in the composite endpoint of death from any cause or disabling stroke (hazard ratio in the TAVI group, 0.89; 95% confidence interval [CI], 0.73 to 1.09; P = 0.25). In addition, the transfemoral subset had a significantly lower rate of death or disabling stroke compared to SAVR (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P = 0.05)(150), a finding that was confirmed in a subsequent meta-analysis (152).

The SURTAVI randomized trial enrolled 1746 intermediate-risk patients to TAVI using the CoreValve system or SAVR. The mean age was 79.8 years with a mean STS score of 4.5%. The SURTAVI trial found no significant difference in the primary endpoint (composite of death from any cause or disabling stroke) between TAVI and SAVR at 2 years (estimated incidence of the primary end-point was 12.6% in the TAVI group and 14.0% in the surgery group [95% interval for difference, −5.2 to 2.3%; p>0.999]) (151).

Whereas both randomized trials demonstrated no differences in the primary outcome, there were significant differences in the complication profiles between TAVI

and SAVR. In the PARTNER 2A trial, the TAVI treatment was associated with a higher rate of major vascular complications (7.9% vs. 5.0%), higher incidence of moderate or severe PVL (8.0% for TAVI arm and 0.6% in the SAVR arm at 2 years), but lower rates of new atrial fibrillation (AF) (9.1% vs. 26.4%) and life-threatening bleeding (10.4% vs. 43.4%) were reported (150). In the SURTAVI trial, TAVI was also associated with higher rates of major vascular complication (6.0 vs. 1.1%), as well as residual moderate or severe PVL (5.3% vs. 0.6%), and PPM implantation (25.9% vs. 6.6%), but lower rates of acute kidney injury (1.7% vs. 4.4%) (151).

Finally, two randomized trials evaluated the TAVI therapy against SAVR in patients at low surgical risk (STS<4%) (153,154), which represents the majority of patients undergoing SAVR (155). In PARTNER 3, 1182 patients suitable for TF TAVI were randomized to TAVI or SAVR. At one year, the incidence of the primary endpoint of all-cause mortality, stroke, or cardiovascular rehospitalization was 15.1% for SAVR *vs*. 8.5% for TAVI, HR 0.54 (95% CI: 0.37–0.79, P=0.001) (**Figure 21**) (153). Regarding PVL, there was no difference in the incidence of moderate or severe PVL at one year, but the proportion of patients with mild PVL were higher (29.4% for TAVI, *vs*. 2.1% SAVR) (153)

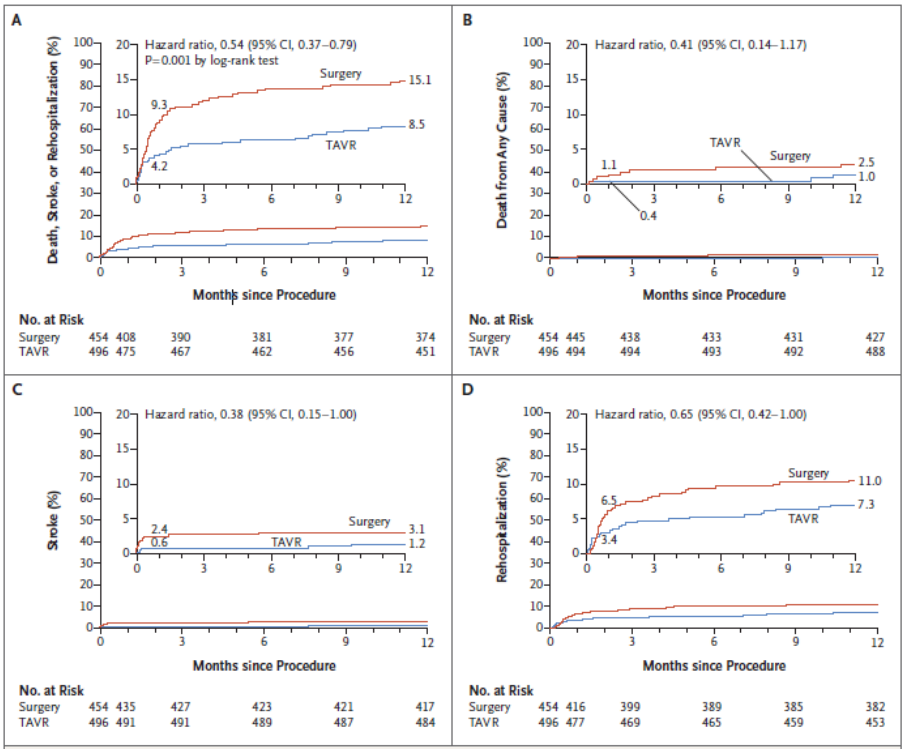

Figure 21. Time-to-Event Curves for the Primary Composite End Point and the Individual Components of the Primary End Point in the Partner 3 trial. **A**. Primary composite end point. **B**. Death from any cause. **C**. Stroke. **D**. Rehospitalization. From Mack et al (153).

In the EVOLUT low-risk study using the self-expandable Evolut valve (Medtronic, Irvine, CA, USA), 1,468 patients were randomized to TAVI or SAVR. The composite endpoint of all-cause mortality or stroke at 24 months was 5.3% *vs.* 6.7%, which was significant for non-inferiority (**Figure 22**) (154). In summary, both PARTNER 3 and EVOLUT low-risk demonstrated that the TAVI procedure performed through the transfemoral approach offers at least equivalence to SAVR in selected low-risk patients.

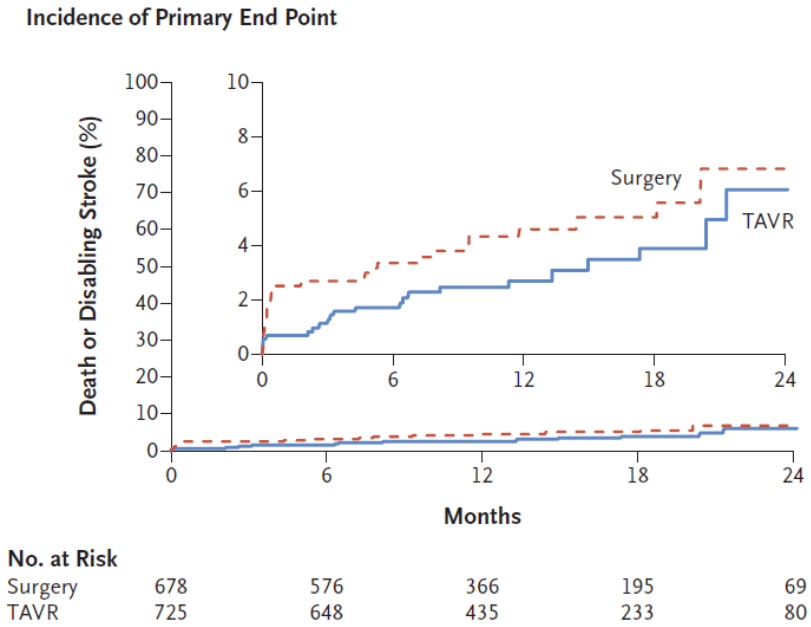

Figure 22. Kaplan-Meier time-to-event curves for death from any cause or disabling stroke (primary end point) at 24 months. From Popma et al (154).

Furthermore, a meta-analysis of all randomized TAVI/SAVR studies reported that TAVI is associated with a reduced risk of mortality when compared to SAVR (17% relative risk reduction). While the risk of stroke, major bleeding, new-onset AF, and acute kidney injury was lower with TAVI, the risk of PPM implantation was higher (116).

The amount of data ranging from inoperable to low-risk patients have extended the FDA approvals regarding TAVI from high-risk (2012), intermediate-risk (2016) to low-risk patients (2019), along with the treatment of patients with degenerated surgically implanted aortic valves (valve-in-valve procedure) (156). Based on the cited evidence, the current American Heart Association guidelines states (43): 1) Either TAVI or SAVR can be performed in patients who are 65 to 80 years of age and have no contraindication to transfemoral TAVI (I-A); 2) Transfemoral TAVI is recommended over SAVR in patients who are > 80 years of age (I-A); 3) TAVI is recommended in patients of any age

with high or prohibitive surgical risk (I-A). Furthermore, the very recent European guidelines recommends TAVI in older patients (≥75 years) irrespective of the surgical risk, or in those who are high risk (STS/EuroSCORE II >8%) or unsuitable for surgery (I-A) (54).

Accordingly, the rapid growth in the indications and the broader spectrum of treated patients has revolutionized the treatment of AS and has made TAVI the current dominant therapy for aortic valve intervention in the United States (**Figure 23**) (115).

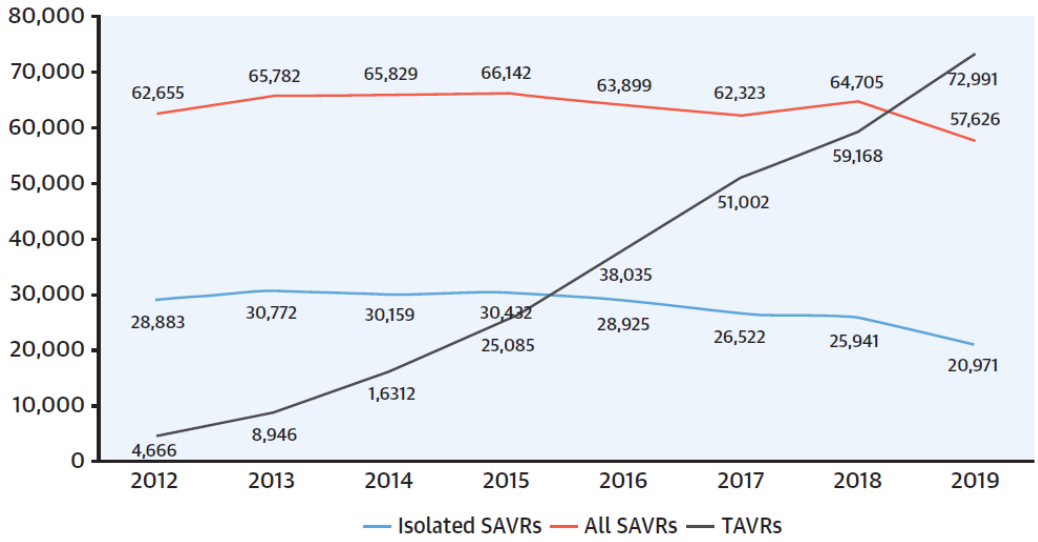

Figure 23. Volume of isolated SAVR, all forms of SAVR (i.e. SAVR and coronary artery bypass grafting, red line), and TAVI (gray line) from 2012 to 2019. From Carrol et al (115).

However, some issues may be improved before TAVI becomes the preferred treatment in the whole spectrum of AS including young (<75 years) patients. First, it must be noted that low-risk patients with unfavorable anatomy (e.g., bicuspid valve) were excluded from the landmark trials (157). As previously stated, the risk of PVL remains higher in TAVI compared to SAVR, including data at long-term follow-up (158). Also, although initial evidence showed promising data regarding very long-term durability (>5 years) of TAVI devices compared to SAVR, these are still preliminary results (159). Overcoming these challenges will represent the definitive shifting trend favoring TAVI as the widespread treatment of AS. **Figure 24** summarizes the most representative moments of TAVI history.

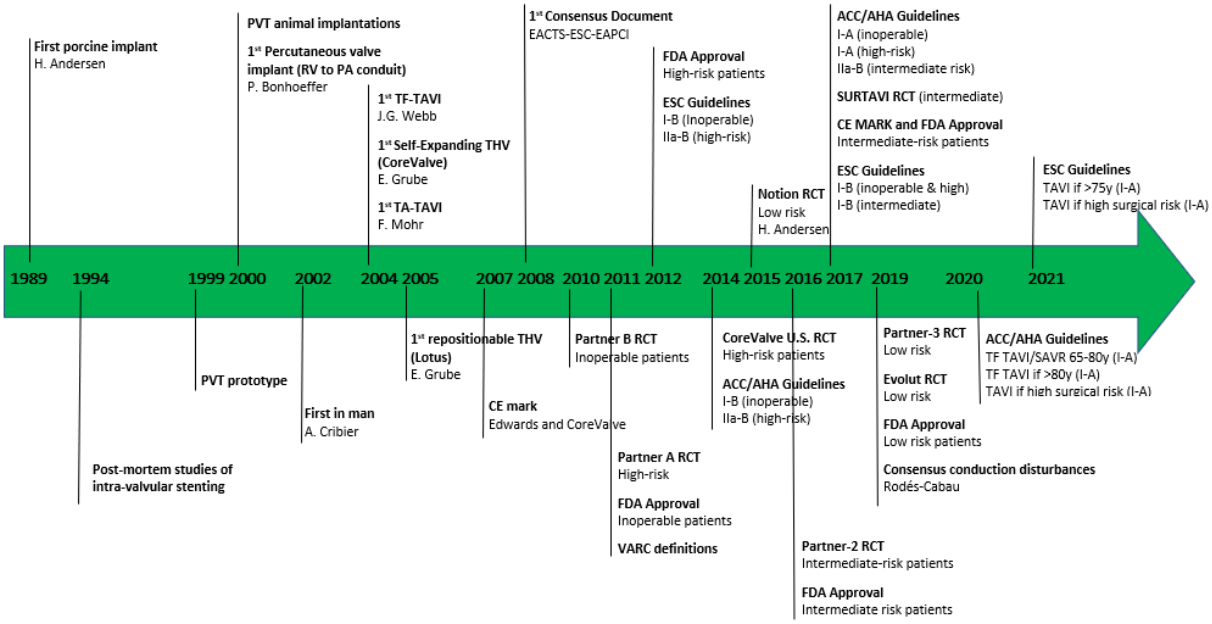

Figure 24. Main representative moments in TAVI history. PA: Pulmonary artery; RCT: Randomized clinical trial; RV: Right ventricle; TA-TAVI: Transapical transcatheter aortic valve implantation; TF-TAVI: Transfemoral transcatheter aortic valve implantation; THV: Transcatheter heart valve.

Finally, the occurrence of arrhythmic disorders (tachy- and bradyarrhythmias) and conduction disturbances (CDs) after TAVI has been a major drawback since the beginning of the therapy (145). First, the injury to the cardiac conduction system related to the therapy itself may lead to new CDs such as new-onset LBBB or high-degree atrioventricular block requiring PPM implantation. Second, new-onset tachyarrhythmias following the procedure may occur, and little is known regarding its incidence after hospital discharge. While the in-hospital periprocedural arrhythmic disorders have been largely studied, little evidence exists regarding those arrhythmic events occurring after hospital discharge.

The present thesis document focuses on this significant clinical issue of late arrhythmic disorders after TAVI, especially CDs.

1.8. ARRHYTHMIC DISORDERS AND TAVI

1.8.1 Anatomy of the aortic valve and implications for conduction disturbances.

The aortic valve is part of the aortic root, which also includes the sinuses of Valsalva, the aorto-ventricular junction (including the inter-leaflets triangles located between the basal attachments of the leaflets) and the sino-tubular junction (160). As depicted in **Figure 1.3**, the aortic valve is composed of three leaflets (the distal parts of each leaflet attachment are called the commissures) 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**.** As no anatomically circular structure in the aortic root exists, no clear structure fits with the commonly used term of aortic annulus (160). However, this term has been used to name two concepts. First, echocardiographers use this term to name a virtual basal ring constructed by joining together the most proximal parts of each leaflet. According to this, the aortic annulus is the smallest area between the left ventricle and the aorta and would determine the size of the prosthetic valve to be implanted during SAVR. Also, its measurement using computed tomography is used to size the TAVI devices (105). Also, this term has been used to determine the position of the prosthesis as 'supra' or 'intra-annular'. Second, for cardiac surgeons, the 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 SAVR procedures. **Figure 25** shows the aortic root (A) and a scheme of the aortic annulus (B) (160).

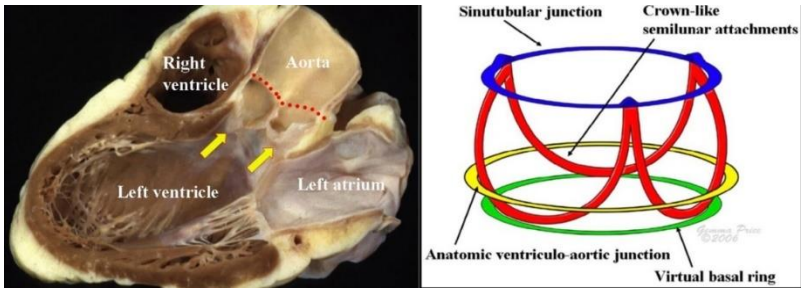

Figure 25.

A. Placement of the aortic root as the centerpiece of the heart. The root extends from the basal attachments of the valvar leaflets within the ventricle (yellow arrows) to the sinutubular junction (red dotted line).

B

B. Scheme corresponding to an idealized aortic root. The attachments of the valvar leaflets, shown in red, extend through the entire length of the root, from the sinutubular junction (blue), to the virtual basal ring, shown in green, and produced by joining together the basal attachments of the leaflets. The crown-like attachments of the leaflets cross the anatomic ventriculo-aortic junction (yellow). From Anderson (160).

The cardiac conduction system is composed of myocytes specialized in the generation and transmission of the cardiac stimulus from the atria to the ventricles. It is composed of the sinus node, the atrioventricular node, the His bundle, the bundle branches, and the Purkinje fibers (**Figure 26**). The sinus node, which cells have the pacemaker function of the heart, is located at the junction of the superior cava vein with the right atrium.

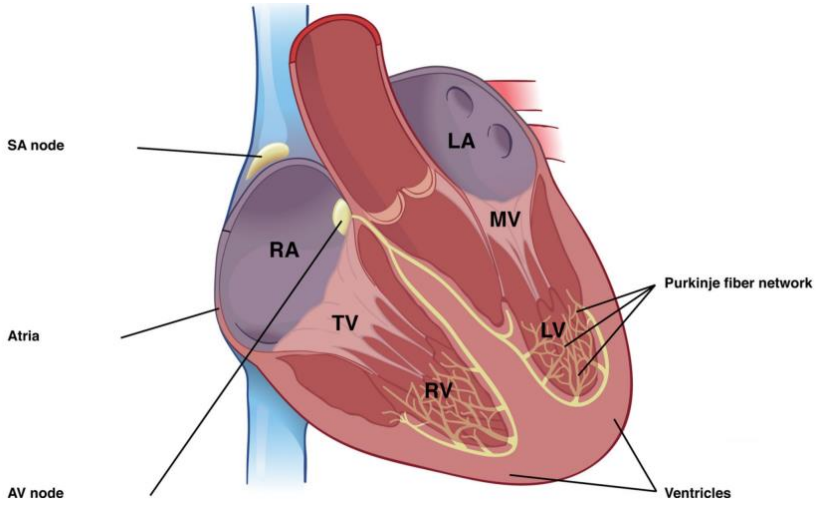

Figure 26. The cardiac conduction system.

The atrioventricular node is located within the triangle of Koch, which is delineated by the tendon of Todaro, the orifice of the coronary sinus, and the insertion point of the tricuspid valve septal leaflet (161–164).

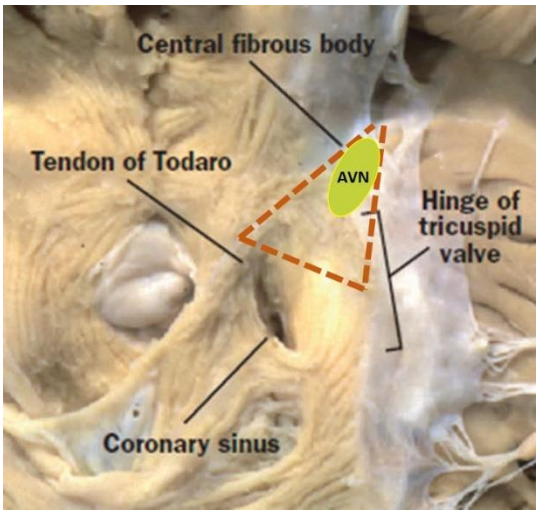

Figure 27. Triangle of Koch. AVN: Atrioventricular node.

Afterwards, the atrioventricular node continues as the bundle of His, penetrating the membranous septum (penetrating bundle) and passing to the left through the central fibrous body. The conduction system exits immediately under the membranous septum and is positioned superficially on the crest of the interventricular septum, where it gives rise to the left bundle branch, which is related to the base of the interleaflet triangle separating the noncoronary and right coronary leaflets (**Figure 28**) (161–163). The left bundle branch has close anatomical proximity to the aortic valve and, as its origin lies below the commissure between the right and non-coronary cusps, 2-3 mm below the attachment of the aortic valve leaflets. In this region, the left brunch is superficial, just under the endocardium (**Figure 28**) (161–163,165).

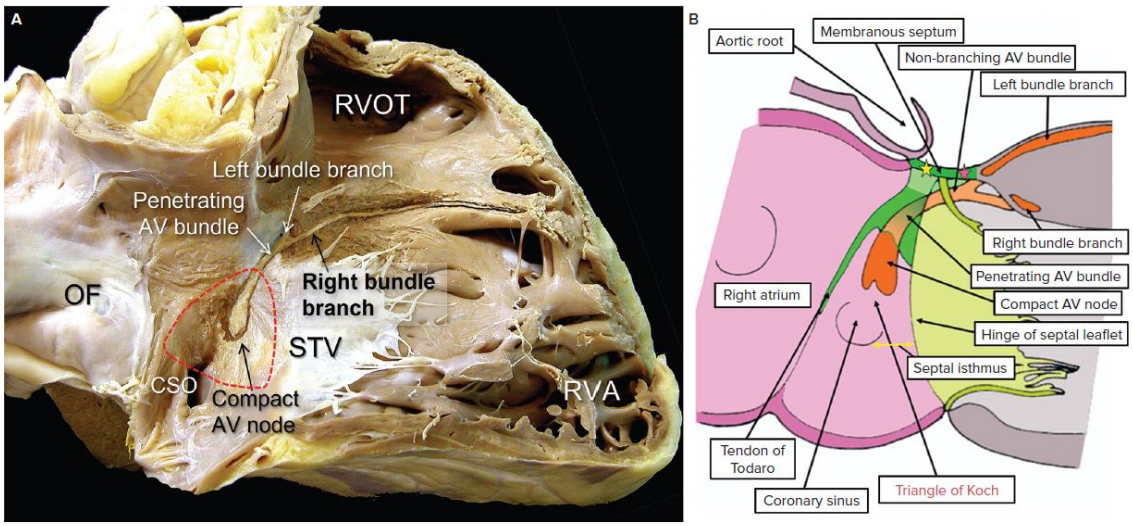

Figure 28. A: Dissection of the human atrioventricular conduction axis relative to the triangle of Koch (dashed red line), revealing the location of the AV node and penetrating bundle. The right bundle branch can be seen on the right side of the interventricular septum. B: Schematic drawing representing the arrangement of the AV conduction axis at the level of the Koch triangle.
CSO = coronary sinus orifice; OF = oval fossa; RVA = right ventricular apex; RVOT = right ventricular outflow tract; STV = septal tricuspid valve.

This close proximity between the conduction system (especially the bundle of His and the left bundle branch) to the base of the non-coronary and right-coronary leaflets is the main explanation of the occurrence CDs after TAVI (**Figure 29**).

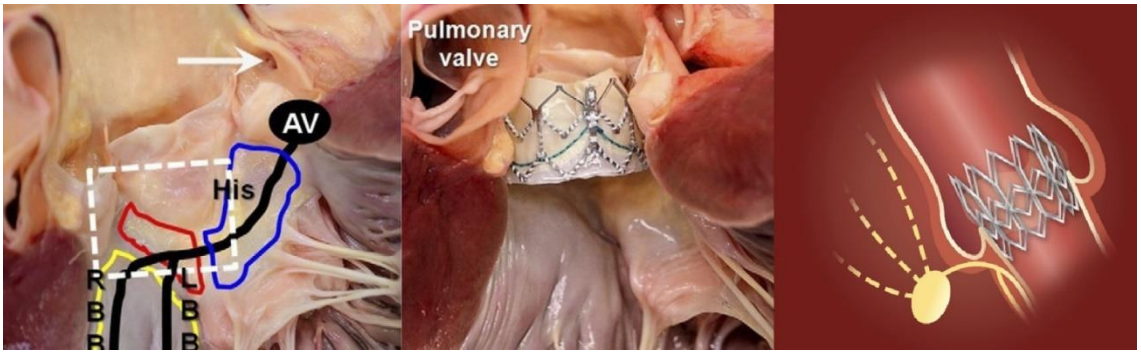

Figure 29. Relationship between TAVI and the conduction system.
Representation of the Cardiac conduction system in a pathological specimen (**Panel A**) The blue-line area highlights the aortic-mitral curtain, the red-line area highlights the membranous septum, and the yellow-line area highlights the muscular septum. The white arrow indicates the left coronary ostium.
The dashed box represents the virtual space where the transcatheter aortic valve would be placed (**Panel B**). **Panel C** is a graphic representation of the interaction of the transcatheter aortic valve and the conduction system (frontal plane). RBB: Right bundle branch. LBB: Left bundle branch.
From Bagur *et al* (Panel A-B) and Muntané-Carol *et al* (Panel C) (166,167).

The interaction with the cardiac conduction system during TAVI can occur during wire insertion, valve implantation, and pre/post balloon dilatation. The deployed valves can cause direct mechanical damage to the conduction system, including edema, hematoma, and ischemia (168), leading to worsening conduction, either transient or permanent. Damage to the atrioventricular node, His, and infra-His system during TAVI procedures has been demonstrated by electrophysiological studies (169).

The effects of the THV on the cardiac conduction system may lead to two main disorders: new-onset LBBB and high degree or complete atrioventricular heart block (HAVB/CHB) leading to PPM implantation.

LBBB is defined as a prolongation of > 120 ms in the QRS from the surface ECG, with a specific ECG pattern (**Figure 30**) defined in detail in an expert consensus (170).

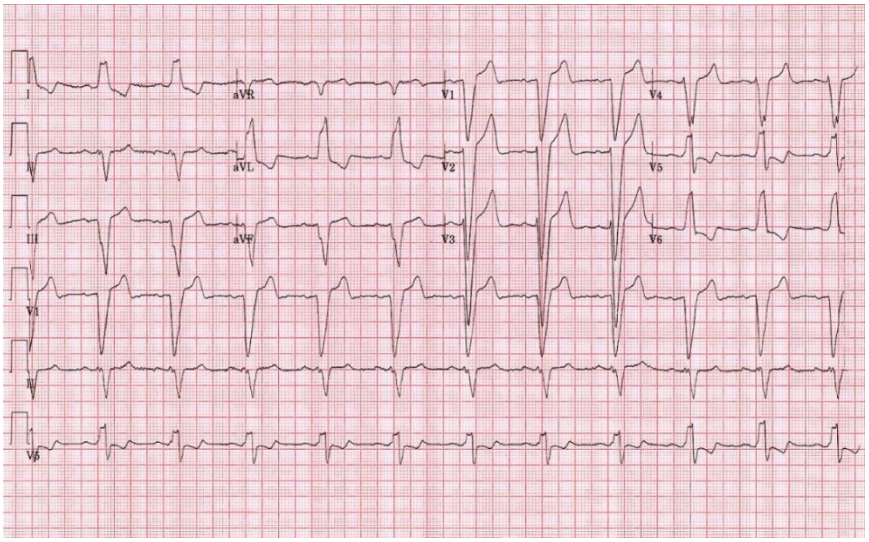

Figure 30. Electrocardiographic pattern of a left bundle branch block.

In patients with LBBB, the left ventricle is activated across the right bundle branch and consequently, the septum is activated from right to left (opposite than in the normal heart). The presence of LBBB generates electrical and mechanical dyssynchcrony, affecting systolic and diastolic (LV filling) cardiac phases (171). Chronically, LBBB is associated with a progressive structural remodeling, promoting a vicious circle of left ventricular dilatation, asymmetric hypertrophy, and wall stress that leads to deterioration of the left ventricular function.

Overall, atrioventricular block is defined as a disorder where the atrial impulses are conducted with delay or are not conducted to the ventricles (excluding the time when the atrioventricular conduction is physiologically in refractory period) (172). Atrioventricular blocks are classified according to ECG findings, as first, second, or third degree, and according to electrophysiological criteria as supra, intra or infrahisian atrioventricular blocks (173). The latter divides atrioventricular blocks in proximal and distal. In proximal block (at the level of the AV node), the origin of the escape rhythm is located above the His bundle bifurcation. Thus, normal QRS duration implies that the block is located proximal to the bifurcation of the bundle of His. Distal block implies an origin below the AV node. Third-degree (complete) atrioventricular blocks may be proximal or distal. In distal block QRS complexes are always wide. In summary, advanced atrioventricular blocks (HAVB/CHB) will normally provoke symptoms (e.g.

dyspnea, lightheadedness, syncope or even sudden death) and will require the implantation of PPM, which is supported by strong evidence (173,174). On the other hand, one A summary of atrioventricular block EKG definitions is shown in **Table 5.**

Table 6.Atrioventricular block EKG definitions (170,173)	
First-degree atrioventricular block	P waves associated with 1:1 atrioventricular conduction and a PR interval >200 ms.
High degree atrioventricular block (HAVB)	- Second-degree AV block type 2 (Mobitz II) in the presence of a QRS ≥120 ms. - 2:1 AV block in the presence of a QRS ≥120 ms. - ≥2 consecutive P waves at a constant physiologic rate that do not conduct to the ventricles. - Transient third-degree atrioventricular block. - In the setting of atrial fibrillation, a prolonged pause (>3 s) or a fixed slow (<50 beats/min) ventricular response rate.
Third degree or complete heart block (CHB)	P waves with a constant rate with dissociated ventricular rhythm (no association between P waves and R waves) or fixed slow ventricular rhythm in the presence of atrial fibrillation.

Like acquired LBBB, the pacing from the apex to the base of the heart in patients with PPM may induce electrical and mechanical dyssynchrony. This long-term apical pacing has been associated with an increased risk of heart failure and mortality, and the occurrence of pacing-induced cardiomyopathy (175–177).

1.8.2. Arrhythmic disorders and degenerative aortic stenosis

The presence of degenerative aortic stenosis *per se* is associated with a deleterious effect on the cardiac conduction system, which may lead to conduction abnormalities (178–187). The close anatomical relationship with the conduction system may explain this association, and several factors such as older age (182), greater severity of AS (187), extensive calcification (187), and left ventricular dysfunction (182,186) has been suggested.

Three recent studies have used continuous ECG monitoring before the TAVI procedure, providing a significant amount of data regarding arrhythmic disorders in patients with AS (188–190). Regarding bradyarrhythmias, HAVB/CHB episodes before

TAVI occurred in 3% (1.9% to 3.2%) of the patients, leading to PPM implantation in 56% of them (188–190). Moreover, severe bradycardia (defined as heart rate <40 beats/min) occurred in 6% of patients (188,190). Whereas the relatively low number of patients included in the studies precluded the identification of independent predictors of severe bradyarrhythmic events, Asmarats et al. showed a higher rate of bradyarrhythmic events in patients with either first-degree atrioventricular block (1-AVB) ($p = 0.047$) or right bundle branch block (RBBB) ($p = 0.008$) at baseline (190).

AF is a supraventricular arrhythmia where a very fast, chaotic rhythm is generated in the atria, which has lost its normal pacemaker capacity that occurs normally in the sinus node. This uncoordinated atrial activation causes ineffective atrial contraction and may lead to fast ventricular rates. AF is the most common cardiac arrhythmia worldwide (191,192). Furthermore, the presence of AF increases the risk of stroke and cardiac and all-cause mortality (193–195). In AS, the occurrence of AF has been reported in 5% of patients (annual incidence of 1.2%), and it has been associated with an increased risk of stroke and heart failure (196).

In the previously cited studies using continuous monitoring before TAVI (188–190), new-onset atrial fibrillation (NOAF) or atrial tachycardia was detected in 6% of the TAVI candidates (188–190). Of note, Urena et al. showed that the occurrence of AF or atrial tachycardia during the 24-h ECG monitoring before the procedure was associated with an increased risk of cerebrovascular events after TAVI (7.1% vs. 0.4%; $p = 0.030$) (188). Overall, the extent of AF in these patients is related to the AS itself but is mainly caused by multiple factors such as left ventricular hypertrophy with diastolic dysfunction, atrial enlargement, and comorbidities (hypertension, older age, etc.).

Finally, the incidence and impact of arrhythmic events including CDs in the setting of SAVR have also been reported. Acute lesions are frequently associated with CDs and are caused by laceration from sutures, residual calcific material, and compression by the seat of the prosthesis (197). The incidence of new-onset LBBB and PPM implantation after SAVR occurred in up to 16-33% and 2-11% of patients in previous studies, respectively (183,198–204). Of note, up to half of these CDs may recover. In this line, current guidelines recommend a period of clinical observation of at least 5 days to assess whether the rhythm disturbance is transient or resolves (174).

1.8.3. Conduction disturbances and TAVI

As illustrated before, the TAVI treatment has revolutionized the management of aortic stenosis. During the last years, the successive improvements in THVs and the growing experience in the field have led to a progressive reduction of periprocedural complications and death (120,121). However, some drawbacks remain to be resolved. CDs such as HAVB requiring PPM implantation and new-onset LBBB have not decreased over time. In fact, the occurrence of CDs persists as the most frequent complication of the procedure (121,145), and even a further increased risk has been reported with the use of some newer generation THVs (114,205–209). This is of major importance when TAVI is now considered for low risk populations.

1.8.3.1 New-Onset left bundle branch block (LBBB

The occurrence of new-onset LBBB remains the most common complication after TAVI. However, the incidence of new-onset LBBB among TAVI recipients has been variable. This may be related to the use of different transcatheter devices, inclusion of transient (vs. persistent) LBBB, unequal baseline risk to develop CDs, and different time-points regarding the ECG acquisition (resulting in different definitions of new-onset LBBB). Thus, the reported incidence of new-onset LBBB in new-generation transcatheter valve systems has ranged from 10% to 77% (153,205,206,210–221) (**Figure 31**).

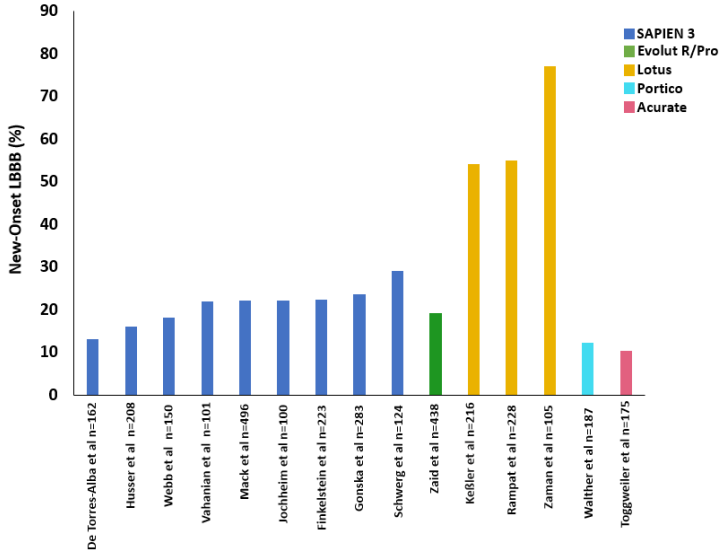

Figure 31. Incidence of new-onset left bundle branch block among new-generation transcatheter heart valves.

Predictors of new-onset LBBB after TAVI have been described with the use of first-generation THVs, being the prosthesis implantation depth the most consistent risk factor (145). Other risk factors included the implantation of a Medtronic Corevalve versus an Edwards Sapien valve, the overexpansion of native annulus, and the utilization of larger valves (**Table 7**) (145).

Table 7. Main predictors of new-onset left bundle branch block after TAVI (145)

Variable	**Multivariable Odds Ratio**
Medtronic CoreValve vs Edwards SAPIEN	2.5-8.5
Depth of implantation, per 1mm	1.15-1.4
Overexpansion of the native aortic annulus	1.8/1%; 5.3 if > 15%
Larger valve size	
Medtronic CoreValve 26 vs 23mm	4.1
Edwards SAPIEN valve 29 vs 20/23mm	3.12

New-onset LBBB post-TAVI occurs in the procedural period or within the first 24 hours in about 90% of cases (222–224). Thus, around 10% of patients will develop new-onset LBBB >24h after the procedure (before discharge) (222). Whereas new-onset LBBB is often transient, about 55% of new-onset LBBBs (ranging from 52 to 62%) will persist at hospital discharge (222,225,226). Also, the resolution of new-onset LBBB may occur during the first year after the procedure in around 20-30% of patients (222). No predictors regarding regression of the LBBB during follow-up have been reported to date.

The clinical impact in new-onset LBBB patients may be determined by two factors: the potential evolution to HAVB and the chronic effect on LVEF. Regarding the progression to HAVB, two meta-analyses have reported an increased risk (about 2-fold in both cases) of PPM implantation after TAVI (227,228). Despite that, current data do not support an indication of systematic prophylactic PPM implantation in these patients. However, some studies have shown that patients with a very long PR interval (>240ms) and/or those exhibiting a QRS interval duration >150–160 ms may have an increased risk of delayed HAVB and sudden death (229–232). Thus, it can be reasonable to implant a

prophylactic pacemaker in this specific subset of patients. Finally, electrophysiological studies in this context may be useful in borderline cases. Nevertheless, the evidence in this field is scarce and controversial due to the low number of patients included (233–236).

On the other hand, the impact on mortality and heart failure rehospitalization at follow-up had shown inconsistent results across the studies with multivariable analysis (222,225,237–241). However, a recent metanalysis demonstrated that new-onset LBBB is associated with an increased risk of all-cause death, cardiac mortality, and heart failure hospitalization (**Figure 32**) (242)

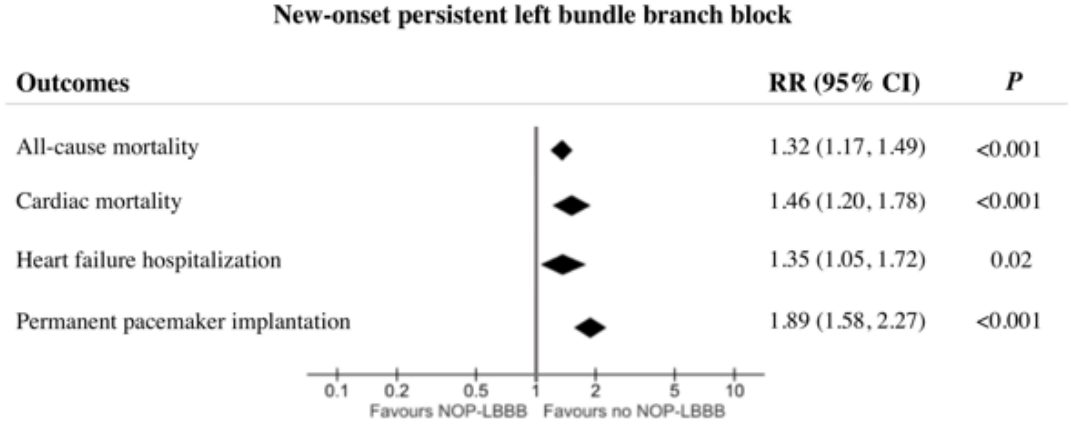

Figure 32. Risk of all-cause death, cardiac death, and heart failure hospitalization in TAVI recipients with new-onset LBBB. From Faroux et al (242).

1.8.3.2 High degree atrioventricular block and pacemaker implantation

TAVI induced-HAVB and therefore PPM implantation is nowadays the main concern after the TAVI procedure. As previously mentioned, the newer iterations of THVs (improved repositioning/retrievability, antiparavalvular leak properties) do not influence the occurrence of conduction disturbances and the PPM implantation rates have not decreased with newer generation devices, being nowadays around ~10-15% (151,205,206,210–214,216–219,229,243–284) (**Figure 33**). HAVB or CHB will occur mostly (60-96%) in the periprocedural (within 24h) setting (166,232,285).

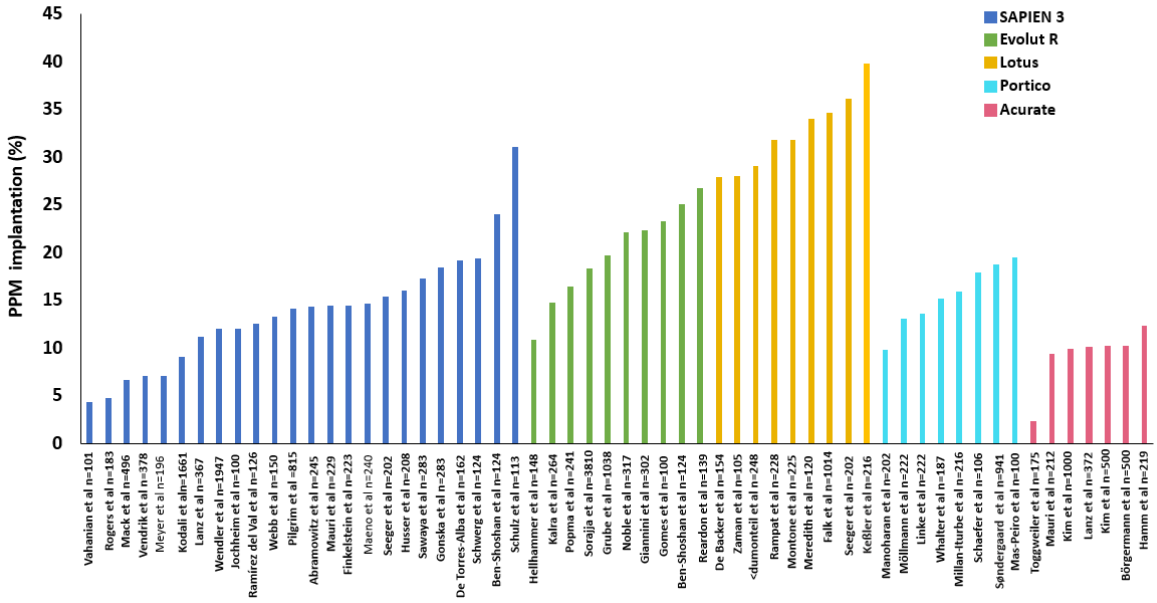

Figure 33. Incidence of PPM implantation among new-generation THVs.

Similar to new-onset LBBB, PPM implantation has been more frequent among first-generation self-expandable CoreValve recipients compared with patients who received a balloon-expandable Edwards SAPIEN/SAPIEN XT valve (145). Among the new-generation valves, the reported PPM implantation rate with the balloon-expandable Sapien 3 valve ranged between 4-24% compared to the 14.7-26.7% with the self-expandable Evolut R valve (**Figure 33**). However, the only randomized comparison between these two THV systems date did not show relevant differences between self-expandable and balloon expandable-valves (286). Of note, it was a non-blinded study and the incidence of PPM implantation was higher than in current clinical practice (19.2% and 23% for balloon- and self-expandable valves, respectively).

Several factors have been associated with PPM implantation post TAVI (**Table 8**). Preprocedural predictors included male sex, age, left anterior hemiblock, first-degree atrioventricular block, and RBBB, being the most consistent factor across studies (145,287). Anatomical factors determined by computed tomography (membranous

septum length, calcium volume, non-coronary cusp device-landing zone calcium volume) have also been identified as risk factors (244,288–290). Finally, associated procedural factors included depth of prosthesis implantation, overexpansion of native annulus and the presence of intraprocedural heart block (145,287,291).

Table 8. Main predictors of PPM implantation after TAVI (145)

Variable	Multivariable Odds Ratio
Baseline right bundle branch block	2.8-46.7
Medtronic CoreValve vs Edwards SAPIEN	2.6-25.7
Depth of implantation	1.1-1.5/1 mm
Overexpansion of the native aortic annulus	1.02-1.5/1%
First-degree atrioventricular block	4.0-11.4

As previously stated, the deleterious effect of long-term right ventricular pacing has been demonstrated in other cardiovascular settings (175–177,292). However, there has been inconsistency regarding clinical consequences in TAVI patients. A publication from the STS-ACC TVT registry including 9785 TAVI recipients demonstrated an increased risk in 1-year overall mortality (293) (HR:1.31; 95% CI, 1.09–1.58; *P*=0.003). In this line, the recent meta-analysis by Faroux et al showed an increased risk of all-cause mortality and heart failure hospitalization, but there was no association with cardiac death (242) (**Figure 34**).

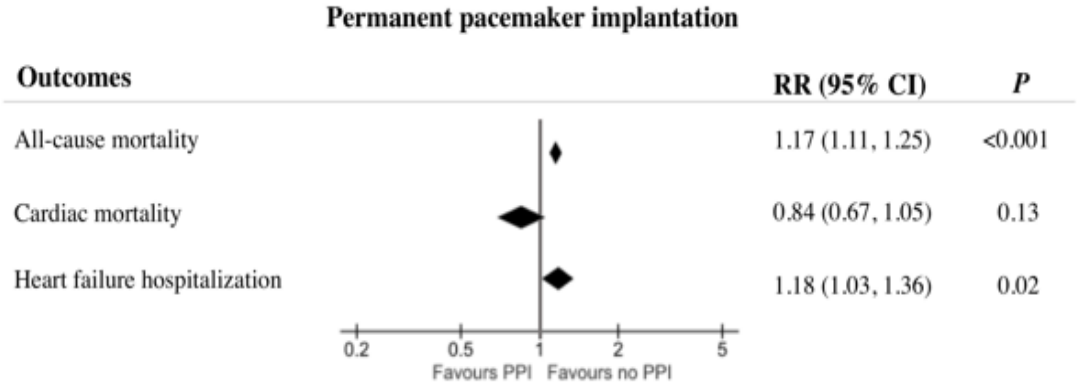

Figure 34. Risk of all-cause death, cardiac death, and heart failure hospitalization in TAVI recipients with new PPM implantation. From Faroux et al (242).

On the other hand, very recent research from the national Swedish registry including 3420 patients (481 of them with PPM implantation following TAVI) and long follow up (median 2.7 years [interquartile range: 2.5-11.8 years]) failed to show differences between patients with and without PPM post-TAVI (multivariable-adjusted HR: 1.03; 95% CI: 0.88-1.22; P = 0.692) (294).

In summary, CDs following TAVI are the most frequent shortcoming of the procedure. Furthermore, there has been an important lack of consensus regarding their definitions and treatment among centers, which has translated into significant differences regarding CDs approach and therefore different PPM implantation rates (295). This heterogeneity is mainly related to the management of new-onset LBBB, the timing for PPM implantation following TAVI, the management of patients with prior conduction disturbances, and the role of continuous ECG monitoring after discharge.

Trying to solve this unmet need, two recent expert scientific panel documents provided the first guide for the management of conduction disturbances post-TAVI (296,297).

1.8.4 Tachyarrhythmias and TAVI

Compared to CDs, the prevalence and clinical impact of new-onset tachyarrhythmias in patients following TAVI have been less studied, especially after hospital discharge. The evaluation of new-onset tachyarrhythmias following TAVI has been mostly limited to the periprocedural TAVI period and focused on AF (298–301) , which is the most detected arrhythmia post-TAVI (302). Although TAVI patients have several comorbidities that may be related to AF such as hypertension, diabetes, or heart failure, the pathophysiology of new-onset atrial fibrillation (NOAF) in patients undergoing TAVI remains poorly understood. Some studies have reported a systemic inflammatory response after TAVI (303), which may trigger the occurrence of AF especially in transapical procedures (304). In this line, the transapical approach along with a larger atrial size have been associated to the occurrence of AF (301).

NOAF detected during the hospitalization period implies an increase in early and late mortality post- TAVI due to thromboembolic and bleeding events and hospitalization

for heart failure (305–308). On the other hand, very scarce data exist on the presence of silent or symptomatic episodes of AF during the follow-up period post- TAVI. More studies are needed to shed more light on the AF burden after discharge in TAVI patients, mainly regarding the indication of anticoagulation treatment to prevent thromboembolic events. Finally, the published data concerning the occurrence of ventricular tachycardia in the follow-up after TAVI is even more limited (309,310).

1.8.5. Late arrhythmic disorders and TAVI

As mentioned before, both brady- and tachyarrhythmias occur mostly in the periprocedural TAVI period, and this period has concentrated most of the research in this field (145). However, some patients may suffer arrhythmic disorders after discharge, especially during the first weeks/months following the TAVI procedure. The occurrence of arrhythmias in the early period following hospitalization could impact the application of a "minimalist" TAVI approach with early (24-48 hours) discharge (126,127,311). In this line, recent research reported an increase in readmission for PPM implantation in the following weeks after TAVI (312).

Ambulatory ECG (AECG) monitoring systems have emerged as a useful tool for the early detection of arrhythmic events in recent years and are widely used in other clinical scenarios (313,314). However, data in TAVI patients are scarce (315). The aim of AECG monitoring is to detect and categorize rhythm abnormalities occurring during daily life, either silent or symptomatic (palpitations, syncope, dizziness, chest pain, or shortness of breath) (316). Nowadays, multiple AECG monitoring technologies are available and can be classified according to their main characteristics, mode of action, and monitoring duration (**Figure 35**, **Table 9**) (315).

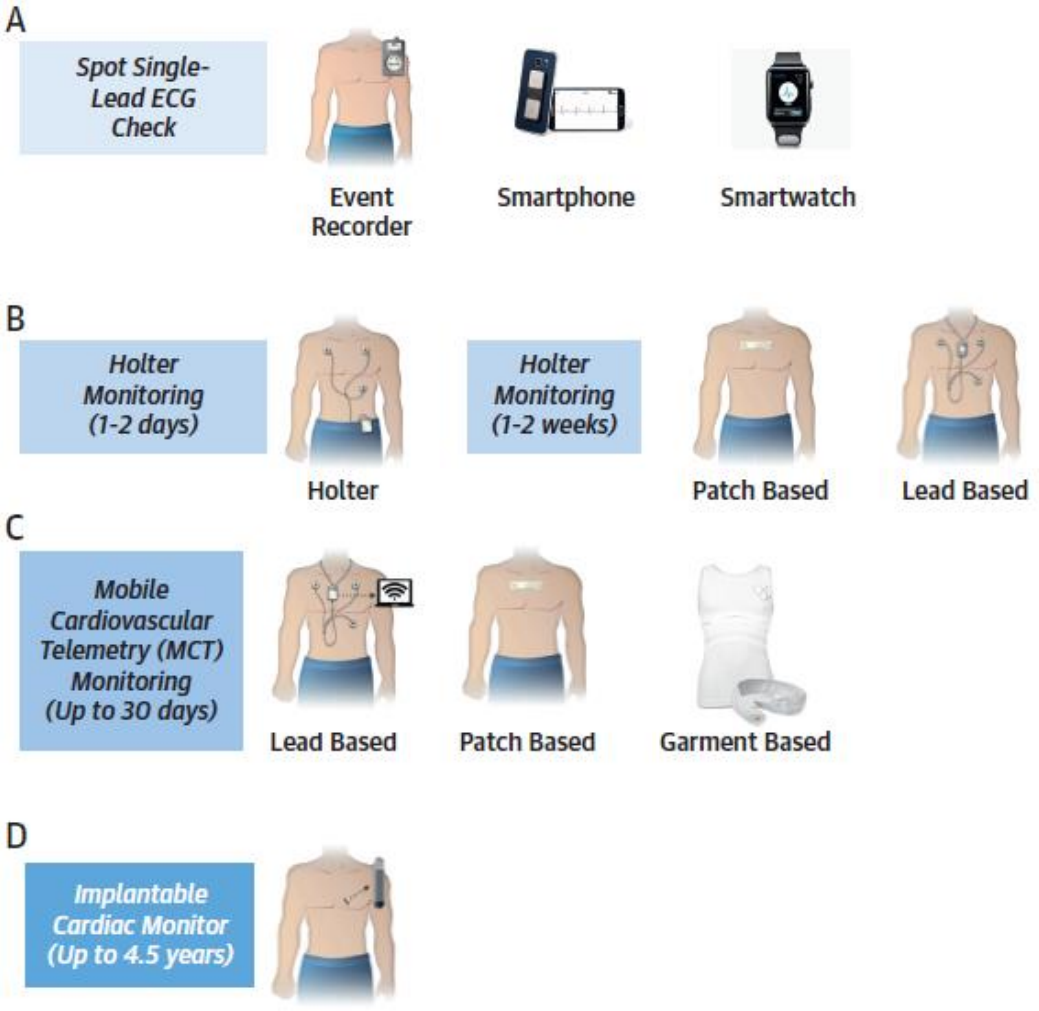

Figure 35. Types of ambulatory ECG monitoring. From Muntané-Carol et al (315).

Table 9. Ambulatory ECG Monitoring Modalities and Technology (315)**.**

Type of recorder	**Duration of recording**	**Modality of recording**	**Advantages**	**Disadvantages**
Standard Holter monitor	24-48h	Continuous single and multi-lead external recorders.	- Ability to record and document single or 3- to 12- lead ECG signal simultaneously.	- Frequent noncompliance with symptom logs and event markers. - Signal quality issues.
External event recorders/Smartphone-based recorder	<1 min	Intermittent external patient- or auto-trigger activated post-event recorders	- Immediate alarm generation upon the event detection. - Well-tolerated for the patient.	- Single-lead devices. - Non-continuous cardiac recording.
Patch ECG recorders	Up to 4 weeks	Continuous single or two lead external recorders without and with wireless data transmission	- Long-term recorder of to 28 days or longer. - Excellent patient acceptance.	- Records a limited ECG from closely spaced electrodes (lack of localization ability of arrhythmia origin). - Inconsistent optimal ECG signal quality due to varying body types.
External loop recorders (ELR)	4-8 weeks	Intermittent external patient- or event-activated (auto-triggered) recorders	- Records only selected ECG segments of fixed duration marked as events either automatically or manually by the patient. - Immediate alarm generation upon event detection.	- Records a single-lead ECG sequence. - P waves may not be visible. - Requires patients to wear electrodes continuously.
Mobile cardiovascular telemetry (MCT) monitoring	Real-time streaming to call centers	External real-time continuous cardiac tele-monitoring systems	- Immediate alarm generation.	- Frequent electrode changes. - Cost.
Implantable cardiac monitors (ICM)	Up to 4.5 years	Intermittent implantable or insertable patient- or auto-trigger activated post-event recorders	- Very long-term recording. - Well-tolerated.	- Cost.

The clinical value of AECG monitoring and its role in early discharge following all TAVI recipients is in its infancy, with three small publications showing its potential usefulness in the TAVI context (317–319).

After preliminary results using AECG monitoring after discharge in all TAVI recipients (320), a subsequent extended analysis including 150 patients was published by Ream et al (317). This was the first study focusing on delayed HAVB (>2 days after the procedure) after discharge using mobile cardiovascular telemetry (MCT) event monitor (Biotel ACT EX, BioTelemetry, Malvern, Pennsylvania). Delayed HAVB (after hospital discharge) was diagnosed in 10% of the patients and 5 of them presented with symptoms, including 2 with syncope. The median time for the development of delayed HAVB was 6 days (range: 3 to 24 days), and all these patients were re-hospitalized for PPM implantation. Of note, no deaths occurred among the patients discharged with AECG monitoring. After adjustment, RBBB was found to be the only independent predictor for delayed HAVB.

Tian et al contributed with novel data on the usefulness of post-discharge AECG monitoring in all TAVI recipients (318). An MCT system (BodyGuardian, Preventice Technologies Inc, Rochester, MN) was applied before hospital discharge for 30-day monitoring. HAVB/CHB (all asymptomatic) and symptomatic sinus pauses were identified in 9 (7.1%) and 2 (1.6%) patients, respectively, and PPM implantation was indicated in all cases (mean time of 21±14 days from TAVI). No deaths occurred within the study period. Patients with RBBB exhibited the highest incidence of late HAVB.

Tarakji et al (319) recently published a prospective, single-center study using AECG monitoring for 2 weeks pre, immediately post, and 2-3 months after TAVI. Of note, caring physicians were blinded to the results of the AECG except when predefined urgent arrhythmias were detected. Of 110 enrolled patients, 81 received AECG monitoring immediately after discharge. Bradyarrhythmias, defined as a pause ≥ 3 seconds, occurred in 12.7% of patients after discharge. In contrast with previous data (317,318), these bradyarrhythmic events were mostly pauses in the context of AF/flutter and sinus pauses, without evidence of HAVB/CHB events. The relatively low number of patients included may partially explain these findings. Also, the authors stated that the fact that the clinician caregivers were blinded to the results of the AECG monitoring

may have mitigated some degree of overtreatment that could exist in the non-blinded previous studies (319).

Finally, a previous publication used long-term monitoring using an implantable cardiac monitor in patients with new-onset LBBB (321). The 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 included 103 consecutive patients with persistent new-onset LBBB (321). The main results of the study were the following: (i) About 50% of patients exhibited either brady- or tachyarrhythmias, and these events led to a treatment change in more than one-third of them, (ii) about 10% of the patients required PPM implantation due to HAVB, (iii) about half of the events occurred within the first 4 weeks following the procedure. However, the follow-up of this initial experience was limited to one year.

As previously stated, it has been a significant discrepancy regarding PPM implantation rates between centers since the beginning of the TAVI technique (295). This stems mainly from the different management of CDs following the procedure, which has been again demonstrated in a very recent publication (322). This heterogeneity partially relates to preprocedural arrhythmic risk evaluation, management of new-onset LBBB, timing and indication for PPM in patients with periprocedural HAVB/CHB, and the management of patients with prior conduction disturbances such as right bundle branch block. Differences in the management of conduction disturbances can have major consequences in the hospitalization length and costs of the TAVI procedure and may also affect clinical outcomes. In addition, the TAVI field has progressively evolved to a "minimalist" approach with a short length of stay (24-48 hours after the procedure or even same-day discharge), which may be controversial regarding the occurrence of delayed arrhythmic disorders. In this context, AECG monitoring during the early postdischarge period has emerged as a tool for the early diagnosis and treatment of delayed arrhythmic events following TAVR. A recent scientific expert panel focusing on CDs after TAVR proposed a tailored postprocedural management on the basis of baseline and post-TAVI electrocardiography, recommending the use of AECG monitoring in specific subsets such as patients with new ECG CDs post TAVI or baseline RBBB (296). However, such a strategy lacks prospective validation. On the other hand, the use of continuous monitoring

may lead to some degree of overdiagnosis of rhythm disorders and in some cases could lead to controversial PPM implantation. To date, the use of post-TAVI AECG monitoring is in its infancy and therefore there is no robust evidence to be able to give solid recommendations. The specific diagnosis between distal versus proximal atrioventricular block can be difficult in this context and therefore each case must be individualized.

The present thesis focuses on some of the unresolved issues in the field of late arrhythmic disorders after TAVI, with special attention to late CDs. First, scarce data reported the long-term ECG and clinical evolution of patients without significant ECG changes after the TAVI procedure. Second, some issues remain unsolved in patients with new-onset LBBB (i.e., predictors of PPM implantation and LBBB regression at follow-up, the timing of late arrhythmic disorders using continuous ACG monitoring). Finally, the use of continuous AECG may partially overcome the clinical dilemma between early discharge after TAVI and delayed arrhythmic disorders.

HYPOTHESIS AND OBJECTIVES

I. HYPOTHESIS.

I.I. General hypothesis

The occurrence of late arrhythmic disorders after TAVI has a significant clinical impact with important implications regarding the overall management of TAVI patients after the procedure.

I.II. Specific hypothesis

1. Patients without ECG conduction disturbances post-TAVI have excellent clinical outcomes at long-term follow-up.

2. No predictive factors associated with the resolution of new-onset LBBB during follow-up have been identified in TAVI recipients and this may impact its clinical management.

3. The arrhythmic burden in new-onset LBBB patients using continuous ECG recording will predominate in the early phase post-discharge.

4. Late cerebrovascular events (>30 days) post-TAVI may impact clinical outcomes. Their predictors including their potential relationship with late arrhythmic disorders have not been studied.

5. Non-invasive ECG continuous monitoring in all TAVI patients is safe and would be useful to diagnose and facilitate the early implementation of specific therapeutic measures.

II. OBJECTIVES

II.I. General objectives

The main objectives of my PhD project are: (i) to assess the incidence and clinical impact of late arrhythmic disorders (post-discharge) in TAVI recipients (ii) to demonstrate the safety and usefulness of non-invasive continuous ECG monitoring post-TAVI.

II.II. Specific objectives

1. To determine the clinical and ECG manifestations in patients without ECG changes post-procedure, comparing patients with normal ECG and those with ECG-conduction disturbances.

2. To assess, in patients with new-onset LBBB, the factors associated with LBBB resolution during follow-up.

3. To determine the arrhythmic burden at 2-years in new-onset LBBB patients using continuous ECG monitoring.

4. To determine the incidence, predictors, and outcomes of late cerebrovascular events (>30 days post-procedure) following TAVI and their potential relationship with arrhythmic disorders post-TAVI.

5. To determine the safety and usefulness of non-invasive ECG continuous monitoring in all TAVI patients after discharge to diagnose late arrhythmic disorders and to facilitate the early implementation of specific therapeutic measures.

CHAPTER 1

Long-Term Electrocardiographic Changes and Clinical Outcomes of Transcatheter Aortic Valve Implantation Recipients Without New Post-Procedural Conduction Disturbances

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1.1 RÉSUMÉ

L'objectif de cette étude était de rapporter les résultats de l'électrocardiogramme (ECG) et de l'évolution clinique à long terme (>1 an) des patients sans changement significatif de leur ECG après implantation d'une valve aortique transcathéter (TAVI). Parmi les 772 patients consécutifs qui ont subi une TAVI, 397 (51%) sans nouveaux changements ECG ont été inclus, divisés selon la présence de troubles de la conduction ECG préexistants (TC-ECG vs non-TC-ECG). Le taux d'implantation d'un stimulateur cardiaque au cours du suivi (médiane: 35 [22-57] mois) était de 3,5% dans le groupe sans TC-ECG contre 15,7% dans le groupe avec TC-ECG (p<0,001). Le groupe TC-ECG présentait un risque plus élevé d'hospitalisation pour insuffisance cardiaque, mais pas d'excès de mortalité lors du suivi. En conclusion, la présence de ECG-TC préexistant était associé à un risque accru de PPM et d'hospitalisation à long terme. Ces résultats soulignent l'importance d'un suivi plus étroit chez les patients avec TC-ECG.

1.2 ABSTRACT

The objective of this study was to determine the long-term (>1 year) electrocardiographic (ECG) and clinical outcomes of patients without significant changes in their ECG after transcatheter aortic valve implantation (TAVI) (including patients with preexisting ECG abnormalities). Among 772 consecutive patients who underwent TAVI in our institution, 397 (51%) without new ECG changes were included. TAVI patients were divided in two groups for the presence of pre-existing ECG-conduction disturbances (ECG-CD: 140 patients, non-ECG-CD: 257 patients). Clinical follow-up (median: 35 [22-57] months) was complete in all patients but 5 (1.3%), and ECG data were available in 291 patients (84.3% of patients at risk) at a median of 29 (20-50) months. In the non-ECG-CD group, most patients (79.8%) remained without significant ECG changes at follow-up, and 16.9% developed 1st degree atrioventricular block (1-AVB) and/or bundle branch block (BBB) over time. The rate of permanent pacemaker implantation (PPM) at follow-up was 3.5% (1.1%/year) in the non-ECG-CD group vs. 15.7% (5.5%/year) in the ECG-CD group ($p<0.001$). The presence of pre-existing CD was an independent predictor of PPM at follow-up (HR: 3.97, 95% CI: 1.87-8.42, $p<0.001$). The ECG-CD group exhibited a higher risk of heart failure (HF) hospitalization (non-ECG-CD: 25%, ECG-CD: 29%, log-rank $p = 0.01$), but not mortality (non-ECG-CD: 50%, ECG-CD: 46%, log-rank $p=0.60$) at 5-year follow-up. In conclusion, the ECG remained unchanged in most TAVI recipients without new post-procedural CD. Pre-existing ECG-CD was associated with an increased risk of PPM and HF hospitalization at long-term follow-up. These results provide reassuring data in the era of TAVI expanding towards candidates with a longer life expectancy, and highlight the importance of a closer follow-up of those patients with pre-existing ECG-CDs.

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1.3. INTRODUCTION

The implications of conduction disturbances (CDs) post-TAVI have been largely evaluated (145,296), but data regarding the long-term (>1 year) electrocardiographic (ECG) and clinical outcomes in patients without ECG changes after the procedure is scarce. While some studies showed reassuring data in patients with narrow QRS after the procedure, the follow-up has been limited to the early post-TAVI period (231,232,323). In addition, poorer outcomes have been reported in patients with baseline right bundle branch block (RBBB) or left bundle branch block (LBBB) (324,325). However, there is a lack of information regarding ECG changes over time in patients with normal or abnormal baseline ECG and without significant changes after the procedure. Thus, it remains unknown whether the mechanical interaction between the transcatheter valve and the conduction system could translate into late and very late ECG changes with potential clinical consequences. The aim of our study was to determine the long-term ECG and clinical outcomes of TAVI recipients without ECG changes related to the procedure.

1.4. METHODS

The flowchart of the study population is shown in **Figure 1.1**. A total of 772 consecutive patients underwent TAVI at our institution between May 2007 and November 2016. Patients with periprocedural death, permanent pacemaker (PPM) prior or after the procedure (during initial hospitalization), and patients with new CDs post-TAVI (*de novo* first-degree atrioventricular block [1-AVB] or complete bundle branch block [BBB]) were excluded, leading to a population of 402 patients without significant new ECG changes between baseline and hospital discharge. Of these, 397 patients completed a clinical follow-up > 1 year (5 patients lost to follow-up, 1.2%). A total of 46 patients died during the first year after TAVI. Among those patients that survived >1 year, 291 patients (84.3% of patients at risk) had an ECG at a median follow-up of 29 (IQR: 20-50) months post-TAVI.

Patients were divided in two groups according to the presence of pre-existing CDs: ECG-conduction disturbances (ECG-CD) *versus* non-ECG-conduction disturbances (Non-ECG-CD) according to baseline ECG analysis. ECG-CD were classified as follows: 1) first degree atrioventricular block (1-AVB), defined as a PR interval > 200 ms; 2) complete bundle branch block (BBB), defined as a QRS duration ≥120 ms and further

classified as LBBB, RBBB or nonspecific intraventricular conduction disturbance (NIVCD). All ECG analysis were performed according to the American Heart Association, American College of Cardiology Foundation, and Heart Rhythm Society recommendations for standardization and interpretation of the ECG (170). Patients with 1°AVB and/or complete BBB were included in the ECG-CD group, and the rest of patients represented the non-ECG-CD group.

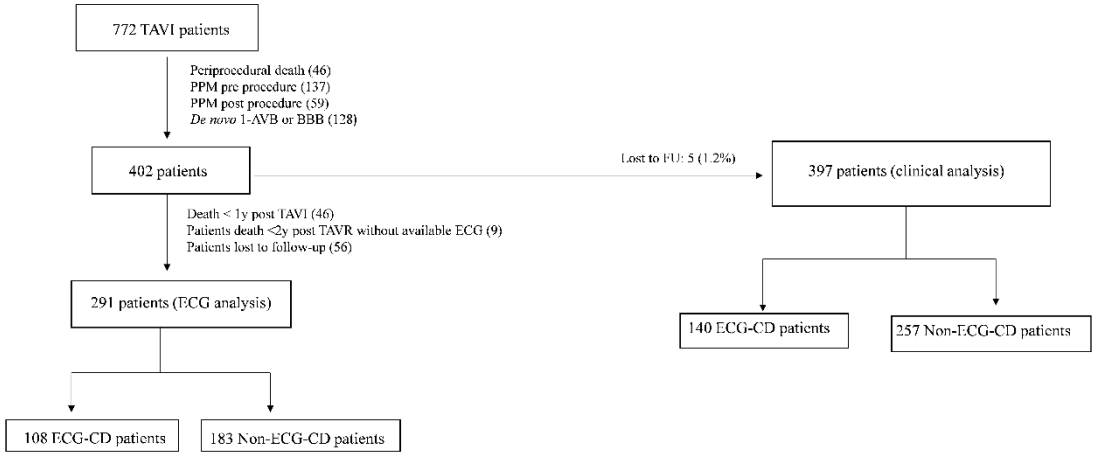

Figure 1.1. Flow chart of the study population.
TAVI: Transcatheter aortic valve implantation. PPM: Permanent pacemaker. 1-AVB: First-degree atrioventricular block. BBB: Bundle Branch Block. FU: Follow up. ECG: Electrocardiogram. CD: Conduction disturbances.

Baseline, procedural and follow-up data were prospectively collected in a TAVI dataset. Clinical follow-up was performed by clinical visits (with ECG acquisition) and/or through telephone contact at 1-, 6-, and 12-months' post-procedure, and yearly thereafter. In patients with phone contact follow-up (usually due to long distance between the hospital and patient's home), an ECG was requested at the center closest to patient's home. Clinical events were defined according to the Valve Academic Research Consortium 2 (VARC 2) criteria (326).

Qualitative variables were reported as percentages and continuous data as mean (standard deviation) or median (interquartile range [IQR]), depending on variable distribution. Continuous variables were compared using t test (2-tailed) or Mann-Whitney rank sum tests as appropriate. Qualitative variables were compared with chi-square or

Fisher exact tests. A paired t-test was used to compare PR and QRS duration between discharge and last ECG at follow-up. Survival curves were summarized using Kaplan-Meier estimates, and long-rank tests were used to compare groups. A Cox multivariate regression analysis was performed to identify independent predictors of PPM during follow up. Variables with clinical interest and p value < 0.05 on univariable analysis were entered in the multivariable analysis. A 2-sided alpha level of 0.05 was used for all statistical testing. All statistical analyses were performed using the statistical package STATA version 14.0 (StataCorp, College Station, Texas).

1.5. RESULTS

Baseline and periprocedural characteristics of the study population according to the presence of pre-existing ECG abnormalities are shown in **Table 1.1**.

Table 1.1 Baseline and periprocedural characteristics according to the presence of ECG-conduction disturbances.

	Overall (n=397)	**Non-ECG-CD (n=257)**	**ECG-CD (n=140)**	**p Value**
Variable				
Baseline characteristics				
Age (years)	78 +/-9	77 +/-9	79+/-8	0.04
Female	206 (51.9%)	142 (55.3%)	64 (45.7%)	0.07
Hypertension	336 (84.6%)	212 (82.9%)	124 (88.6%)	0.11
Diabetes mellitus	128 (32.2%)	87 (33.9%)	41 (29.3%)	0.35
Chronic obstructive pulmonary disease	116 (29.2%)	73 (28.4%)	43 (30.7%)	0.63
Peripheral artery disease	123 (31.0%)	78 (30.4%)	45 (32.1%)	0.71
Cerebrovascular disease	62 (15.6%)	35 (13.6%)	27 (19.3%)	0.14
Coronary artery disease	261 (65.7%)	166 (64.6%)	95 (67.9%)	0.51
Previous cardiac surgery	166 (41.8%)	105 (40.9%)	61 (43.6%)	0.60
Chronic renal disease (estimated glomerular filtration rate <60 mL/min)	210 (52.9%)	136 (52.9%)	74 (52.9%)	0.99
Creatinine (mmol/L)	98 (79-123)	97 (77-120)	99 (80-129)	0.28
Hemoglobin (g/L)	116.9 +/-16	115.9 +/-15	118.7+/-17	0.10
Atrial fibrillation or flutter	103 (25.9%)	70 (27.2%)	33 (23.6%)	0.43

Porcelain aorta	91 (23.0%)	66 (25.9%)	25 (17.9%)	0.07
Society of Thoracic Surgeons Predicted Risk of Mortality (%)	5.4 (3.6-8.2)	5.1 (3.3-7.9)	6.22 (4.1-9.3)	0.01
Beta blocker treatment	137 (34.8%)	92 (36.2%)	45 (32.1%)	0.42
Calcium channel blockers	24 (6.1%)	21 (8.2%)	3 (2.1%)	0.02
Amiodarone treatment	17 (4.3%)	11 (4.3%)	6 (4.3%)	0.98
Digoxin treatment	10 (2.5%)	7 (2.8%)	3 (2.1%)	1
Echocardiography at baseline				
Left ventricular ejection fraction <50%	103 (25.9%)	41 (16.0%)	62 (44.3%)	<0.001
Mean aortic gradient (mmHg)	41 (31-52)	43 (32-54)	37 (30-48)	0.004
Aortic valve area (cm^2)	0.65 (0.51-0.8)	0.64 (0.5-0.8)	0.67 (0.54-0.8)	0.27
Aortic Regurgitation >2	65 (16.5%)	42 (16.5%)	23 (16.6%)	0.98
Mitral Regurgitation >2	76 (19.2%)	53 (20.8%)	23 (16.4%)	0.29
Pulmonary artery systolic pressure (mmHg)	40 (31-51)	40 (31-50.5)	38 (32-51)	0.98
Procedural characteristics				
Valve-in-Valve	51 (12.9 %)	34 (13.2%)	17 (12.1%)	0.76
Primary access				
Transfemoral	211 (53.2%)	131 (51.0%)	80 (57.1%)	0.24
Non-transfemoral	186 (46.6%)	126 (49.0%)	60 (42.9%)	
Predilatation	307 (77.3%)	200 (77.8%)	107 (76.4%)	0.75
Valve type				
Balloon-Expandable	343 (86.6%)	226 (88.3%)	117 (83.6%)	0.19
Self-Expandable	53 (13.4%)	30 (11.7%)	23 (16.4%)	
Mean area oversizing (%)	11.1 +/-12.8	12.4 +/-12.8	8.9 +/-12.7	0.08
Echocardiography post procedure				
Mean valve gradient (mmHg)	11 (8-14)	11 (8-15)	10 (8-13)	0.18
Aortic valve area (cm^2)	1.4 (1.2-1.8)	1.4 (1.2-1.7)	1.45 (1.2-1.8)	0.16
Aortic Regurgitation >2	18 (4.7%)	11 (4.5%)	7 (5.2%)	0.75

Values are mean ± SD, median and interquartile range or n (%).

The main ECG changes over time in the non-ECG-CD and ECG-CD groups are summarized in **Figure 1.2**. In the non-ECG-CD group, most patients (146/183, 79.8%) remained without significant changes in the ECG. A total of 17 patients (9.3%) and 19 patients (10.4%) developed 1-AVB and BBB, respectively. Of these, 5 patients (2.7%) had both 1-AVB and BBB at follow-up. In patients with new BBB; LBBB, RBBB and NIVCD occurred in 14 (7.7%), 3 (1.6%), and 2 (1.1%) patients, respectively.

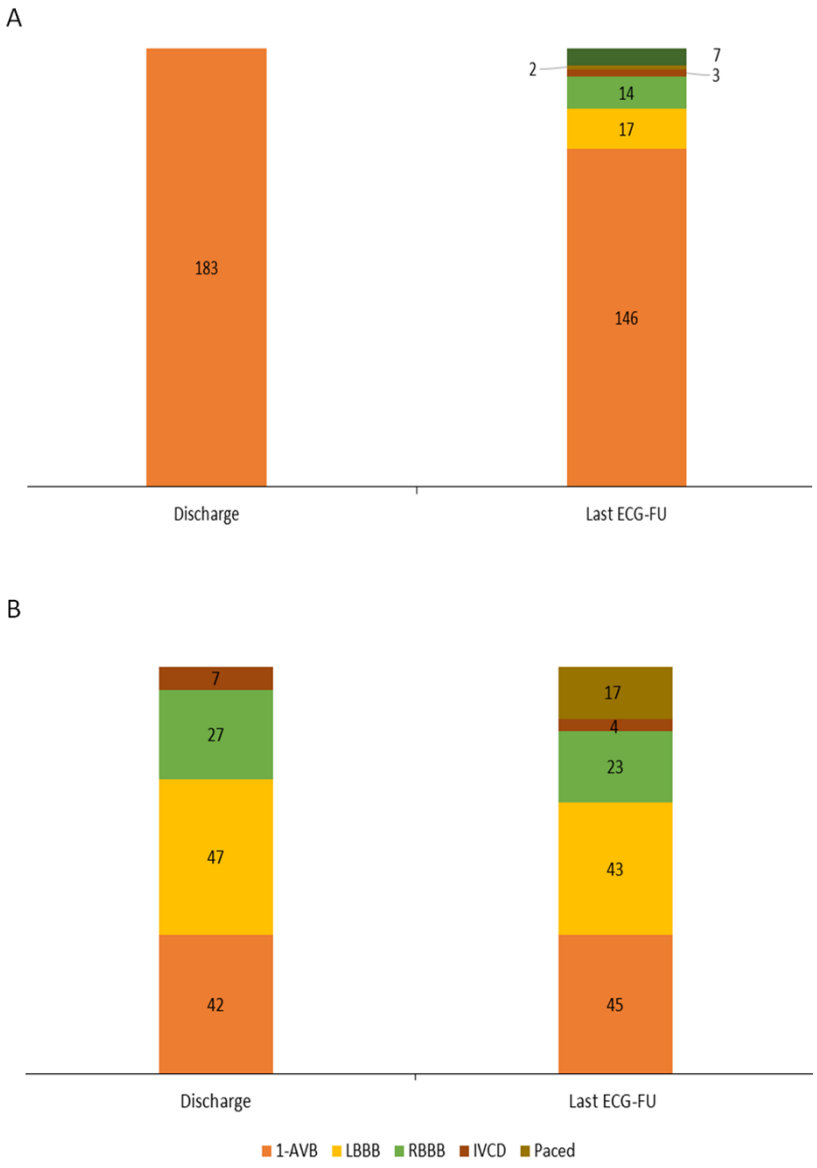

Figure 1.2. ECG at follow-up according to the presence of ECG conduction disturbances pre-TAVI.
A. Non-ECG-CD patients. **B.** ECG-CD patients.
1-AVB : First-degree atrioventricular block. LBBB: Left bundle branch block. RBBB: Right bundle branch block. NIVCD: nonspecific intraventricular conduction disturbance.

Overall, there was a mild but significant increase in mean PR and QRS duration at follow-up (p<0.01 for both) (**Figure 3.1**). A PPM was implanted in 9 patients (3.5%) during follow-up, with an annual PPM rate of 1.1% per year. PPM was implanted at a median time of 33 months [IQR: 14 to 40 months]), and the reason was high-degree or complete heart block in 5 patients, severe bradycardia in 2 patients and AV node ablation due to rapid atrial fibrillation in 2 patients. The PPM rate related to severe bradyarrhythmias was 2.7% (0.8% /year).

In the ECG-CD group, 80 patients (91%) remained with similar ECG findings at last ECG recording, and 3 cases exhibited a resolution of ECG abnormalities at follow-up. Overall, there was a modest but significant increase in PR and no statistically significant changes in QRS duration over time (**Figure 1.3**).

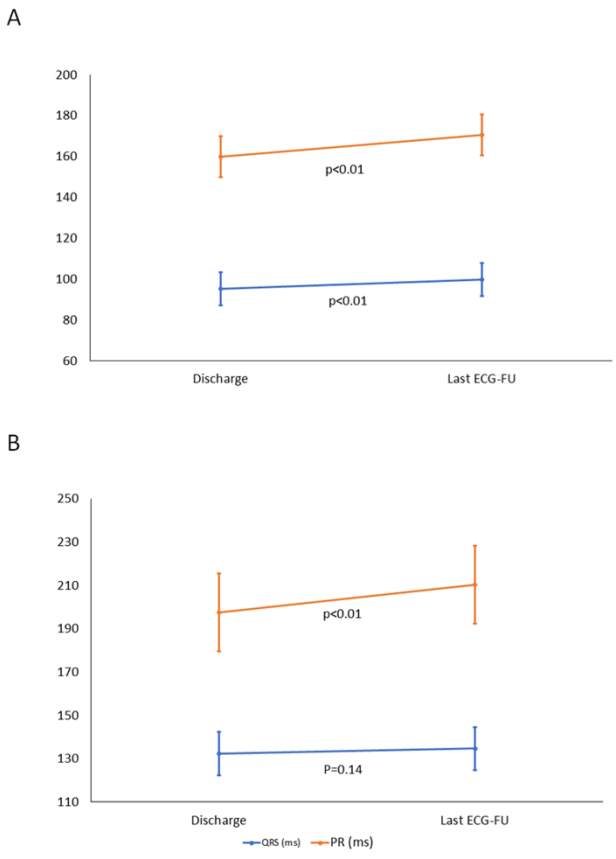

Figure 1.3. Changes in PR and QRS duration over time.
A. Non-ECG-CD patients. B. ECG-CD patients

A total of 22 patients (15.7%) had PPM implantation, with an annual PPM rate of 5.2%. PPM was implanted at a median time of 14 months post-TAVI (IQR: 8 to 26

months). High-degree or complete heart block was the PPM indication in 19 patients (86.4%) and severe bradycardia in 1 patient (4.5%). Two patients (9.1%) received a PPM in the setting of cardiac resynchronization therapy. The PPM rate due to severe bradyarrhythmias was 14.3% (4.8%/year). Patients in the ECG-CD exhibited a higher rate and earlier PPM implantation over time (15.7%; PPM related to severe bradyarrhythmias: 90.1%) compared to non-ECG-CD group (3.5%; PPM related to severe bradyarrhythmias: 77.8%), p<0.001.

The Kaplan-Meier curves for PPM implantation up to 5-year follow-up are shown in **Figure 1.4**.

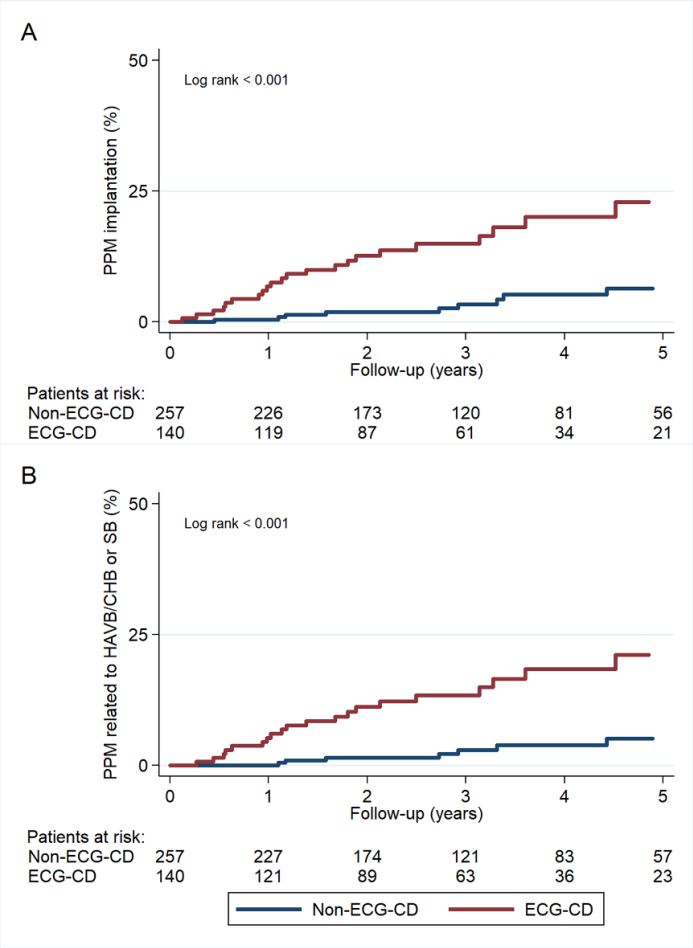

Figure 1.4. Kaplan-Meier curves at 5-year follow-up for PPM implantation according to the presence of ECG-CD.
A. All PPM.
B. PPM related to HAVB/CHB or SB.
PPM: Permanent pacemaker. HAVB/CHB: High-degree atrioventricular block/complete heart block. SB: Severe bradycardia.

The uni- and multivariable analyses for determining factors associated with PPM at follow up are shown in **Table 1.2**. The single independent predictor of PPM at follow-up was the presence of pre-existing ECG-CD (HR: 3.97; 95% CI: 1.87-8.42, p<0.001).

Table 1.2. Predictors of PPM implantation during follow-up

	Univariate model		Multivariate model	
	HR (95%CI)	**p Value**	**HR (95%CI)**	**p Value**
Left ventricular ejection fraction <50%	2.30 (1.13-4.66)	0.02	-	-
Self-Expandable Valve	2.40 (1.02-5.62)	0.04	2.15 (0.92-5.06)	0.08
Electrocardiographic conduction disturbances	4.82 (2.22-10.48)	<0.001	4.67 (2.15-10.16)	<0.001

The Kaplan-Meier curves for clinical outcomes (heart failure [HF] hospitalization, cardiovascular mortality, all-cause mortality) at 5-year follow-up are shown in **Figure 1.5**.

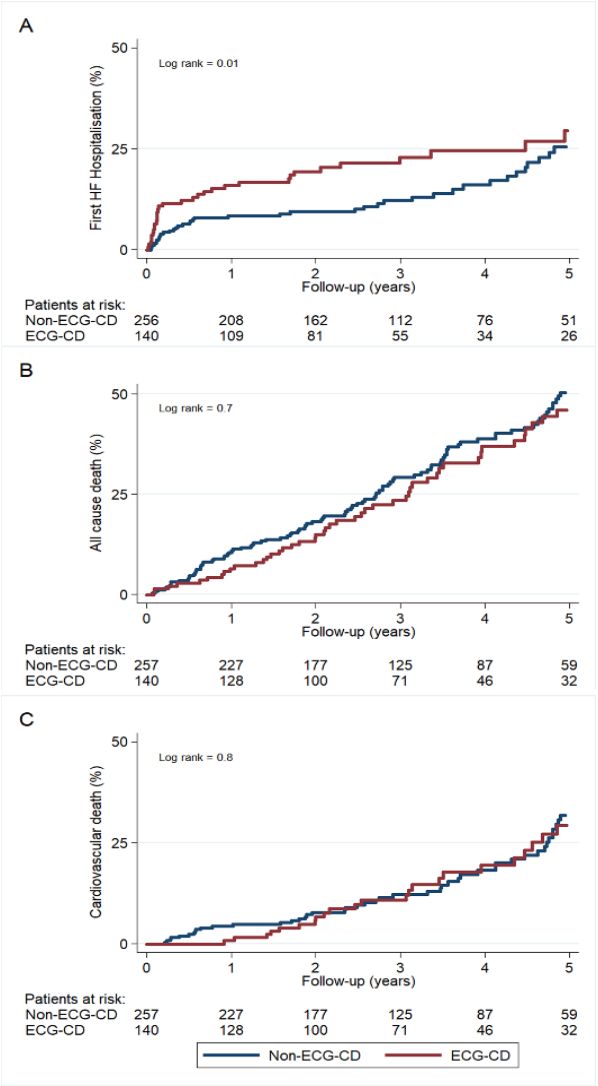

Figure 1.5. Figure 5. Kaplan-Meier curves at 5-year follow-up for mortality and heart failure hospitalization according to ECG-CD. A. Heart failure hospitalization. B. All-cause mortality. C. Cardiovascular mortality. PPM: Permanent pacemaker. HAVB/CHB: High-degree atrioventricular block/complete heart block. SB: Severe bradycardia.

1.6. DISCUSSION

The present study provided, for the first time, long-term ECG data in those patients without new CDs in the post-procedural TAVI period. In those patients without pre-existing CDs, most patients remained without significant ECG changes after a mean follow-up of 2 years. This suggests a lack of a late significant interaction between the transcatheter valve and the conduction system late (within the weeks-months) and very late (years) after the procedure. Also, the rate of advanced CDs requiring PPM was low (3.5% at 5-year follow-up), with PPMs being implanted at a median time of about 3 years post-TAVI, which would reflect the spontaneous occurrence, unrelated to TAVI, of conduction abnormalities in an elderly population with multiple risk factors for PPM. In a population-based observational study, Bradhsaw et al (327) reported an annual incidence of PPM of ~0.5% in elderly people (≥75 years), a rate slightly lower than that observed in our study. However, it is known that the presence of calcific aortic stenosis can have a deleterious effect on the conduction system (180), likely contributing to the mild increased rate of CDs within the years following the TAVI procedure in those patients with normal ECG. Overall, our findings add reassuring data regarding the safety of transcatheter heart valves at long-term follow-up. Some studies with short-term follow up (up to 30 days) suggested that early discharge post-TAVI was safe in patients without ECG-CD (231,232,323). However, only 1 previous study provided data beyond 30 days (328), showing the lack of any episodes of HAVB/CHB (high-degree atrioventricular block/complete heart block) at 10-month follow-up. Our data confirm the good outcomes at long-term follow-up regarding HAVB/CHB in this group of patients. Interestingly, the median time of advanced CDs leading to PPM was >2 years post-TAVI, suggesting a spontaneous progression of conduction abnormalities related to the ageing of the population as underlying mechanism, and no direct relationship with the TAVI procedure. On the other hand, new-onset 1-AVB and LBBB appeared in 9.3% and 7.6% patients, respectively, at follow-up. Previous data in this field are scarce and limited to the occurrence of new-onset LBBB between discharge and 12 months post-TAVI, showing an incidence that ranges from 0 to 2.9% (222,226,329).

The presence of pre-existing ECG-CD (even in the absence of ECG changes post-TAVI) was associated with an increased risk of HAVB/CHB at follow-up. Thus, the overall PPM rate at 5-year follow-up was 15.6% (5.3% per year), 14.3% when considering only PPM related to severe bradyarrhythmias (4.8% per year), a rate about 4

times higher than the annual rate observed in non-ECG-CD patients. This annual PPM incidence is also much higher than the 1-2% annual rate reported in non-TAVI patients with BBB (330,331). This, along with the fact that PPM was implanted within the 1st year post-TAVI in a significant proportion of patients (median time of PPM: 14 months), suggest a potential delayed negative effect of the transcatheter valve in this group. Among the patients with ECG-CD and PPM implantation during follow up, LBBB, RBBB, NIVCD and isolated 1-AVB were present at discharge in 32%, 36%, 14% and 20% of patients, respectively.

In the TAVI field, only a few previous studies reported outcomes in patients with baseline BBB (RBBB or LBBB) (324,325). Fischer et al evaluated the impact of previous LBBB, showing a higher cumulative rate of PPM at 20-month follow-up (325). However, there were no differences in PPM rate after excluding the initial 30-day period. Auffret et al determined the impact of RBBB on late outcomes post-TAVI, showing an increased risk (>2 times) of the composite of sudden death or PPM among RBBB-TAVI recipients (324). These results agree with those observed in our study and suggest that a closer follow-up, probably with continuous ECG monitoring systems, should probably be implemented in TAVI recipients with pre-existing BBB (particularly RBBB).

Previous studies have shown the negative impact of BBB (particularly LBBB) on left ventricular function and HF hospitalization in non-TAVI and TAVI patients (239–241,332,333). In accordance with these results, our study showed a higher risk of HF hospitalization at follow-up among TAVI recipients with pre-existing CDs. This highlights the importance of a systematic implementation of optimal medical/device HF therapies (including cardiac resynchronization) in such patients within the months following TAVI (334,335). Despite an increased rate of HF hospitalization in ECG-CD patients, there were no differences in mortality between ECG-CD and non-ECG-CD groups. Several reasons may explain this finding. First, the relatively small sample of the study may have limited this analysis. Second, our study mixed patients with baseline RBBB and LBBB. Previous data have shown poorer hard outcomes in TAVI patients with baseline RBBB (324), but this finding has not been confirmed in patients with baseline LBBB (325). Finally, our study focused on patients without changes between pre- and post-procedure ECG. Patients at higher risk such as those with periprocedural death and with new-onset CDs were excluded. The latter may have selected a cohort where hard endpoints such as mortality were more balanced than expected between the two groups.

This study has some limitations. Although data were recorded prospectively, this analysis was of retrospective nature. No event adjudication was done, nor echocardiographic and ECG core laboratories available. Finally, this was a single center study with a relatively small sample size, which could have restricted the analysis of hard endpoints as mortality.

1.7. ACKNOWLEDGMENTS

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CHAPTER 2

Late Electrocardiographic Changes in Patients with New-Onset Left Bundle Branch Block Following Transcatheter Aortic Valve Implantation

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2.1. RESUMÉ

L’objectif était de déterminer, chez les patients TAVI présentant un bloc de branche gauche persistant *de novo* (BBG-P), l'incidence et les facteurs associés à: (i) récupération du BBG-P et (ii) implantation d'un cardiostimulateur permanent (CP) à 1 an. Étude multicentrique incluant 153 patients. Une récupération du BBG-P a été observée chez 50 patients (33 %) et 14 patients (9 %) ont nécessité un CP. Aucune variable n'a été associée à la récupération du BBG-P. La fibrillation auriculaire au départ et un PR plus long à la sortie de l'hôpital étaient associés à un risque de CP. En conclusion, le BBG-P post-TAVI s'est résolu chez un tiers des patients lors du suivi à 1 an. Aucune variable clinique ou ECG n'était associée à la récupération du BBG-P. À l'inverse, un rythme non sinusal au départ et un PR plus long étaient associés à un risque accru d'implantation de CP.

2.2. ABSTRACT

This study sought to determine, in patients with new-onset persistent left bundle branch block (NOP-LBBB) after transcatheter aortic valve implantation (TAVI), the incidence and factors associated with (i) LBBB recovery and (ii) permanent pacemaker implantation (PPI) at 1-year follow-up. This was a multicenter study including 153 patients (mean age: 81±5 years, 56% of women) with NOP-LBBB post-TAVI (balloon-expandable valve in 112 patients). Delta PR (ΔPR) and delta QRS (ΔQRS) were defined as the difference in PR and QRS length between baseline and hospital discharge ECG, and the relative ΔPR and ΔQRS as absolute ΔPR and ΔQRS divided by baseline PR and QRS length, respectively. The patients had a clinical visit and 12-lead ECG at 1-year follow-up. LBBB recovery was observed in 50 patients (33%) and 14 patients (9%) had advanced conduction disturbances requiring PPI during the follow-up period. No clinical or ECG variables were associated with LBBB recovery, including prosthesis type (self- or balloon-expandable valve, p=0.563), QRS width at baseline/discharge or absolute/relative ΔQRS (p>0.10 for all). The presence of atrial fibrillation at baseline (0.026), a longer PR interval at discharge (0.009) and a longer absolute and relative ΔPR (p=0.002 and p=0.004, respectively) were associated with an increased risk of PPI at 1-year follow-up. In conclusion, NOP-LBBB post-TAVI resolved in one third of patients at 1-year follow-up, but no clinical or ECG variables were associated with LBBB recovery. Conversely, a non-sinus rhythm at baseline and a longer ΔPR were associated with an increased risk of PPI within the year after TAVI.

2.3. INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is projected to expand towards the treatment of lower risk patients in the near future (153,154,336). However, the occurrence of conduction disturbances remains the most frequent drawback of the procedure (145,153,154). New-onset persistent left bundle branch block (NOP-LBBB) occurs in about 25% of TAVI procedures (145), and it has been associated with an increased risk of advanced CD requiring permanent pacemaker implantation (PPI) (145,227). In addition, LBBB may induce a reduction of ventricular function (337–339). Current guidelines state that PPI may be considered in patients with NOP-LBBB post-TAVI (173), and some authors suggested that cardiac resynchronization therapy (CRT) could confer some benefit (171). However, about one third of post-procedural NOP-LBBB abnormalities recover and only about 10% exhibit a progression towards advanced CD within the months post-TAVI (321). Determining the factors associated with the regression-progression of NOP-LBBB would be key to optimize the management of such patients. We aimed to determine, in patients with NOP-LBBB post-TAVI, the factors associated with (i) ECG recovery, and (ii) progression towards advanced CD requiring PPI within the year following the procedure.

2.4. METHODS

This multicenter study included 153 patients with NOP-LBBB after TAVI with either the self-expanding CoreValve/Evolut R system (Medtronic, Dublin, Ireland) or the balloon-expanding SAPIEN XT/3 valve (Edwards Lifesciences, Irvine, CA) between 2007 and 2018. Patients were on continuous ECG monitoring during the hospitalization period (or at least the first 72h), and a 12-lead ECG was performed daily until hospital discharge in all patients. NOP-LBBB was defined as a new LBBB that occurred peri-procedurally and persisted at day 3 following the procedure. ECG interpretation and intraventricular CD definitions followed the ACC/AHA/HRS guidelines(170). Patients with prior PPI or complete bundle branch block, PPI during the TAVI hospitalization, and a follow-up <12 months were excluded. Data were collected in accordance to the ethics committee of each participating center, and all patients provided signed informed consent for the procedures. A total of 98 patients had been part of the MARE trial (321).

LBBB recovery was based on 12-lead ECG findings at 1-year follow-up. If complete LBBB or a paced rhythm was found at 1-year ECG, patients were considered as no-LBBB recovery. PPI during the follow-up period was indicated if third-degree or advanced second-degree atrioventricular block occurred or in the presence of sinus node dysfunction and documented symptomatic bradycardia, as recommended by current guidelines (173,340).

An exploratory analysis was performed in 37 patients with post-TAVI angiography available to investigate a potential relationship between transcatheter valve implantation depth and LBBB recovery. Implantation depth was determined on the basis of post-implantation aortography and was defined as the average distance from the native aortic annulus plane to the most proximal edge of the implanted prosthesis, as previously described (245).

Qualitative variables were expressed as number (percentage), and continuous data as mean (standard deviation) or median (interquartile range [IQR]) according to variable distribution. Categorical variables were compared using the chi-square or Fisher exact test as appropriate. Numerical variables were compared using the Student t-test or U Mann-Whitney non-parametric test according to their distribution (assessed by the Kolmogorov-Smirnov test). Comparison of QRS width measured at different time points was performed using the Wilcoxon signed-rank test. Receiving-operating characteristic (ROC) curves were used to compare abilities of QRS length at baseline/discharge and absolute/relative ΔQRS to predict LBBB recovery. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA) and Prism version 8.1.2 (GraphPad Software, San Diego, CA, USA).

2.5. RESULTS

The main baseline, procedural and ECG data of the study population are shown in **Table 2.1**. The median age of the patients was 81 (IQR: 76 to 85) years and the median STS-PROM was 5.2% (IQR: 3.2% to 7.7%). A total of 71 patients (47%) received beta-blocker therapy and 37 (24%) had a history of atrial arrhythmias. Most procedures (71%) were performed through transfemoral approach and 112 patients (73%) received a balloon-expanding valve, whereas 41 patients (27%) received a self-expanding valve.

Most patients (86%) were on sinus rhythm at baseline. A 1st degree atrioventricular block (AVB) was identified in 35 patients (27%) and the median QRS duration at baseline was 92 msec (IQR: 80 to 100 msec). Absolute and relative ΔQRS were 50 msec (IQR: 40 msec to 60 msec) and 55% (IQR: 40% to 71%), respectively.

Table 2.1. Baseline, Procedural and ECG Characteristics of the Study Population

Baseline variables	
Age, years	81 (76-85)
BMI, kg/m^2	27.2 (23.8-30.0)
Women	86 (56.2)
Hypertension	133 (86.9)
Diabetes mellitus	72 (47.1)
CKD	62 (42.2)
Previous CAD	75 (49.0)
STS-PROM, %	5.2 (3.2-7.7)
Beta-blocker	71 (46.4)
Digoxin	6 (3.9)
Calcium-blocker	55 (36.0)
Amiodarone	2 (1.3)
LVEF, %	60 (55-61)
Mean AV gradient, mmHg	42 (35-50)
AV area, cm^2	0.70 (0.54-0.84)
Procedural characteristics	
Trans-femoral approach	108 (70.6)
Valve-in-valve	17 (11.3)
Pre-dilatation	80 (52.6)
Self-expanding valve	41 (26.8)
New-generation valves	
SAPIEN 3	49 (32.0)
Evolut R	28 (18.3)
Post-dilatation	30 (19.6)
New-onset AF	20 (13.1)
Baseline ECG	
Sinus rhythm	132 (86.3)
PR interval, msec	178 (159-200)
1st degree AVB (n=132)	35 (26.5)
QRS width, msec	92 (80-100)
QRS morphology:	
Normal	112 (73.1)
Incomplete LBBB	28 (18.3)
Incomplete RBBB	1 (0.7)
Anterosuperior hemiblock	8 (5.2)
Inferoposterior hemiblock	1 (0.7)
Non-specific disturbances	3 (2.0)
Discharge ECG	
Sinus rhythm	128 (83.7)

PR interval, msec	190 (165-212)
1st degree AVB (n=128)	54 (42.2)
Absolute ΔPR, msec	10 (0-33)
Relative ΔPR, %	6 (0-21)
QRS width, msec	140 (130-152)
Absolute ΔQRS, msec	50 (40-60)
Relative ΔQRS, %	55 (40-71)

AF: Atrial fibrillation; AV: Aortic valve; AVB: Atrio-ventricular block; BMI: Body mass index; CAD: Coronary artery disease; CKD: Chronic kidney disease; LBBB: Left bundle branch block; LVEF: Left ventricular ejection fraction; RBBB: Right bundle branch block; STS: Society of thoracic surgeons;

Fifty patients (33%) exhibited a LBBB recovery whereas 103 patients (67%) had persistent LBBB or paced QRS at 1-year follow-up. The changes in QRS duration over time in the LBBB recovery and no-LBBB recovery groups are shown in **Figure 2.1**. The main baseline, procedural and ECG characteristics according to the occurrence of LBBB recovery are shown in **Table 2.2**.

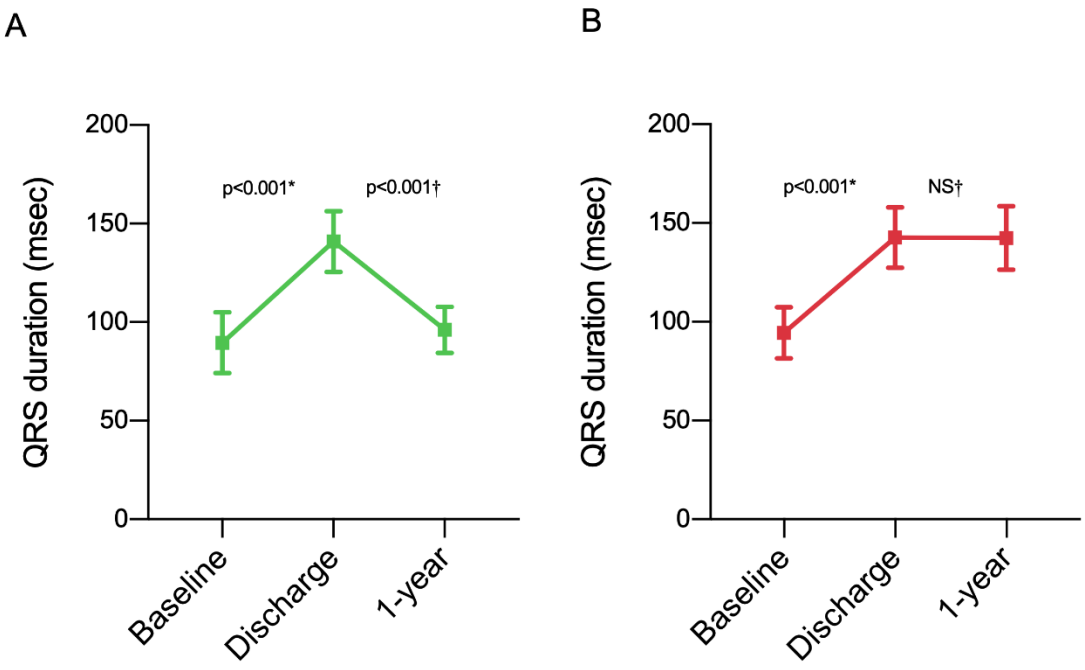

Figure 2.1. Evolution of mean ± standard deviation of QRS duration at baseline, discharge and 1-year follow-up in the "LBBB recovery" group (A) and the "no LBBB recovery" group (B).
* Discharge vs. Baseline p-value; † 1-year vs. Discharge p-value
LBBB: Left bundle branch block

Table 2.2 Baseline, Procedural and ECG Characteristics According to LBBB recovery

	No LBBB recovery (n=103)	LBBB recovery (n=50)	p-value
Baseline variables			
Age, years	81 (76-85)	82 (76-85)	0.978
BMI, kg/m^2	26.8 (23.9-29.6)	27.5 (23.2-30.2)	0.711
Women	56 (54.4)	30 (60.0)	0.603
Hypertension	90 (87.4)	43 (86.0)	0.803
Diabetes mellitus	52 (50.5)	20 (40.0)	0.233
CKD	39 (37.9)	23 (46.0)	0.286
Previous CAD	54 (52.4)	21 (42.0)	0.234
STS-PROM, %	5.0 (3.2-7.9)	5.4 (3.2-6.7)	0.797
Beta-blocker	51 (49.5)	20 (40.0)	0.303
Digoxin	4 (3.9)	2 (4.0)	1.000
Calcium-blocker	35 (34.0)	20 (40.0)	0.478
Amiodarone	1 (1.0)	1 (2.0)	0.548
LVEF, %	60 (55-60)	60 (50-65)	0.904
Mean AV gradient, mmHg	42 (35-50)	42 (35-50)	0.469
AV area, cm^2	0.70 (0.54-0.74)	0.66 (0.54-0.82)	0.639
Procedural characteristics			
Trans-femoral approach	71 (68.9)	37 (74.0)	0.574
Valve-in-valve	12 (11.7)	5 (10.0)	1.000
Pre-dilatation	52 (50.5)	28 (56.0)	0.490
Self-expanding valve	26 (25.2)	15 (30.0)	0.563
New-generation valves (n=77):			
SAPIEN 3 (n=49)	35 (70.0)	14 (51.9)	0.140
Evolut R (n=28)	15 (30.0)	13 (48.2)	
Post-dilatation	21 (20.4)	9 (18.0)	0.829
New-onset AF	14 (13.6)	6 (12.0)	1.000
Baseline ECG			
Sinus rhythm	87 (84.5)	45 (90.0)	0.456
PR interval, msec	174 (160-200)	180 (150-185)	0.328
1st degree AVB (n=132)	26 (29.9)	9 (20.0)	0.299
QRS width, msec	95 (81-104)	90 (80-100)	0.148
QRS morphology:			
Normal	76 (73.8)	36 (72.0)	0.453
Incomplete LBBB	19 (18.5)	9 (18.0)	
Incomplete RBBB	1 (1.0)	0 (0)	
Anterosuperior hemiblock	4 (3.9)	4 (8.0)	
Inferoposterior hemiblock	0 (0)	1 (2.0)	
Non-specific disturbances	3 (2.9)	0 (0)	
Discharge ECG			
Sinus rhythm	83 (80.6)	45 (90.0)	0.167
PR interval, msec	190 (165-220)	188 (170-210)	0.516
1st degree AVB (n=128)	38 (45.8)	16 (35.6)	0.349
Absolute ΔPR, msec	6 (0-36)	12 (0-32)	0.481

Relative ΔPR, %	3 (0-21)	6 (0-21)	0.504
QRS width, msec	140 (130-153)	140 (130-152)	0.629
Absolute ΔQRS, msec	50 (40-60)	55 (40-65)	0.230
Relative ΔQRS, %	52 (40-71)	60 (41-75)	0.123

AF: Atrial fibrillation; AV: Aortic valve; AVB: Atrio-ventricular block; BMI: Body mass index; CAD: Coronary artery disease; CKD: Chronic kidney disease; LBBB: Left bundle branch block; LVEF: Left ventricular ejection fraction; RBBB: Right bundle branch block; STS: Society of thoracic surgeons

There were no differences in clinical and ECG characteristics between patients with and without LBBB recovery at 1-year follow-up. In addition, ROC curve analyses showed that QRS length at baseline (area under the curve [AUC], 0.572; 95% confidence interval [CI], 0.475-0.668; p=0.151), QRS length at discharge (AUC, 0.524; 95% CI, 0.426-0.623; p=0.631), absolute ΔQRS between baseline and hospital discharge (AUC, 0.541; 95% CI, 0.446-0.634; p=0.394) and relative ΔQRS between baseline and hospital discharge (AUC, 0.549; 95% CI, 0.455-0.643; p=0.300) had no association with LBBB recovery at 1-year follow-up (**Figure 2.2**).

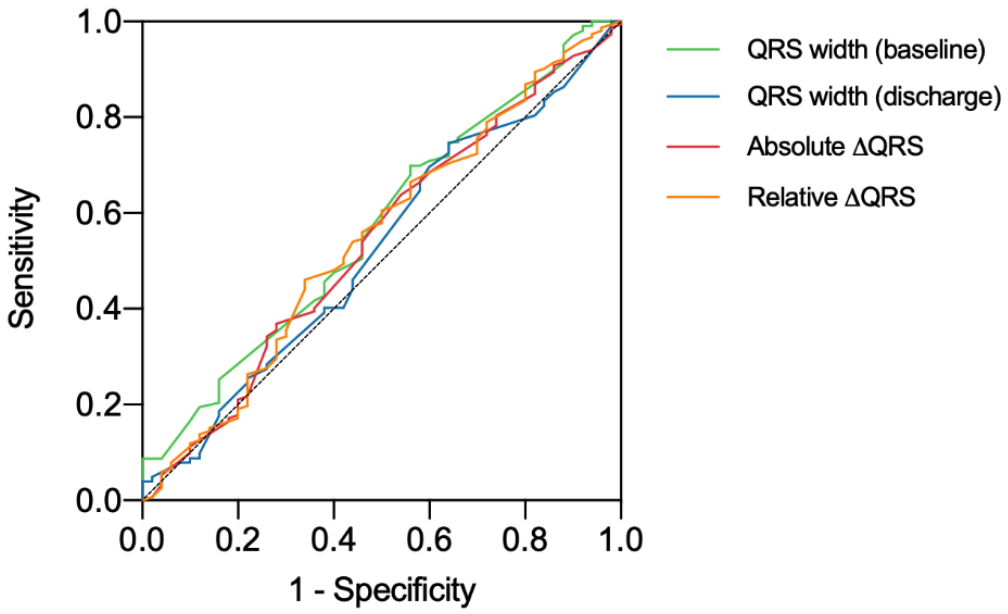

Figure 2.2. Receiving-operator characteristics curves of the QRS duration at baseline (green), QRS duration at discharge (blue), absolute QRS increase (red) and relative QRS increase (orange) to predict the LBBB recovery at 1 year.

Sub-analyses were performed in both balloon-expandable and self-expanding valve population and failed to find any factor associated with LBBB recovery (**Supplemental Table 2.1**). Of the 37 patients with angiographic data available for valve implantation depth evaluation, 15 (41%) exhibited LBBB recovery at 1-year follow up.

The mean implantation depth was 7.7 ± 5 mm and 7.6 ± 2.4 mm in the LBBB recovery and no-LBBB recovery groups, respectively (p=0.795).

A total of 14 patients (9%) had a PPI during the follow-up period (13 patients in the no-LBBB recovery group and 1 patient in the LBBB recovery group [13% vs. 2%, p=0.037]). The reasons for PPI were advanced or complete AVB in 10 patients and severe bradycardia in 4 patients. One-third of PPIs were performed within the first month following TAVI (**Figure 2.3**), and 9 patients (6% of the total population, 64% of the PPI population) presented paced QRS at 1-year ECG.

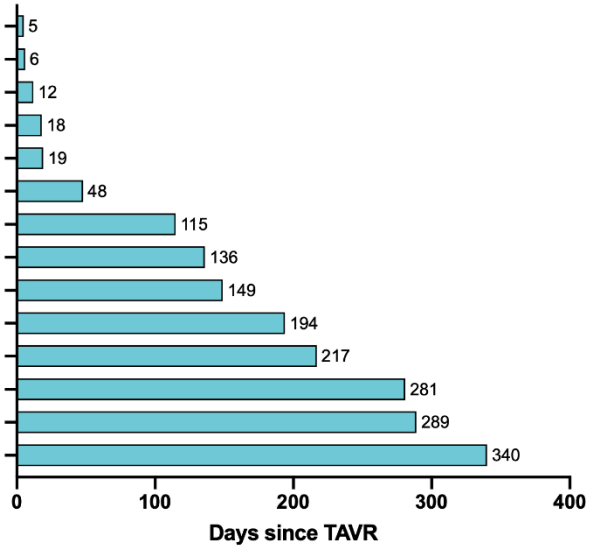

Figure 2.3. Days between TAVI and PPI.
PPI: Permanent pacemaker implantation; TAVI: Transcatheter aortic valve implantation

The main baseline, procedural and ECG characteristics according to the need of PPI during the follow-up period are shown in **Table 2.3**. A non-sinus rhythm at baseline (p=0.026), a longer PR interval at discharge and a longer absolute and relative ΔPR (p=0.009, p=0.002 and p=0.004, respectively) were associated with an increased risk of PPI. Patients who benefited from PPI within the year after TAVI had less frequent LBBB recovery than patients without PPI at follow-up (p=0.037). Finally, a sub-analysis was performed according to valve type (balloon-expandable and self-expanding) and found similar results to those obtained in the whole population analysis (**Supplemental Table 2.2**).

Table 2.3. Baseline, Procedural and ECG Characteristics According to Permanent Pacemaker Implantation

	No PPI (n=139)	PPI (n=14)	p-value
Baseline variables			
Age, years	81 (76-85)	80 (74-84)	0.551
BMI, kg/m^2	27.1 (23.8-30.0)	27.3 (24.8-31.3)	0.512
Women	80 (57.6)	6 (42.9)	0.398
Hypertension	121 (87.1)	12 (85.7)	1.000
Diabetes mellitus	67 (48.2)	5 (35.7)	0.414
CKD	54 (38.8)	8 (57.1)	0.154
Previous CAD	66 (47.5)	9 (64.3)	0.271
STS-PROM, %	5.0 (3.2-7.7)	5.4 (3.2-7.9)	0.768
Beta-blocker	64 (46.0)	7 (50.0)	0.787
Digoxin	4 (2.9)	2 (14.3)	0.095
Calcium-blocker	50 (40.0)	5 (35.7)	1.000
Amiodarone	2 (1.4)	0 (0)	1.000
LVEF, %	60 (55-62)	60 (55-60)	0.600
Mean AV gradient, mmHg	42 (35-51)	41 (36-46)	0.503
AV area, cm^2	0.77 (0.55-0.83)	0.76 (0.52-0.90)	0.312
Procedural characteristics			
Trans-femoral approach	98 (70.5)	10 (71.4)	1.000
Valve-in-valve	13 (9.4)	4 (28.6)	0.054
Pre-dilatation	73 (52.5)	7 (50.0)	1.000
Self-expanding valve	36 (25.9)	5 (35.7)	0.527
New-generation valves (n=77):	43 (63.2)	6 (66.7)	1.000
SAPIEN 3 (n=49)	25 (36.8)	3 (33.3)	
Evolut R (n=28)			
Post-dilatation	26 (18.7)	4 (28.6)	0.485
New-onset AF	18 (13.0)	2 (14.3)	1.000
Baseline ECG			
Sinus rhythm	123 (88.5)	9 (64.3)	0.026
PR interval, msec	177 (160-199)	200 (155-216)	0.241
1st degree AVB (n=132)	30 (24.4)	5 (55.6)	0.055
QRS width, msec	90 (80-100)	99 (90-105)	0.117
QRS morphology:			
Normal	104 (74.8)	8 (57.1)	0.214
Incomplete LBBB	23 (16.6)	5 (35.7)	
Incomplete RBBB	1 (0.7)	0 (0)	
Anterosuperior hemiblock	8 (5.8)	0 (0)	
Inferoposterior hemiblock	1 (0.7)	0 (0)	
Non-specific disturbances	2 (1.4)	1 (7.1)	
Discharge ECG			
Sinus rhythm	119 (85.6)	9 (64.3)	0.055
PR interval, msec	188 (165-210)	228 (200-260)	0.009

1st degree AVB (n=128)	48 (40.3)	6 (66.7)	0.166
Absolute ΔPR, msec	6 (0-30)	42 (30-48)	0.002
Relative ΔPR, %	4 (0-20)	24 (13-29)	0.004
QRS width, msec	140 (130-152)	143 (140-156)	0.191
Absolute ΔQRS, msec	50 (40-60)	48 (40-58)	0.718
Relative ΔQRS, %	56 (40-72)	50 (40-63)	0.416

AF: Atrial fibrillation; AV: Aortic valve; AVB: Atrio-ventricular block; BMI: Body mass index; CAD: Coronary artery disease; CKD: Chronic kidney disease; LBBB: Left bundle branch block; LVEF: Left ventricular ejection fraction; RBBB: Right bundle branch block; STS: Society of thoracic surgeons;

2.6. DISCUSSION

The present study is, to the best of our knowledge, the first to investigate the factors associated with LBBB recovery and progression to advanced CD requiring PPI in patients with NOP-LBBB post-TAVI. The main findings can be summarized as follows: (i) in a population of patients with NOP-LBBB post-TAVI, a LBBB recovery was observed in 33% of patients whereas 9% benefited from a PPI within the year post-TAVI; (ii) no clinical or ECG variables including prosthesis type and QRS evolution between baseline and discharge were associated with LBBB recovery; and (iii) a non-sinus rhythm at baseline and a longer ΔPR in sinus rhythm patients were associated with an increased risk of PPI within the year after TAVI.

In accordance with prior studies (222,329), NOP-LBBB recovered in about one third of patients in the present study. However, QRS width at baseline/discharge or absolute/relative ΔQRS failed to predict LBBB recovery. These findings highlight the difficulties to identify patients in whom LBBB would recover over time. This also highlights the potential limitations of electrophysiological studies performed within the days following TAVI in NOP-LBBB patients since changes in conduction properties can evolve over time. A deeper valve implantation has been shown to be a major predictor of NOP-LBBB, and the mean implantation depth >7 mm in a subset of patients from our study is in accordance with previous studies including LBBB post-TAVI patients (245,289). However, the implantation depth sub-analysis failed to show any differences between LBBB and no-LBBB recovery patients, further underscoring the complexity of ECG changes in this context. Some studies have shown significant inter-individual differences in both the septum membranous length and His bundle location (289,341),

which may translate into different mechanical interaction forces despite similar valve implantation depth. Further studies with a more detailed anatomical analysis in NOP-LBBB patients are warranted.

The use of a self-expanding valve has been associated with an increased risk of NOP-LBBB and PPI post-TAVI (145,222,230), as well as with a lower rate of conduction disturbances recovery over time. The present study including exclusively patients with NOP-LBBB post-TAVI showed that the type of valve (i.e. balloon-expandable or self-expanding) did not impact the likelihood of late PPI or LBBB recovery, and similar results were obtained in a sub-analysis including exclusively new generation devices (i.e. SAPIEN 3 and Evolut R). This finding suggests that, similar to the balloon-expanding valve systems, the mechanical interaction and potential damage of the conduction system induced by self-expanding valves occurs early post-valve implantation and does not persist during the follow-up period in most patients. This is also supported by the fact that QRS width did not increase between discharge and 1-year follow-up in the "no-LBBB recovery" group.

PR length at discharge and absolute and relative ΔPR between baseline and discharge were found to be associated with a higher risk of PPI within the year after TAVI. These results are consistent with prior studies demonstrating that 1st degree AVB (145) was associated with an increased risk of PPI post-TAVI, and that post-TAVI PR interval (231) and ΔPR between baseline and 48H post- TAVI (230) were predictors of late PPI. Of note, the increased risk of PPI in these studies was limited to the month following TAVI (230,231), whereas more than half of the advanced conduction abnormalities requiring PPI in the present study occurred after the first month post-TAVI. Careful ECG evaluation post TAVI should be performed since the absolute change in PR interval in the PPI group was only 42 ms and the median PR interval at discharge 228 ms. Also, the presence of atrial arrhythmias was associated with a higher rate of PPI within the year after TAVI in patients with NOP-LBBB. These results are in accordance with previous studies reporting a trend toward a higher rate of PPI in patients with atrial fibrillation (220,241,293). These results would support the implementation of strategies with close follow-up and ambulatory continuous cardiac monitoring after discharge in patients with NOP-LBBB post-TAVI (296), particularly in those exhibiting features of increased risk.

Given the nonrandomized nature of the study, the presence of unmeasured confounders cannot be excluded. In addition, the relatively small sample size may limit the statistical power and does not allow to perform multivariate analysis, particularly regarding the factors associated with PPI at follow-up. Finally, the sub-analysis of valve implantation depth included a small number of patients, and the results on the clinical impact of this factor on ECG changes over time should be interpreted as hypothesis generating.

Although current guidelines suggest that PPI may be considered in patients with NOP-LBBB post-TAVI (class IIb recommendation) (173), the high proportion (~90%) of patients with LBBB stability/recovery over time would not support such a recommendation particularly in patients with no change in PR interval after TAVI. In fact, a recent expert consensus document on the management of conduction disturbances post-TAVI did not recommend PPI in the majority of NOP-LBBB patients (296). On the other hand, no clinical or ECG variables (including prosthesis type and QRS evolution between baseline and discharge) were able to predict LBBB recovery, and progression from LBBB to advanced conduction disturbances requiring PPI after hospital discharge occurred in about 1 out of 10 patients. These findings highlight the importance of a close follow-up with more frequent visits and continuous ECG monitoring in those patients at increased risk (non-sinus rhythm, long ΔPR in sinus rhythm patients) (296). Also, the potential role of electrophysiological studies in high-risk patients should be further evaluated. Finally, continuous efforts to identify new anatomical parameters determining LBBB progression-regression are of paramount clinical importance.

2.7. ACKNOWLEDGEMENTS

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2.8. SUPPLEMENTAL MATERIAL

Supplemental Table 2.1: Sub-analysis of factors associated with LBBB recovery according to valve type

	Balloon-expandable valve (n=112)			Self-expanding valve (n=41)		
Variable	**LBBB recovery**		**p-value**	**LBBB recovery**		**p-value**
	No (n=77)	**Yes (n=35)**		**No (n=26)**	**Yes (n=15)**	
Trans-femoral approach	50 (64.9%)	23 (65.7%)	1.000	21 (80.8%)	14 (93.3%)	0.388
Valve-in-valve	8 (10.4%)	3 (8.8%)	1.000	4 (16.0%)	2 (13.3%)	1.000
Pre-dilatation	44 (57.1%)	23 (65.7%)	0.415	8 (30.8%)	5 (35.7%)	1.000
Post-dilatation	16 (21.9%)	6 (17.7%)	0.798	5 (19.2%)	3 (21.4%)	1.000
New-onset atrial fibrillation	12 (15.6%)	5 (14.3%)	1.000	2 (7.7%)	1 (6.7%)	1.000
Baseline ECG						
Sinus rhythm	64 (83.1%)	32 (91.4%)	0.383	23 (88.5%)	13 (86.7%)	1.000
PR interval (msec)	180 (160-200)	166 (148-188)	0.063	160 (150-195)	180 (178-180)	0.179
1st degree atrio-ventricular block	21 (32.8%)	6 (18.8%)	0.228	5 (21.7%)	3 (23.1%)	1.000
QRS width (msec)	96 (85-106)	95 (80-100)	0.203	90 (80-100)	80 (80-100)	0.573
QRS morphology:						
Normal	55 (71.4%)	25 (71.4%)		21 (80.8%)	11 (73.3%)	
Incomplete LBBB	15 (19.5%)	8 (22.9%)		4 (15.4%)	1 (6.7%)	
Incomplete RBBB	1 (1.3%)	0 (0%)	0.826	0 (0%)	0 (0%)	0.358
Left anterior hemiblock	3 (3.9%)	2 (5.7%)		1 (3.9%)	0 (0%)	
Left posterior hemiblock	0 (0%)	0 (0%)		0 (0%)	1 (6.7%)	
Non-specific disturbances	3 (3.9%)	0 (0%)		0 (0%)	0 (0%)	
Discharge ECG						
Sinus rhythm	60 (77.9%)	32 (91.4%)	0.111	23 (88.5%)	13 (86.7%)	1.000
PR interval (msec)	190 (164-218)	185 (165-200)	0.393	200 (180-200)	200 (180-230)	0.766
1st degree AVB	25 (41.7%)	9 (28.1%)	0.259	13 (56.5%)	7 (53.9%)	1.000
Absolute ΔPR (msec)	5 (0-29)	11 (0-30)	0.400	20 (0-45)	20 (0-40)	0.973
Relative ΔPR (%)	3 (0-16)	6 (0-19)	0.436	10 (0-29)	11 (0-25)	0.959
QRS width (msec)	140 (132-150)	140 (128-152)	0.683	152 (128-160)	140 (132-150)	0.704
Absolute ΔQRS (msec)	50 (38-57)	50 (40-62)	0.342	55 (41-67)	60 (50-65)	0.635
Relative ΔQRS (%)	50 (36-67)	54 (40-68)	0.245	61 (50-75)	70 (68-75)	0.323

Supplemental Table 2.2: Sub-analysis of factors associated with permanent pacemaker implantation according to valve type

	Balloon-expandable valve (n=112)			Self-expanding valve (n=41)		
Variable	**Permanent Pacemaker Implantation**		**p-value**	**Permanent Pacemaker Implantation**		**p-value**
	No (n=103)	**Yes (n=9)**		**No (n=36)**	**Yes (n=5)**	
Trans-femoral approach	68 (66.0%)	5 (55.6%)	0.717	30 (83.3%)	5 (100%)	1.000
Valve-in-valve	8 (7.8%)	3 (33.3%)	0.044	5 (14.3%)	1 (20.0%)	1.000
Pre-dilatation	63 (61.2%)	4 (44.4%)	0.480	10 (28.6%)	3 (60.0%)	0.307
Post-dilatation	20 (20.4%)	2 (22.2%)	1.000	6 (17.1%)	2 (40.0%)	0.257
New-onset atrial fibrillation	15 (14.6%)	2 (22.2%)	0.624	3 (8.3%)	0 (0%)	1.000
Baseline ECG						
Sinus rhythm	90 (87.4%)	6 (66.7%)	0.118	33 (91.7%)	3 (60.0%)	0.104
PR interval (msec)	173 (154-199)	216 (200-230)	0.004	180 (160-195)	150 (140-155)	0.036
1st degree atrio-ventricular block	22 (24.4%)	5 (83.3%)	0.006	8 (24.2%)	0 (0%)	1.000
QRS width (msec)	95 (82-104)	100 (96-106)	0.124	88 (80-100)	95 (90-98)	0.342
QRS morphology:						
Normal	76 (73.8%)	4 (44.4%)		28 (77.8%)	4 (80.0%)	
Incomplete LBBB	19 (18.4%)	4 (44.4%)		4 (11.1%)	1 (20.0%)	
Incomplete RBBB	1 (1.0%)	0 (0%)	0.108	0 (0%)	0 (0%)	0.731
Left anterior hemiblock	5 (4.9%)	0 (0%)		3 (8.3%)	0 (0%)	
Left posterior hemiblock	0 (0%)	0 (0%)		1 (2.8%)	0 (0%)	
Non-specific disturbances	2 (1.9%)	1 (11.2%)		0 (0%)	0 (0%)	
Discharge ECG						
Sinus rhythm	86 (83.5%)	6 (66.7%)	0.200	33 (91.7%)	3 (60.0%)	0.104
PR interval (msec)	184 (163-210)	229 (227-260)	0.008	200 (180-220)	200 (180-280)	0.646
1st degree AVB	30 (34.9%)	4 (66.7%)	0.189	18 (54.6%)	2 (66.7%)	1.000
Absolute ΔPR (msec)	5 (0-30)	32 (28-14)	0.018	10 (0-40)	45 (40-130)	0.053
Relative ΔPR (%)	3 (0-16)	14 (13-20)	0.055	6 (0-25)	29 (29-87)	0.038
QRS width (msec)	140 (130-150)	140 (140-152)	0.483	143 (130-157)	155 (145-156)	0.337
Absolute ΔQRS (msec)	50 (40-60)	41 (40-52)	0.405	57 (44-66)	58 (54-60)	0.984
Relative ΔQRS (%)	53 (36-70)	46 (40-52)	0.210	64 (50-75)	63 (59-68)	0.873

CHAPTER 3

Arrhythmic Burden in Patients with New-Onset Persistent Left Bundle Branch Block After Transcatheter Aortic Valve Implantation: Two-year results of the MARE Study

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3.1. RÉSUMÉ

Étude prospective multicentrique (n=103) où l'objectif était de déterminer le type d'arythmies à 2 ans de suivi chez les patients présentant un bloc de branche gauche (BBG) après une procédure TAVI. Un moniteur cardiaque implantable a été mis en place avant la sortie de l'hôpital. 1836 nouveaux événements arythmiques sont survenus après 2 ans. Au total, 71 bradyarythmies tardives ont été détectées chez 17 (21 %) patients. À deux ans, 18 (17 %) patients avaient reçu un stimulateur cardiaque. L'implantation d'un stimulateur cardiaque a prédominé dans la phase précoce post-TAVI, avec seulement 1 événement après 1 an. Les patients avec BBG après une TAVI ont présenté un nombre élevé d'événements arythmiques à 2 ans de suivi. Alors que les nouveaux événements tachyarrhytmiques étaient répartis de manière homogène, la majorité des nouveaux épisodes conduisant à l'implantation d'un stimulateur cardiaque permanent sont survenus tôt après l'intervention.

3.2. ABSTRACT

Aim: We determined the incidence and type of arrhythmias at 2-year follow-up in patients with new-onset persistent left bundle branch block (LBBB) following transcatheter aortic valve implantation (TAVI).

Methods: Multicenter prospective study including 103 consecutive patients with new-onset persistent LBBB post-TAVI (SAPIEN XT/3: 53; CoreValve/Evolut R: 50). An implantable cardiac monitor (Reveal XT, Reveal Linq) was implanted before hospital discharge, and patients had continuous monitoring for up to 2 years. Arrhythmic events were adjudicated in a central core lab.

Results: 1836 new arrhythmic events (tachyarrhythmias: 1655, bradyarrhythmias: 181) occurred at 2 years. Of these, 283 (15%) occurred beyond 1 year (tachyarrhythmias 212, bradyarrhythmias 71) in 33 (36%) patients, without differences between valve type. Most late (>1 year) arrhythmic events were asymptomatic (94%) and led to a treatment change in 17 (19%) patients. A total of 71 late bradyarrhythmias (high-degree atrioventricular block [HAVB]: 3, severe bradycardia: 68) were detected in 17 (21%) patients. At 2-years, 18 (17%) patients had received a permanent pacemaker (PPM) or implantable cardiac defibrillator (ICD). PPM implantation due to HAVB predominated in the early phase post-TAVI, with only 1 HAVB event requiring PPM implantation after 1 year.

Conclusions: Patients with new-onset LBBB post-TAVI exhibited a very high burden of arrhythmic events within the 2 years post-procedure. While new tachyarrhythmic events were homogeneously distributed over time, the vast majority of new HAVB episodes leading to PPM implantation occurred early after the procedure. These results should help to guide the management of this challenging group of patients. (clinicaltrials.gov: NCT02153307)

3.3 INTRODUCTION

Conduction disturbances (high-degree atrioventricular block [HAVB] and new-onset left bundle branch block [LBBB]) after transcatheter aortic valve implantation (TAVI) have not decreased over time (145) and their management is still under discussion (296). The incidence of new-onset LBBB post-TAVI has ranged from 6 to 77% with the use of newer generation transcatheter heart valve (THV) systems and remains the most frequent drawback of the procedure (167). The clinical impact and management of new-onset LBBB have been under debate since the beginning of TAVI. A recent meta-analysis (242) showed an increased risk of permanent pacemaker (PPM) implantation and mortality at 1-year follow-up among patients with new-onset LBBB post-TAVI, further highlighting the need to better understand the clinical evolution (mainly regarding new arrhythmic events) of this challenging group of patients. The 1-year follow-up results of the MARE study (321), which used an implantable cardiac monitor in new-onset LBBB post-TAVI patients, showed a high burden of tachy- and bradyarrhythmias. However, scarce data exist on arrhythmic events beyond 1-year follow-up in such patients (167), and to date, no studies using continuous ECG monitoring have evaluated the occurrence of late (>1 year) arrhythmic events in TAVI recipients. The role of the mechanical interaction between the THV and the conduction system regarding the occurrence of bradyarrhythmias in the long-term is largely unknown. On the other hand, the mechanical dyssynchrony and potential lack of systolic function improvement seen in patients with new-onset LBBB after TAVI may be associated with a higher risk of tachyarrhythmias. This study reports the 2-year results of the MARE study, focusing on the occurrence of new late (>1 year) arrhythmic events in patients with new-onset persistent LBBB following TAVI.

3.4. METHODS

The details of the MARE study (NCT02153307) design have been previously described (321). The MARE study was a prospective, multicenter study including patients that underwent TAVI with either self- or balloon-expanding valves (CoreValve or Evolut R [Medtronic, Minneapolis, Minnesota]; Edwards SAPIEN XT or SAPIEN 3 [Edwards Lifesciences, Irvine, California]). Patients with new-onset LBBB that persisted ≥3 days received a Reveal ICM XT or LINQ (Medtronic) as implantable loop recorder before

hospital discharge. LBBB was defined according to the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) recommendations (170). Patients were followed for 24 months, and in-office visits and 12-lead electrocardiogram (ECG) were performed at 1- and 12-, and 24-month follow-up. Automatic wireless transmission of data was obtained in those patients with the Reveal LINQ device and device interrogation at 1-, 3-, 6-, 9-, 12-, 24- month follow-up was performed in those patients who received the Reveal XT device. Clinical events were defined according to the Valve Academic Research Consortium 2 (VARC 2) criteria (326).

The primary outcomes were the incidence of arrhythmic events leading to a treatment change at 12 and 24-month follow-up, and the incidence of adjudicated HAVB at 12- and 24-month follow-up. All arrhythmic episodes and electrocardiograms were adjudicated in a central core lab. Significant arrhythmias were defined according to the ACC/AHA/HRS guidelines (342) and classified as: 1) significant bradyarrhythmia (HAVB, severe bradycardia [heart rate <30 bpm for 4 consecutive beats or pause >3 sec]; 2) atrial fibrillation (AF)/atrial flutter (AFL)/atrial tachycardia/supraventricular tachycardia episodes lasting >30 s; 3) ventricular tachycardia (nonsustained: lasting between 6 and 30 s; sustained: lasting >30 s); and 4) ventricular fibrillation.

3.4.1. Statistical analysis

Qualitative variables were expressed as percentages and numerical variables as mean SD or median (interquartile range [IQR]) according to variable distribution. Categorical variables were compared using the chi-square or Fisher exact test as appropriate. Numerical variables were compared using the t-test or Wilcoxon test as appropriate. Event rates over time were summarized using Kaplan-Meier estimates, and log-rank tests were used to perform comparisons between groups. Changes in LVEF over time between groups (according to the occurrence of tachyarrhythmias) were evaluated using a repeated-measures mixed-model with group by time interaction as fixed effects. Posterior comparisons were performed using the Tukey technique. A p value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using the statistical package STATA version 14.0 (StataCorp, College Station, Texas).

3.5 RESULTS

The MARE study included 103 patients with new-onset persistent LBBB post-TAVI (321). Baseline and procedural characteristics of the study population are summarized in **Table 3.1**.

Table 3.1. Baseline and Procedural Characteristics of the Population.

	Overall (n = 103)	**Sapien XT/3 (n = 53)**	**CoreValve/EvolutR (n = 50)**	**p Value**
Age, yrs	80 +/-7	79 +/-8	82+/-7	0.13
Female	59 (57)	24 (45)	35 (70)	0.01
Diabetes mellitus	44 (43)	27 (51)	17 (35)	0.10
Atrial fibrillation, n (%)	27 (26)	17 (32)	10 (20)	0.20
Paroxysmal	13 (48)	9 (53)	5 (50)	
Permanent	14 (52)	8 (47)	5 (50)	1
STS-PROM score, %	5.0 (3.3-7.7)	5.0 (3.1-9.2)	4.7 (3.6-7.1)	0.26
CHADS-VASc score, %	4.7 +/- 1.4	4.6 +/- 1.5	4.9 +/- 1.2	0.39
ECG				
PR interval, ms	183 +/-36	181 +/-35	186 +/-38	0.51
QRS duration, ms	102 +/-24	103 +/-21	103 +/-27	0.90
Echocardiography				
LVEF, %	56 +/-11	55 +/-11	56 +/-11	0.67
Mean gradient, mmHg	41 +/-14	41 +/-14	41 +/-15	0.87
Aortic valve area, cm2	0.70 (0.52-0.82)	0.72 (0.62-0.87)	0.60(0.50-0.80)	0.19
Approach				
Transfemoral	89 (86)	44 (83)	45(90)	0.92
Transapical/transaortic	10 (10)	9 (17)	1 (2)	0.01
Subclavian/transcarotid	4 (4)	0 (0)	4 (8)	0.05
New-onset persistent LBBB				
PR interval, ms	197 +/-42	188 +/-32	207 +/-50	0.07
QRS duration, ms	142 +/-20	144 +/-18	141 +/-22	0.40
Time to implantable monitor, days post-TAVI	4 (3-6)	5 (3-7)	4 (2-6)	0.22
Type of device, XT/LINQ	8/95	5/47	3/45	0.53
Hospitalization length, days	7 (5-8)	7 (6-8)	6 (4-8)	0.71

Values are mean +/- SD, n (%), or median (interquartile range).
ECG = electrocardiogram; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality;

The arrhythmic events up to 1-year follow-up have been previously reported (321). Briefly, a total of 1553 new arrhythmic events were detected in 44 patients (1443 episodes of tachyarrhythmia in 26 patients [atrial fibrillation/flutter/atrial tachycardia: 1427, ventricular tachycardia: 16]; 110 episodes of bradyarrhythmia in 21 patients [HAVB: 54, severe bradycardia: 56]). The arrhythmic event led to a treatment change in 19 patients (18%), and 11 patients (11%) required pacemaker or implantable cardioverter-defibrillator implantation (due to HAVB, severe bradycardia or ventricular tachycardia

episodes in 9, 1, and 1 patient, respectively). A total of 12 patients died at 1-year follow-up, 1 from sudden death.

3.5.1. Late (> 1 year) arrhythmic burden

The clinically significant arrhythmic events detected between 12 and 24 months are shown in **Table 3.2.**

Table 3.2. Late (>12 months) Arrhythmic Events.

	Overall (n = 91)	Sapien XT/3 (n = 45)	CoreValve/ Evolut R (n = 46)	p
Global Arrhythmic Burden				
Total number of new arrhythmic events	283	76	207	-
Patients with arrhythmic events	33 (36)	16 (36)	17 (37)	0.89
Arrhythmic events per patient	3 (1-7)	3 (1-5)	3 (1-13)	0.46
Patients with arrhythmic events requiring treatment	17 (19)	8 (18)	9 (20)	0.83
Bradyarrhythmias*				
Total number of events	71	36	35	-
High-degree atrioventricular block	3	3	0	-
Severe Bradycardia	68	33	35	-
Patients with bradyarrhythmic events	17 (21)	8 (21)	9 (22)	0.88
Patients with high-degree atrioventricular block	1 (1)	1 (3)	0	0.49
Patients with severe bradycardia	16 (20)	7 (18)	9 (22)	0.66
Patients with bradyarrhythmias requiring treatment	11 (14)	4 (10)	7 (17)	0.38
Pacemaker implantation	5 (6)	2 (4)	3 (7)	1
Change in medical treatment	6 (8)	2 (5)	4 (10)	0.68
Tachyarrhythmias				
Total number of events	212	39	173	-
Atrial arrhythmias	74	19	55	-
Atrial fibrillation/atrial flutter	43	18	25	-
Atrial tachycardia	27	0	27	-
Supraventricular tachycardia	4	1	3	-
Ventricular arrhythmias	138	20	118	-
Sustained ventricular tachycardia	109	5	104	-
Nonsustained ventricular tachycardia	25	11	14	-
Atrial Fibrillation/atrial flutter				
Patients with new episodes of atrial fibrillation/atrial flutter**	8/52 (15)	3/19 (16)	5/33 (15)	0.48
Atrial fibrillation episodes per patient	2 (1-8)	1 (1-8)	2 (2-8)	0.37
Duration of atrial fibrillation episodes per patient, min	7 (0.5-883)	608 (6-4202)	1.5 (0.5-883)	0.11
Patients with new episodes of atrial fibrillation/atrial flutter leading to anticoagulation therapy	2 (4)	1 (5)	1 (3)	1
Ventricular Tachycardia				
Patients with episodes of ventricular tachycardia	13 (14)	7 (16)	6 (13)	0.73
Ventricular tachycardia episodes per patient	1 (1-7)	1 (1-5)	6 (1-33)	0.35
Duration of ventricular tachycardia episodes per patient, seconds	12 (8-16)	7 (7-7)	13 (9-16)	0.20
Patients with ventricular tachycardia episodes who had a treatment modification	4 (4)	3 (7)	1 (2)	0.36
Implantable cardioverter defibrillator	2 (2)	1 (2)	1 (2)	1

Values are n, n (%), n/N (%), or median (interquartile range). *Only patients without pacemaker or cardiac defibrillator implanted during the first year in the denominator for the %.
**Only patients without prior atrial fibrillation in the denominator for the %.

Recurrent AF/AFL episodes in patients already diagnosed during the 1st year post-procedure were not included in this analysis. A total of 283 new arrhythmic events (94% silent) were detected in 33/91 (36%) patients, with no differences between valves. Arrhythmic events leading to a treatment change occurred in 17 (19%) patients. After the exclusion of the patients with PPM/ICD implantation during the first year, a total of 71 clinically significant bradyarrhythmic events were detected occurring in 17/80 (21%) patients. Of them, 10 (13%) episodes were symptomatic and 1 patient (1%) suffered 3 episodes of HAVB. As a result, 5 (6%) patients required PPM implantation due to bradyarrhythmias. Regarding episodes of tachyarrhythmia, a total of 212 episodes occurred between 12 and 24-months of follow-up. Eight patients had new AF/AFL episodes (15% among those patients without previously diagnosed AF/AFL), leading to the implementation of anticoagulation treatment in 25% of them. All AF/AFL episodes were silent. A total of 138 episodes of ventricular tachycardia occurred in 13 patients (14%), leading to a treatment change in 4 (31%) of them. Of these, 109 episodes occurring in 3 (3%) patients consisted of sustained ventricular tachycardia.

3.5.2. Cumulative 2-year rate of the first arrhythmic episode

The cumulative 2-year rate of new arrhythmic events (first event of any type of arrhythmia) are summarized in **Table 3.3**.

Table 3.3. Cumulative Rate of First Arrhythmic Event at 2-year of Follow-up (n= 103 patients)

	At 12 months	Between 13-24 months	At 24 months
Global Arrhythmic Burden			
Patients with first arrhythmic event	44 (43)	19 (21)	63 (61)
Bradyarrhythmias			
Patients with first bradyarrhythmic event	21 (20)	15 (16)	36 (35)
Patients with high-degree atrioventricular block	15 (15)	1 (1)	16 (16)
Pacemaker implantation	10 (10)	5 (5)	15 (15)
Atrial Fibrillation/atrial flutter			
Patients with new episodes of atrial fibrillation/atrial flutter*	13/76 (17)	8/52 (15)	21/76 (28)
Ventricular Tachycardia			
Patients with new episodes of ventricular tachycardia	13 (13)	9 (10)	22 (21)
Implantable cardioverter defibrillator	2 (2)	1 (1)	3 (3)

Values are n, n (%), n/N (%)
*Only patients without prior atrial fibrillation in the denominator for the %.

A total of 63 patients (61%) suffered at least 1 arrhythmic episode throughout the study period. At two-year of follow-up, 36 (35%) patients suffered a bradyarrhythmic event, 16 (44%) of them classified as HAVB. A total of 21 (28%) patients presented at least one episode of AF/AFL, and 22 (24%) patients suffered at least one episode of ventricular tachycardia.

The Kaplan-Meier curves regarding the time to the first arrhythmic episode (overall, bradyarrhythmic [HAVB, severe bradycardia], tachyarrhythmic and AF/AFL events); in the whole cohort and according to valve type are shown in **Figures 3.1** and **3.2.**

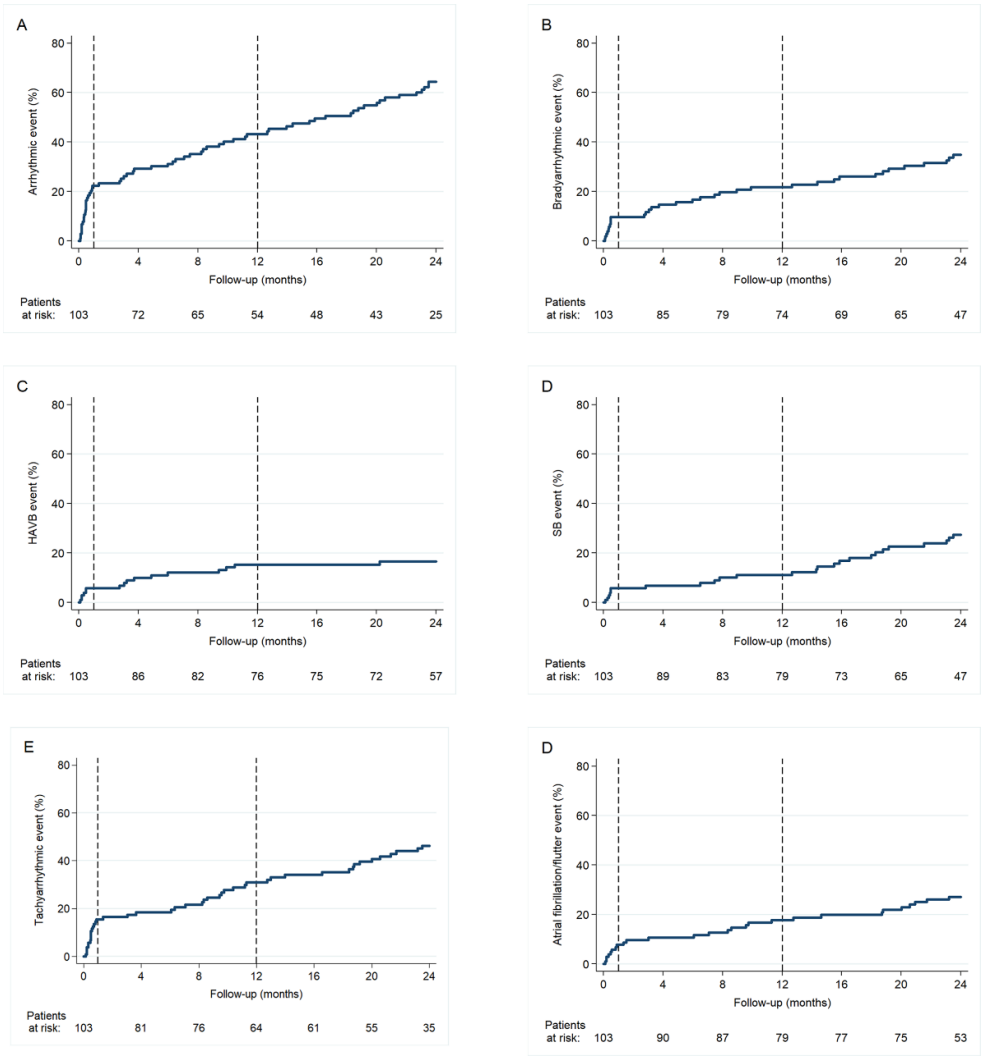

Figure 3.1. Time to First Arrhythmic event Post-TAVI for the Entire Study Population.
A. Time to the first arrhythmic (brady- or tachyarrhythmia) episode. B. Time to the first episode of bradyarrhythmia. C. Time to the first episode of high-degree atrioventricular block. D. Time to the first episode of severe bradycardia. E. Time to the first episode of tachyarrhythmia. F. Time to the first episode of atrial fibrillation/atrial flutter.

TAVI: Transcatheter Aortic Valve Implantation, HAVB: high-degree atrioventricular block, SB: Severe bradycardia.

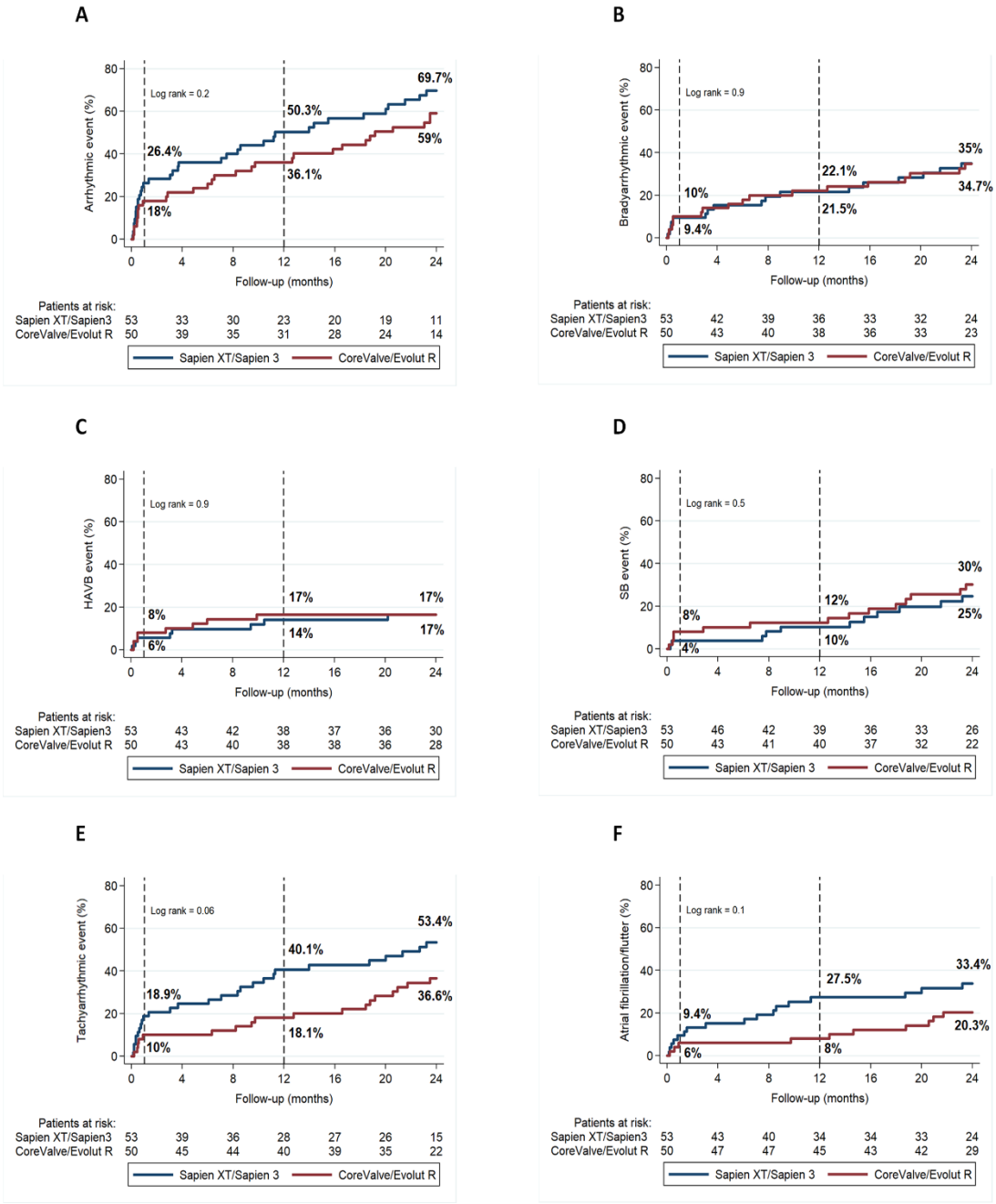

Figure 3.2. Time to First Arrhythmic Event Post-TAVI, According to Valve Type.
A. Time to the first arrhythmic (brady- or tachyarrhythmia) episode. B. Time to the first episode of bradyarrhythmia. C. Time to the first episode of high-degree atrioventricular block. D. Time to the first episode of severe bradycardia. E. Time to the first episode of tachyarrhythmia. F. Time to the first episode of atrial fibrillation/atrial flutter.
TAVI: Transcatheter Aortic Valve Implantation, HAVB: high-degree atrioventricular block, SB: Severe bradycardia.

There were no significant differences in arrhythmic events between valve types. Landmark analysis regarding the first arrhythmic episode (overall, bradyarrhythmic, and

tachyarrhythmic events) at different time periods (<1 month, 1-12 months, 13-24 months) are depicted in **Figure 3.3**. The overall rate of arrhythmic events was similar between periods, but the distribution of bradyarrhythmic episodes followed different patterns. While HAVB episodes dropped drastically after 1-year, severe bradycardia episode tended to increase during the same period.

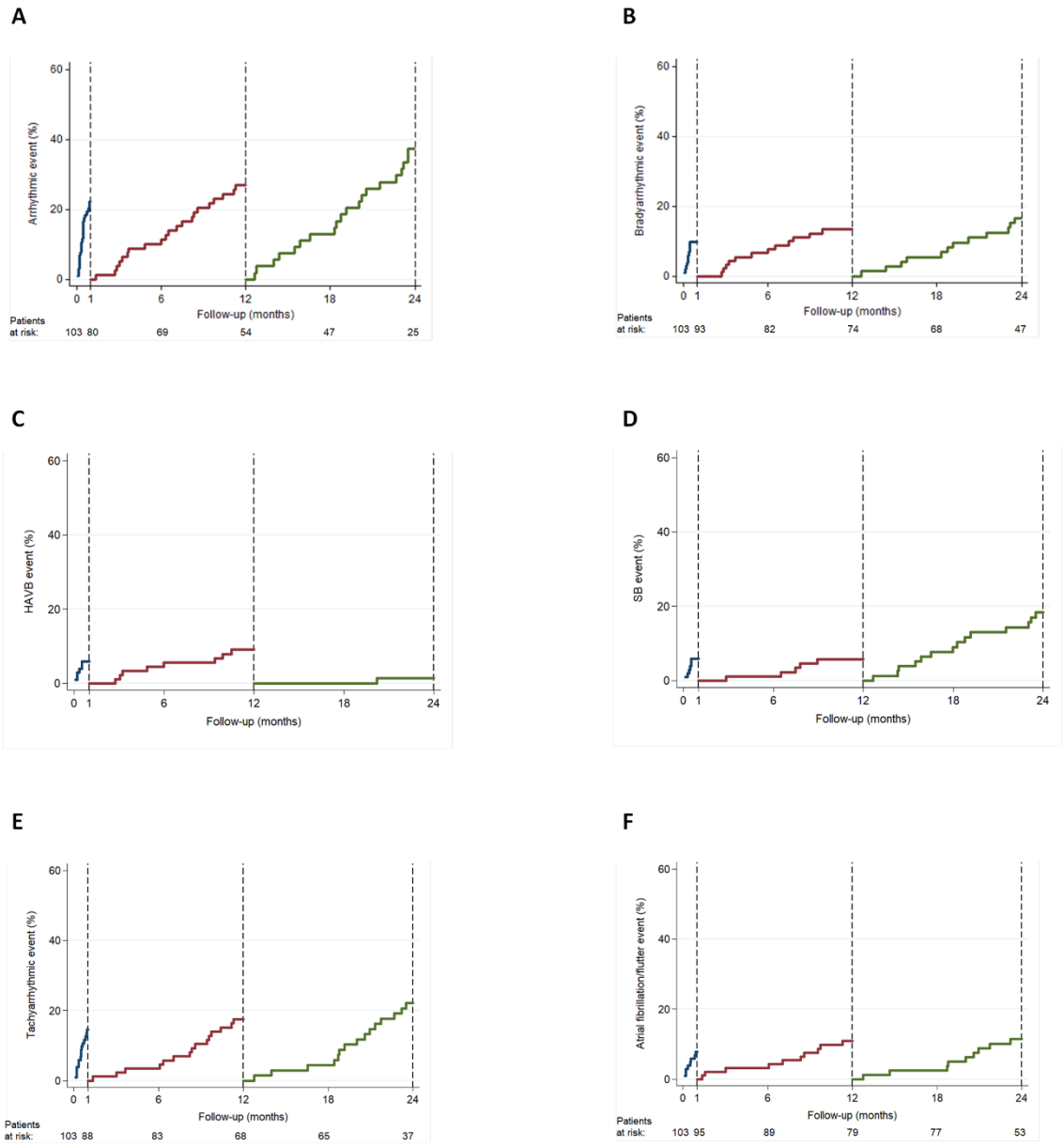

Figure 3.3. Landmark analysis showing first arrhythmic episode according to 3 time periods (<1 month, 1-12 months, and 13-24 months).
A. Time to the first arrhythmic (brady- or tachyarrhythmia) episode. B. Time to the first episode of bradyarrhythmia. C. Time to the first episode of high-degree atrioventricular block. D. Time to the first episode of severe bradycardia. E. Time to the first episode of tachyarrhythmia. F. Time to the first episode of atrial fibrillation/atrial flutter.

TAVI: Transcatheter Aortic Valve Implantation, HAVB: high-degree atrioventricular block, SB: Severe bradycardia

3.5.3. PPM/ICD implantation.

Individual data of the 18 patients (17%) who received a PPM/ICD device during the study period are shown in **Supplemental Table 3.1**. The indications for PPM/ICD according to time period (<1 month, 1 to 12 months, 13-24 months) are shown in **Figure 3.4**. PPM implantation due to HAVB predominated in the early phase post-TAVI, as 5/10 (50%) of the episodes occurred <1-month post-TAVI, and 8/10 (80%) within the first 4 months after the procedure. The annual rate of PPM implantation during the study period was 7.3%. The **Supplemental Table 3.2** depicts the baseline, electrocardiographic and procedural characteristics according to PPM implantation at follow-up. There were no statistically significant differences between groups.

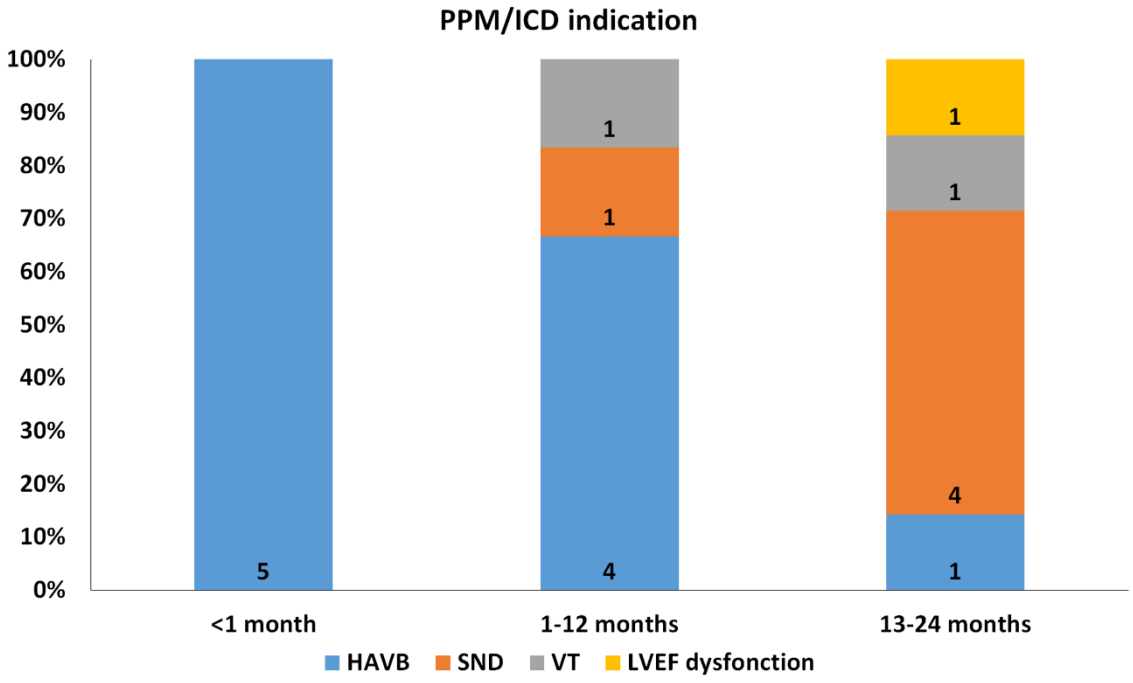

Figure 3.4. Reason for PPM/ICD implantation according to time period following TAVI (<1month, 1 to 12 months, 13-24 months).
PPM: Permanent pacemaker, ICD: Implantable cardiac defibrillator, HAVB: high-degree atrioventricular block, SND: Sinus node disease; VT: ventricular tachycardia, LVEF: left ventricular ejection fraction.
* 1 patient with ICD implantation <1 month post-TAVI suffered both HAVB and VT.

3.5.4 Overall clinical outcomes.

The clinical outcomes, overall and according to valve type, at 1-year and at 1- to 2-year follow-up are shown in **Supplemental Table 3.3**. The overall and cardiac mortality rates were 17% and 6%, respectively. Two patients suffered a sudden death during the study period. The first one was 10 months after TAVI and was likely secondary to a coronary event. The second sudden death occurred 19 months post-TAVI. The patient had coronary artery disease at baseline and suffered an unwitnessed cardiac arrest. No tachyarrhythmic events were detected in the Reveal device within the weeks preceding the sudden death. However, the patient had suffered 17 asymptomatic pauses (~3 seconds in the context of chronic atrial fibrillation) within the 4 months before the sudden death. Unfortunately, no arrhythmic data were available concerning the two last days before the unwitnessed death. Finally, a total of 3 (3%) patients (none of them under anticoagulation therapy) suffered an ischemic stroke during the second year of follow-up and of these, 1 patient had new-onset AF.

Overall, there was a significant reduction in left ventricular ejection fraction over time (p=0.02) (**Supplemental Figure 3.1-A**). Data regarding the changes in left ventricular ejection fraction over time according to the occurrence of tachyarrhythmias during the follow-up period are shown in **Supplemental Figure 3.1-B**. The left ventricular ejection fraction decreased (p=0.04) and tended to increase (p=0.10) in patients with and without tachyarrhythmias, respectively (p=0.07 for the comparison between groups).

3.6. DISCUSSION

The 2-year results of the MARE study showed a very high arrhythmic burden in new-onset persistent LBBB post-TAVI patients, with about two-thirds of patients suffering at least one arrhythmic episode. However, the time distribution of new arrhythmic events varied according to the type of arrhythmia. New episodes of tachyarrhythmia (AF/AFL, ventricular tachycardia) were homogenously distributed over time, with no decrease in its incidence beyond 1 year. On the other hand, a higher rate of bradyarrhythmic events was observed within 1-year follow-up (particularly within the 1st month), with a major decline in HAVB episodes beyond 1 year.

Conduction disturbances and particularly new-onset LBBB post-procedure are nowadays the main drawback of TAVI (145,167). In addition to the initial harm caused by the deployment of the valve, on may wonder if the interaction between the THV and the cardiac conduction system may extend beyond the initial period post-TAVI. Previous studies reported a PPM implantation rate of 5 to 20% at 1-year follow-up in new-onset LBBB patients, with HAVB episodes being the most frequent indication (47-100%) (167). In the current analysis, results at 2-year follow-up showed that 16% of patients suffered an episode of HAVB. Hence, most patients (84%) did not present HAVB events, reinforcing the concept that preventive PPM should not be recommended in all patients with new-onset LBBB post-TAVI. Interestingly, all HAVB episodes leading to PPM implantation but one occurred within the first year post-procedure. PPM implantation due to HAVB predominated in the early phase post-TAVI, with 50% and 80% of the events occurring within the first and 4 months after the procedure, respectively. These results do not support a continuous harm to the conduction system and reinforce the safety of THVs in the long-term follow-up. However, a more intense clinical surveillance with ECG monitoring may be necessary during the first weeks post TAVI.

The annual rate of PPM implantation in the MARE study was 7.3%. A recent study analyzed the clinical outcomes of patients that underwent TAVI and had no ECG changes after the procedure (343), showing an annual rate of PPM implantation of 2.5% (1.1% and 5.2% in patients without and with pre-procedural ECG conduction disturbances, respectively), much lower than the rate observed in the MARE study. Furthermore, it is known that the annual rate of PPM implantation in patients with LBBB in the general population is around 1-2% (340) . Of note, 7 out of 15 patients who received a PPM in the current cohort did not present symptoms. While all arrhythmic events fulfilled the criteria for PPM implantation, this may have increased the PPM rate in our study.

No significant differences between the valve type (CoreValve/Evolut R system or SAPIEN XT/ 3 valve) were observed at 2-year follow-up (overall and by time period, before and after 1 year). While several studies have shown an increased risk of peri-procedural conduction disturbances and PPM among CoreValve/Evolut (vs. SAPIEN) recipients (145), the risk of late arrhythmic events according to different valve types remains largely unknown. A continuous expansion of the nitinol frame was suggested to

explain the hemodynamic changes and paravalvular regurgitation improvement over time in CoreValve recipients (344). Whereas this could have translated into a higher incidence of late CDs compared to the balloon-expandable system, the results of the MARE study failed to show any increase in late CDs in CoreValve/Evolut patients. Other factors such as valve positioning and baseline risk factors favoring the development of conduction disturbances might have also contributed to the occurrence of late bradyarrhythmias in both valve groups (145), and will need to be evaluated in future studies. Also, the need for optimizing valve implantation depth should be underlined in order to avoid damaging of the conduction system and prevent the occurrence of conduction disturbances.

New-onset AF is common after TAVI and its occurrence in the early postprocedural period has been associated with poorer outcomes, with an increased risk of mortality and stroke (299). However, very limited data exist regarding the occurrence of silent/subclinical or symptomatic AF beyond the hospitalization period following TAVI. A very recent publication (345) including 172 patients with PPM implantation post-TAVI evaluated the occurrence of AF episodes during device interrogation at follow-up. After a median follow-up of 15 months, one fourth of patients exhibited at least one episode of AF, which indeed was associated with an increased risk of stroke. In accordance with these results, 28% of the patients in the MARE study exhibited new-onset AF episodes at 2-year follow-up. However, no relationship with cerebrovascular events was found in our cohort, likely related to the relatively small number of patients and short duration of the AF episodes. Contrary to HAVB, the risk of late NOAF (beyond the hospitalization period) did not seem to decrease over time in the new-onset LBBB population.

AF is the most common cardiac arrhythmia worldwide and its presence implies an increased risk of stroke. Nevertheless, silent AF is common and may be associated with a higher risk of stroke (346). A study using an implantable cardiac monitor (Reveal) in a high-risk population (mean CHADS-VASc of 4.4) showed an AF detection rate of 29% at 18 months (347), comparable to the one observed in our study. On the other hand, TAVI recipients have an increased risk of AF and silent episodes may be present before the TAVI procedure (188), identifying a potential subset of patients that may benefit from anticoagulant therapy. The relatively high rate of AF in the MARE study may support the use of anticoagulation therapy following TAVI. A recent publication focusing on late

cerebrovascular events (LCVEs) post-TAVI (348) showed that the lack of anticoagulation at discharge was associated with an increased risk of ischemic cerebrovascular events. Echocardiographic data at the time of stroke failed to show any relationship with valve thrombosis or structural degeneration, indirectly suggesting the potential implication of subclinical AF. On the other hand, Chakravarty et al (349) reported that subclinical leaflet thrombosis (as determined by 4D-CT) was associated with ischemic LCVEs and anticoagulation appeared to be an effective preventive therapy. Finally, the results of the very recent GALILEO trial (350) advise against the systematic use of anticoagulation treatment post-TAVI (especially if added to an antiplatelet agent). Future studies will provide definite evidence on the potential role of anticoagulation post-TAVI. Meanwhile, identifying those patients with atrial arrhythmias prior to the procedure may be useful for implementing a tailored antithrombotic approach following the TAVI procedure.

The burden of ventricular arrhythmias following TAVI is largely unknown. To date, data with ECG monitoring is limited to one single study using 24-hour Holter monitoring performed 1-year post-procedure (310). The authors reported a 2% rate of ventricular tachycardia episodes (all of them non-sustained). In our cohort, the cumulative rate of newly diagnosed ventricular arrhythmia events at 2 years reached 21%. Despite of this high incidence, an ICD was implanted in a relatively low number of patients (3%). More data with a larger number of patients are needed to identify patients at risk of ventricular events.

3.6.1 Study limitations

The MARE study was a single-arm, non-randomized study with relatively low sample size. While arrhythmic events were adjudicated in a central core lab, the initial diagnosis and management was performed in each participating center. Some variability in the interpretation and management of the events between centers cannot be excluded. Finally, the non-randomized nature of the study and the relatively limited sample size precluded to drawn definite conclusions regarding the comparison between valve types. Future randomized trials are needed to provide definite data on potential differences in late arrhythmic events between valve types.

3.7. CONCLUSIONS

In conclusion, the 2-year follow-up results of the MARE study provided unique data on the long-term arrhythmic burden in the high-risk group of patients with new-onset LBBB following TAVI. About two thirds of the patients exhibited at least one arrhythmic episode, reflecting the very high arrhythmia burden in this group of patients. While a continuous risk of significant bradyarrhythmias was observed throughout the 2-year period, HAVB events were mainly limited to the initial months after the procedure. These results suggest the lack of delayed damage of the conduction system in such patients, do not support systematic prophylactic PPM implantation, and favor limiting the use of continuous ECG monitoring to the initial period after TAVI. The high rate of new-onset AF/AFL episodes, with no significant decrease beyond 1 year, may suggest a role for anticoagulation therapy in such patients, and highlight the importance of further studies determining the optimal antithrombotic treatment in TAVI recipients. Finally, 1 out of 5 patients exhibited episodes of ventricular arrhythmias, with a similar burden early and late after TAVI. Future studies are needed to determine the potential role of ventricular arrhythmias on the increased risk of death among new-onset LBBB patients.

3.8. FUNDING

Dr. Muntané-Carol is supported by a research grant from the Fundación Alfonso Martín Escudero (Madrid, Spain). Dr. Rodés-Cabau holds the Research Chair “Fondation Famille Jacques Larivière” for the Development of Structural Heart Disease Interventions.

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3.9. SUPPLEMENTAL MATERIAL

Supplemental Table 3.1. Individual Characteristics of the Patients Requiring Permanent Pacemaker or Implantable Cardioverter Defibrillator Implantation at 2 years

Age yrs (Sex)	Valve Type	Timing of PPM or ICD (days)	PPM or ICD	Reasons for PPM or ICD
65 (male)	Sapien 3	5	ICD-CRT	HAVB (A), low LVEF
90 (male)	Evolut R	5	PPM	HAVB (S), syncope
73 (male)	Evolut R	6	PPM	HAVB (S), pre-syncope
81 (male)	Sapien 3	12	ICD	HAVB (A)/VT (S)
85 (male)	CoreValve	18	PPM	HAVB (S), pre-syncope
84 (female)	Sapien 3	42	PPM	HAVB (A)
75 (female)	Sapien 3	108	PPM	HAVB (S), pre-syncope
86 (male)	Sapien XT	127	PPM	HAVB (A)
75 (female)	CoreValve	217	ICD	Polymorphic NSVT (A)
85 (female)	Evolut R	280	PPM	HAVB (A)
83 (male)	Sapien 3	281	PPM	Severe bradycardia (A)
89 (male)	CoreValve	455	PPM	Sinus pause (A)
84 (female)	Evolut R	483	PPM	Sinus pause (S)
90 (female)	Evolut R	571	PPM	Tachy-Brady Syndrome (S)
78 (male)	Sapien 3	580	ICD-CRT	VT and low LVEF
88 (male)	Sapien XT	613	ICD-CRT	Clinical HF and low LVEF
88 (male)	Sapien XT	641	PPM	HAVB (S), pre-syncope
92 (female)	Sapien XT	663	PPM	Sinus pause (S), pre-syncope

A = asymptomatic; HAVB = high-degree atrioventricular block; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; PPM = permanent pacemaker implantation; S = symptomatic; VT = ventricular tachycardia.

Supplemental Table 3.2. Baseline and Procedural Characteristics of the Population according to pacemaker implantation after TAVI

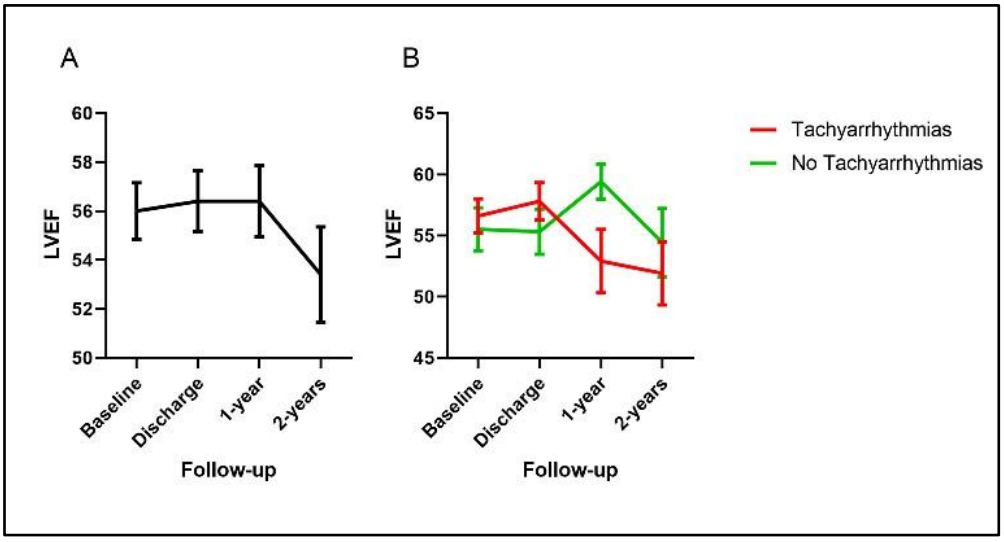
	PPM implantation (n=15)	No PPM implantation (n= 88)	p Value
Age, yrs	83 +/- 7	80 +/- 8	0.20
Female	6 (40)	53 (60)	0.17
Diabetes mellitus	3 (20)	41 (47)	0.09
Atrial fibrillation (paroxysmal or permanent)	6 (40)	21 (24)	0.22
STS-PROM score, %	4.5 (3.5-9.1)	5.2 (3.2-7.1)	0.20
CHADS-VASc score, %	4.2 +/- 0.8	4.8 +/- 1.4	0.30
ECG			
Sinus rhythm, %	9 (60)	73 (83)	0.08
PR interval, ms	177 +/- 43	177 +/- 31	0.98
1-AVB, %	1 (11)	13 (18)	1
QRS duration, ms	93 +/- 12	96 +/- 20	0.61
QRS≥ 120ms, %	0 (0)	10 (12)	0.35
QRS morphology			
Normal	9 (64)	59 (70)	
RBBB	0 (0)	0 (0)	
Left anterior or posterior hemiblock	0 (0)	9 (11)	
Incomplete RBBB	1 (7)	1 (1)	
Incomplete LBBB	2 (14)	10 (12)	
NIVCD	2 (14)	5 (6)	0.22
Echocardiography			
LVEF, %	57 +/- 18	57 +/- 14	0.77
Mean gradient, mmHg	45 +/- 19	40 +/- 13	0.20
Aortic valve area, cm2	0.50 (0.46-0.75)	0.70 (0.57-0.83)	0.36
Computed Tomography			
Surface, mm2	465 (332-585)	431 (341-528)	0.76
Agatston score	1912 (1879-3018)	1990 (1112-2918)	0.88
Procedure			
Transfemoral approach (vs other)	14 (93)	75 (85)	0.69
Pre-dilatation, %	8 (62)	34 (40)	0.15
Valve-in-valve, %	1 (7)	10 (12)	1
≤23 mm valve (vs > 23 mm)	2 (13)	20 (23)	0.52
Edwards Sapien valve (vs Medtronic CoreValve/Evolut)	8 (53)	45 (51)	0.88
Post-dilatation, %	2 (15)	15 (19)	1
ECG prior to discharge			
Sinus rhythm, %	9 (60)	71 (81)	0.1
1-AVB, %	3 (38)	30 (45)	1
PR interval, ms	184 +/- 33	198 +/- 42	0.36
QRS duration, ms	147 +/- 20	141 +/- 20	0.42

Values are mean +/- SD, n (%), or median (interquartile range).

ECG = electrocardiogram; NIVCD: Unspecific intraventricular conduction delay; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; RBBB: right bundle branch lock; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Supplemental Table 3.3. Clinical outcomes according to time period and valve type								
At 12 months					**Between 13 and 24 months**			
	Overall (n=103)	**Sapien XT/3 (n =53)**	**CoreValve /Evolut R (n = 50)**	**p**	**Overall (n=91)**	**Sapien XT/3 (n = 45)**	**CoreValve/ Evolut R (n = 46)**	**p**
Overall Death	12 (12)	8 (15)	4 (8)	0.26	5 (5)	2 (4)	3 (7)	1
Cardiovascular Death	4 (4)	2 (4)	2 (4)	1	2 (6)	1 (6)	1 (6)	1
Sudden Death	1 (1)	1 (2)	0 (0)	1	1 (1)	0 (0)	1 (2)	1
Stroke/TIA	8 (8)	4 (8)	4 (8)	1	3 (3)	0	3 (7)	0.22
Myocardial Infarction	4 (5)	2 (4)	2 (4)	1	1 (1)	1 (2)	0 (0)	0.49
Rehospitalization	19 (18)	12 (23)	7 (14)	0.26	19 (21)	7 (16)	12 (26)	0.45
Rehospitalization because of cardiac causes	12 (12)	8 (15)	4 (8)	0.26	18 (20)	6 (13)	12 (26)	0.31
PPM/ICD implantation	11 (11)	6 (11.3)	5 (10)	0.83	7 (8)	4 (9)	3 (7)	0.8

TIA = Transient ischemic attack. Other abbreviations as in Supplemental Table 3.1.



Supplemental Figure 3.1. Evolution of the mean left ventricular ejection fraction (LVEF, mean and standard error) in the global cohort (Panel A) and according to the occurrence of tachyarrhythmias during the follow-up (Panel B). Panel A shows a significant reduction in left ventricular ejection fraction over time (mixed model p=0.02). In panel B, patients with and without tachyarrhythmias present a statistically significant decrease (mixed model p=0.04) and a non-statistically significant increase (mixed model p=0.10) in left ventricular ejection at follow-up (mixed model p=0.07 for the comparison between groups). LVEF: Left ventricular ejection fraction.

CHAPTER 4

Late Cerebrovascular Events Following Transcatheter Aortic Valve Implantation

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4.1 RÉSUMÉ

Il existe peu de données concernant les événements cérébrovasculaires tardifs (>30 jours) après une procédure TAVI. Cette étude a inclus 3750 patients et a déterminé l'incidence, les caractéristiques cliniques, les facteurs associés et l'impact des événements cérébrovasculaires tardifs. Les événements cérébrovasculaires tardifs sont survenus chez 5,1% des patients après un suivi médian de 2 ans. Deux tiers des événements cérébrovasculaires tardifs étaient invalidants et associés à des taux de mortalité élevés. La plupart des événements cérébrovasculaires tardifs étaient ischémiques, et l'âge avancé, les antécédents de maladie cérébrovasculaire, un gradient aortique plus élevé, un accident vasculaire cérébral périprocédural et l'absence d'anticoagulation à la sortie de l'hôpital étaient associés à un risque accru. Ces résultats peuvent éclairer les études futures concernant les mesures préventives potentielles des événements cérébrovasculaires tardifs après une procédure TAVI.

4.2 ABSTRACT

Objectives: To determine the incidence, predictors, clinical characteristics and outcomes of late cerebrovascular events (LCVEs, >30 days post-procedure) following transcatheter aortic valve implantation (TAVI).

Background: Scarce data exist on LCVEs following TAVI.

Methods: This was a multicenter study including 3750 consecutive patients (mean age: 80 ± 8 years, 50.5% of women) who underwent TAVI and survived beyond 30 days. LCVEs were defined according to VARC-2 criteria.

Results: LCVEs occurred in 192 (5.1%) patients (stroke: 80.2%, TIA: 19.8%) after a median follow-up of 2 (1 to 4) years. Late stroke was of ischemic, hemorrhagic and undetermined origin in 80.5%, 18.8% and 0.7% of patients, respectively. Older age, previous cerebrovascular disease, higher mean aortic gradient at baseline, the occurrence during the periprocedural TAVI period, and the lack of anticoagulation (NOACs or vitamin K antagonists) post-TAVI were independent predictors of late ischemic stroke/TIA ($p<0.05$ for all). Echocardiographic data showed no signs of valve thrombosis or degeneration in the vast majority (97%) of patients. Late stroke was disabling in 107 (69.5%) patients (ischemic: 68%, hemorrhagic 79%), and associated with an in-hospital mortality rate of 29.2%.

Conclusions: LCVEs occurred in 5.1% of TAVI recipients after a median follow-up of 2 years. LCVEs were ischemic in most cases, with older age, previous cerebrovascular events, higher mean aortic gradient at baseline, the occurrence during the periprocedural TAVI period, and lack of anticoagulation (but not valve thrombosis/degeneration) determining an increased risk. Late stroke was disabling in most cases and associated with dreadful early and midterm outcomes.

4.3. INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become the preferred treatment for patients with severe symptomatic aortic stenosis at intermediate to high surgical risk (336), and recent data from 2 randomized trials have provided the basis for its expansion toward the treatment of low-risk patients (153,154). However, periprocedural stroke remains one of the most worrisome complications of TAVI, and numerous studies have evaluated its incidence, predictive factors, and clinical impact (351,352). Also, substantial efforts (particularly with the use of embolic protection devices) have been undertaken for its prevention (353).

Although the risk of cerebrovascular events post- TAVI peaks within the days following the procedure, it persists later on (beyond the 30-day period) (354). However, scarce data exist on the occurrence, clinical characteristics, and factors associated with late cerebrovascular events (LCVEs) post-TAVI (134,136,137). Also, recent data suggest a potential relationship between subclinical transcatheter valve thrombosis and cerebrovascular events (particularly transient ischemic attack [TIA]) (349), further fueling the interest on the most appropriate antithrombotic treatment for preventing cerebrovascular events post-TAVI. Finally, no studies to date have determined the clinical impact of late stroke among TAVI recipients. Thus, the objectives of our study were to determine the incidence, clinical characteristics, associated factors, and impact of LCVEs (>30-day) following TAVI.

4.4. METHODS

This multicenter study included a total of 3,750 consecutive patients from 7 centers (Canada, France, and Spain) who underwent TAVI and survived the periprocedural (30-day) period. Procedural aspects, valve type, access, and post-procedural management were at the discretion of the heart team in each center. Baseline, procedural, and follow-up data were prospectively collected in each center. Follow-up (at 1 and 12 months, and yearly thereafter) was completed in all patients but 180 (4.8% of patients lost to follow-up). Clinical follow-up was performed in each participating center, either by medical visit or by telephone. If the patient went to a different center for the neurological event, that center was contacted to obtain the information about the event. Cerebrovascular events were defined according to the Valve Academic Research

Consortium 2 (VARC 2) criteria (326). LCVEs were defined as those occurring after 30 days (355). Stroke was defined as an acute episode of focal or global neurological dysfunction caused by a brain, spinal cord, or retinal vascular injury because of infarction or hemorrhage. Ischemic stroke was defined as an acute neurological episode caused by infarction of central nervous system tissue. Hemorrhagic stroke was defined as an acute neurological episode caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. The stroke was classified as "undetermined" if there was insufficient information to assess this categorization. The stroke event was considered as disabling if resulted (at 90 days after stroke onset) in a modified Rankin Score (mRS) score of ≥2 and an increase in ≥1 mRS category from an individual's pre-stroke baseline (326). A nondisabling stroke was the one that resulted (at 90 days after stroke onset) in an mRS score of <2 or that did not result in an increase in ≥1 mRS category from an individual's pre-stroke baseline. TIA was defined as a transient episode of focal neurological dysfunction caused by the brain, spinal cord, or retinal ischemia without acute infarction. The difference between TIA and ischemic stroke was the presence of tissue damage on neuroimaging studies or new sensory–motor deficit persisting >24 h. As a result, TIA was not associated with any lasting disability. When an LCVE was identified, echocardiographic data and antithrombotic treatment at the time of the event were recorded. The presence of valve hemodynamic deterioration, a possible surrogate of valve thrombosis, was evaluated in the echocardiography performed at the time of the LCVE (79). Also, inhospital and late clinical outcomes following the LCVE were recorded. All clinical events were defined according to the VARC-2 criteria.

4.4.1. Statistical analysis

Qualitative variables were reported as percentages and continuous data as mean (standard deviation) or median (interquartile range [IQR]), depending on their distribution. Continuous variables were compared using Student's t-test (2-tailed) or Mann-Whitney U rank sum tests as appropriate. Qualitative variables were compared with chi-square or Fisher exact tests. Survival curves were summarized using Kaplan-Meier estimates, and log-rank tests were used to compare groups. Cox multivariable regression analysis was performed to identify independent predictors of ischemic cerebrovascular events (TIA and ischemic stroke) and the predictors of mortality in the whole TAVI cohort. Variables with clinical interest and with $p < 0.05$ on univariable

analysis were entered in a multivariable analysis. The multivariate analysis was performed using backward stepwise Cox regression. All analyses were performed using a hierarchical method to account for between-center variability. A 2- sided alpha level of 0.05 was used for all statistical testing. Data of patients were censored after the first LCVE. All statistical analyses were performed using STATA version 14.0 (StataCorp, College Station, Texas) and SAS version 9.4 (SAS Institute, Cary, North Carolina).

4.5. RESULTS

Baseline, procedural characteristics, and in-hospital outcomes of the study population are shown in **Table 4.1**.

Table 4.1. Baseline, procedural characteristics, and in-hospital outcomes according to the occurrence of late cerebrovascular events.

	Overall (n=3750)	LCVEs (n=192)	No LCVEs (n=3558)	p Value
Baseline characteristics				
Age, years	80 +/-8	82 +/-7	80 +/-8	0.001
Female	1894 (50.5)	104 (54.2)	1790 (50.3)	0.301
BMI, kg/m^2	26.7 (23.8-30.4)	27.0 (24.2-30.1)	26.8 (23.8-30.5)	0.911
HTA	2999 (80.1)	158 (82.2)	2841 (80.01)	0.439
DM	1272 (33.9)	74 (38.5)	1198 (33.7)	0.167
History of smoking	712 (26.6)	32 (21.9)	680 (26.9)	0.186
COPD	859 (22.9)	43 (23.3)	816 (22.9)	0.899
Cerebrovascular disease	464 (12.4)	40 (20.8)	424 (11.9)	<0.001
Peripheral artery disease	747 (19.9)	38 (19.7)	709 (19.9)	0.956
Coronary artery disease	1648 (44.0)	78 (40.8)	1570 (44.2)	0.358
Atrial fibrillation or flutter	1169 (31.2)	56 (29.3)	1113 (31.3)	0.557
Chronic renal disease (eGFR (<60 mL/min)	1986 (53.1)	100 (52.0)	1886 (53.1)	0.775
CHADS score (mean)	3.17 (1.04)	3.42+/-1.18	3.15+/-1.03	<0.001
STS-PROM (%)	4.93 (3.37-7.53)	4.85 (3.22-8)	4.95 (3.38-7.5)	0.865
Echocardiography baseline findings				
LVEF, %	60 (48-62)	60 (50-65)	60 (48-61)	0.044
Median aortic gradient, mmHg	45 (37-55)	47 (38-59)	45 (36-55)	0.027

Aortic valve area, cm^2	0.70 (0.55-0.8)	0.66 (0.5-0.8)	0.70 (0.56-0.8)	0.058
MR>2	493 (13.9)	22 (12.0)	473 (13.9)	0.580
Procedural and in-hospital outcomes				
Valve-in-Valve	190 (5.1)	7 (3.7)	183 (5.2)	0.353
Primary access, n (%)				
Transfemoral	2970 (80.51)	156 (81.25)	2814 (80.4)	0.790
Non-transfemoral	719 (19.4)	36 (18.7)	683 (19.5)	
Valve type, n(%)				
Balloon-Expandable	1699 (45.7)	88 (46.3)	1611 (45.7)	0.874
Self-Expandable	2014 (54.2)	102 (53.6)	1912 (54.2)	0.874
Valve Embolization	28 (0.8)	3 (1.5)	25 (0.7)	0.183
Need 2nd valve	86 (2.4)	5 (2.7)	81 (2.4)	0.803
Acute renal failure	360 (9.9)	19 (10.2)	341 (9.9)	0.886
Major vascular complication	249 (6.6)	14 (7.2)	235 (6.6)	0.716
Stroke (Hospitalization)	74 (1.9)	10 (5.2)	64 (1.8)	0.004
New-onset atrial fibrillation	334 (12.8)	20 (13.6)	314 (12.7)	0.774
Echocardiography post procedure				
LVEF, %	60 (50-61)	60 (55-65)	60 (50-60)	0.005
Mean valve gradient, mmHg	10 (7-13)	9 (7-12)	10 (7-13)	0.302
Aortic valve area, cm^2	1.6 (1.3-1.9)	1.6(1.3-1.9)	1.6(1.3-1.9)	0.950
AR >2	118 (3.3)	11 (6.1)	107 (3.1)	0.031
Treatment at discharge				
MAPT	578 (15.4)	29 (15.1)	549 (15.4)	0.903
DAPT	1752 (47.2)	102 (53.1)	1650 (46.8)	0.092
Anticoagulation	1299 (34.6)	60 (31.2)	1239 (34.8)	0.311

Values are mean ± SD, median and interquartile range or n (%). LCVEs: late cerebrovascular events; BMI: Body mass index; HTA: Hypertension; D.M. Diabetes mellitus; COPD: chronic obstructive pulmonary disease; CABG: Coronary artery bypass grafting; NYHA: New York heart association; eGFR: estimated glomerular filtration rate; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

MAPT: mono antiplatelet therapy; DAPT: dual antiplatelet therapy; LCVEs: Late cerebrovascular events; LVEF: Left ventricular ejection fraction; AR: Aortic regurgitation; MR: Mitral regurgitation; TR: Tricuspid regurgitation.

Mean age of the patients was 80 +/- 8 years, 50.5% were women, and the mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 4.9% (IQR: 3.4% to 7.5%). Most procedures (80.5%) were performed through the transfemoral approach and balloon- and self-expanding transcatheter valves were used in 46% and 54% of cases, respectively. Inhospital stroke occurred in 2% of patients, and 34.6% of patients were discharged on anticoagulation therapy. Among them, 77.1% and 22.9% were under vitamin K antagonists (VKA) and novel oral anticoagulants (NOACs), respectively. Patients not receiving anticoagulation therapy were under mono or dual-antiplatelet therapy in 24.8% and 75.2% of cases, respectively. **Supplemental Tables 4.1 and 4.2** provide details about antithrombotic treatment at discharge (according to the occurrence of late ischemic or hemorrhagic cerebrovascular events).

4.5.1. Incidence, type, and factors associated with LCVEs

After a median follow-up of 2 years (IQR: 1 to 4 years), a total of 192 (5.1%) patients had an LCVE. The LCVE occurred at a median of 16 months (IQR: 5 to 33 months) post-TAVI, and the annual incidence (up to 4-year follow-up) ranged from 1.5% to 2.1% (2.14 per 100 person-years) (**Central Illustration 4.1**). The LCVE consisted of a stroke and a TIA event in 154 (80.2%) and 38 (19.8%) patients, respectively. The stroke was of ischemic, hemorrhagic, and undetermined origin in 124 (80.5%), 29 (18.8%), and 1 (0.7%) patients, respectively (**Figure 4.1**).

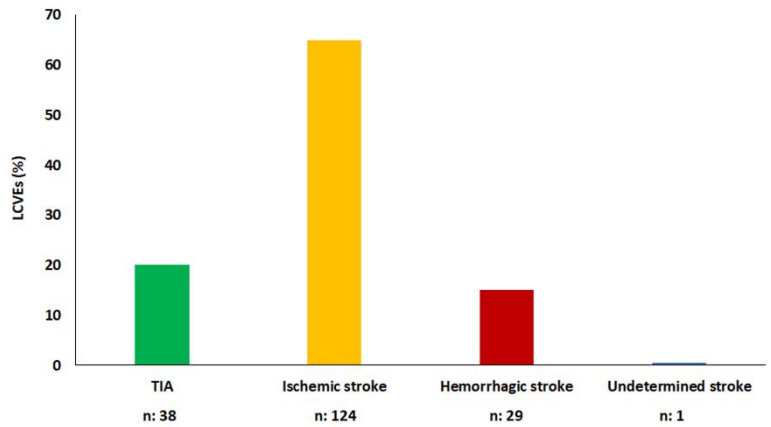
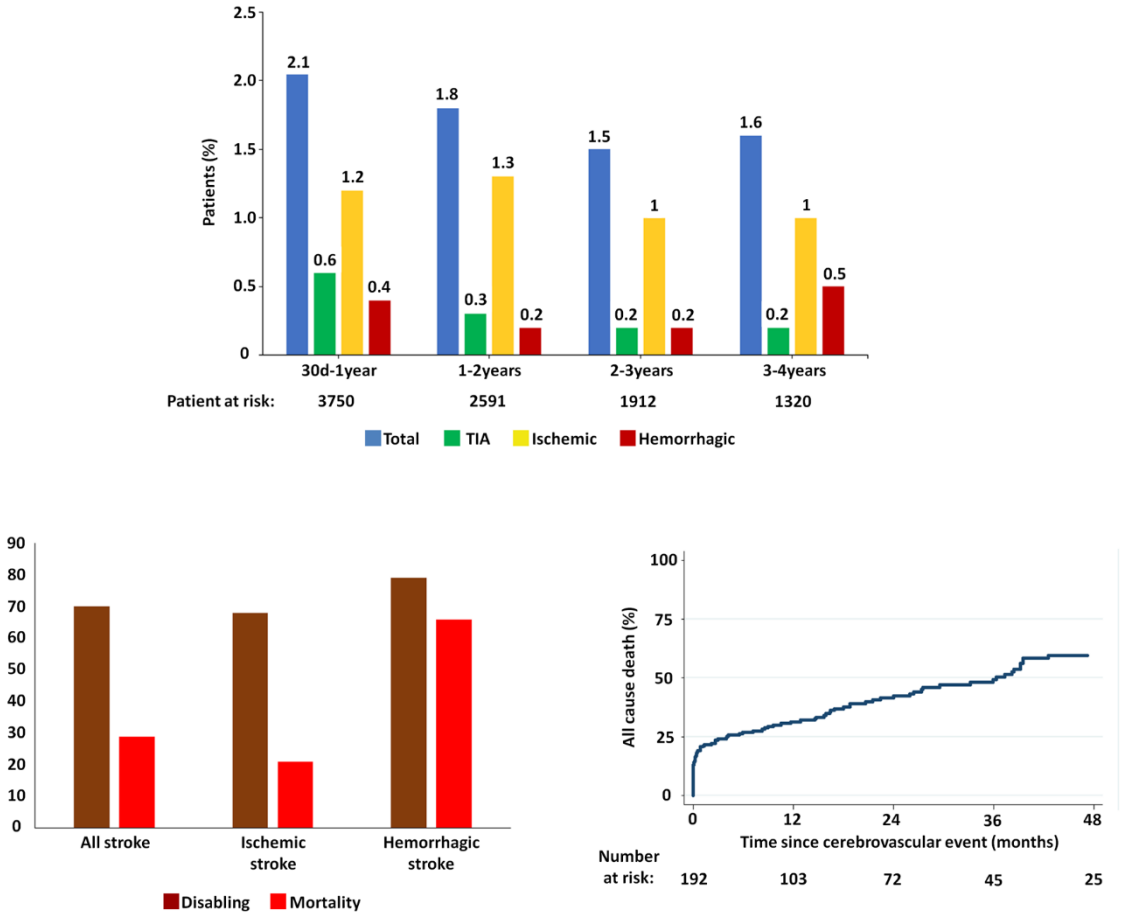


Figure 4.1. Type of LCVEs post-TAVI. TIA: Transient ischemic attack.



Central Illustration 4.1. Annual incidence, clinical severity and survival after LCVEs. Annual incidence of LCVEs in the first 4 years after the TAVI procedure (top), stroke severity (bottom, left), Kaplan-Meier curve for all-cause mortality up to 4 years following LCVE (bottom, right).
TIA: Transient ischemic attack.

The clinical and procedural characteristics of patients according to the occurrence of a LCVE are shown in **Table 4.1**. Patients with an LCVE were older, had more frequently a history of cerebrovascular disease, a higher CHADs score, a more severe aortic stenosis (higher transvalvular gradient), and had presented more frequently a stroke event during the periprocedural period ($p < 0.05$ for all). The clinical and procedural characteristics of patients who had an ischemic and hemorrhagic LCVE are shown in **Supplemental Tables 4.3 and 4.4**, respectively. The univariable and multivariable analyses for determining the predictors of LCVEs of ischemic origin (ischemic stroke or TIA) are shown in **Table 4.2**. The independent predictors of late ischemic events were older age (hazard ratio [HR]: 1.04 for each increase of 1 year; 95% confidence interval [CI]: 1.02 to 1.06), history of cerebrovascular disease (HR: 1.87; 95% CI: 1.57 to 2.21), higher baseline mean aortic gradient (HR: 1.05 for each increase of 10 mm Hg; 95% CI:

1.01 to 1.09), periprocedural stroke at the time of the TAVI procedure (HR: 3.21; 95% CI: 1.46 to 7.07), and the lack of anticoagulation (hence, patients that had received either single or dual-antiplatelet treatment) therapy at hospital discharge (HR: 1.41; 95% CI: 1.20 to 1.64).

Table 4.2. Factors associated with late ischemic events (TIA, ischemic stroke) after TAVI.

	Univariable model		Multivariable model	
	HR (95%CI)	**p value**	**HR (95%CI)**	**p value**
Age, years	1.04 (1.02-1.06)	<0.001	1.04 (1.02-1.06)	<0.001
Cerebrovascular disease	1.85 (1.53-2.24)	<0.001	1.87 (1.57-2.21)	<0.001
Baseline mean aortic gradient, mmHg*	1.08 (1.03-1.13)	<0.001	1.05 (1.01-1.09)	0.035
Periprocedural stroke during TAVI	3.55 (1.50-8.38)	0.004	3.21 (1.46-7.07)	0.004
Lack of anticoagulation at discharge	1.33 (1.01-1.64)	0.005	1.41 (1.20-1.64)	<0.001

*For each increase in 10 mmHg

Antithrombotic treatment according to the type of stroke is shown in **Figure 4.2**. Whereas most patients who had an ischemic stroke were on single antiplatelet therapy, anticoagulation treatment was more frequent in patients who had a hemorrhagic stroke (48.3% vs. 27.4%; p = 0.027) (**Supplemental Table 5.4**). Among the 14 patients under anticoagulation therapy who suffered a hemorrhagic stroke, 5 (36%) were also under antiplatelet treatment at the time of the event.

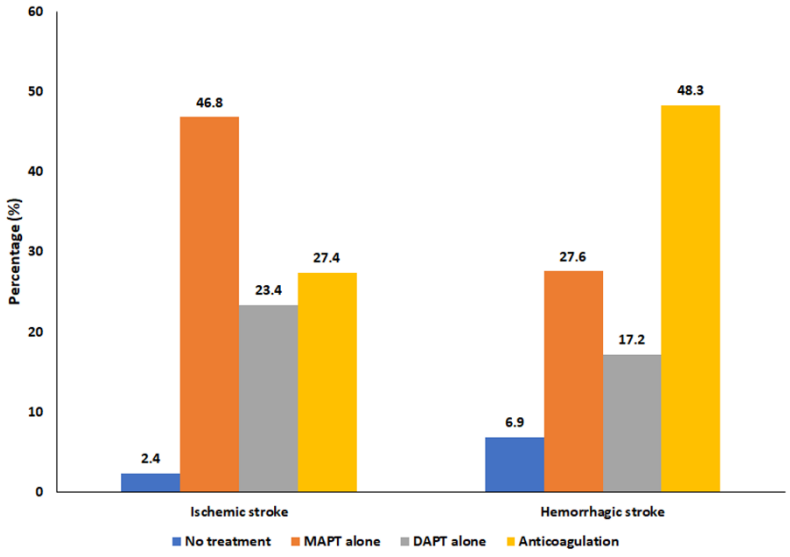


Figure 4.2. Antithrombotic treatment at the time of the stroke event, according to stroke type.
MAPT: Mono-antiplatelet therapy. DAPT: Dual antiplatelet therapy.

4.5.2. Echocardiographic assessment at the time of LCVE

Among those patients with late ischemic cerebrovascular events (TIA and ischemic stroke), transthoracic echocardiography at the time of the event was available in 94 patients (58% of patients at risk). No signs suggestive of valve thrombosis were detected in any of these patients, and the mean transvalvular gradient at the time of the event was similar to the values obtained at hospital discharge post-TAVI (**Figure 4.3**). The presence of possible structural valve degeneration (increase in mean gradient >10 mm Hg) was found in 2 (2.1%) patients and clinically relevant structural valve degeneration was present in 1 (1%) patient.

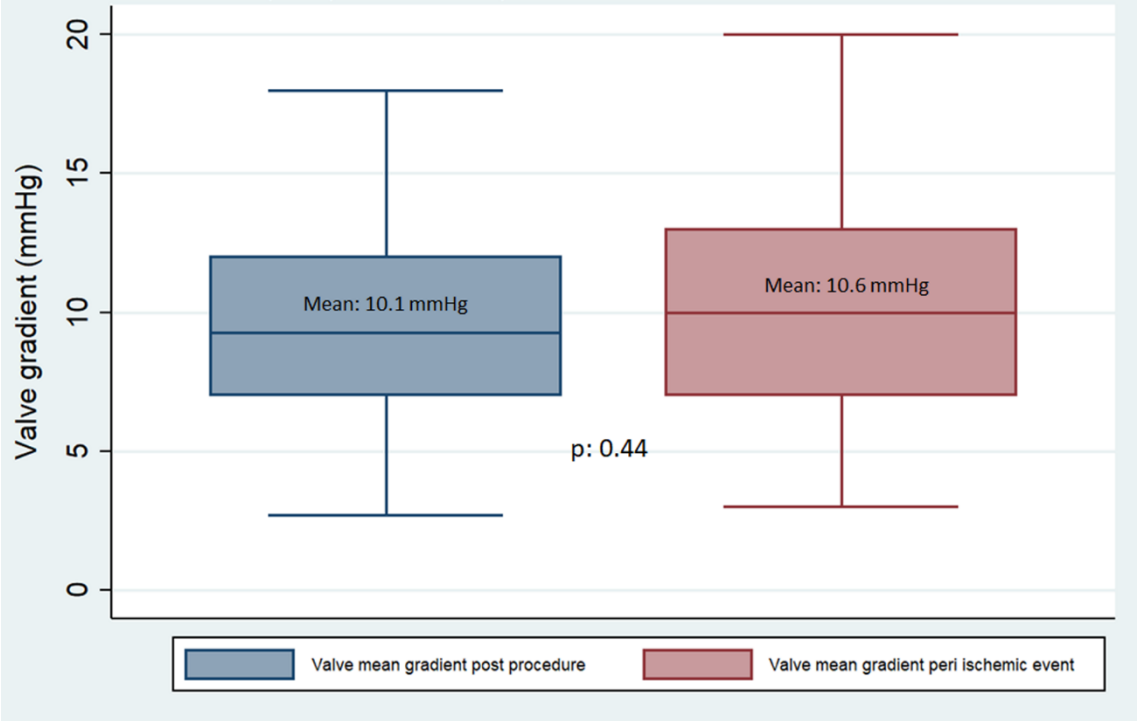


Figure 4.3. Changes in aortic valve gradient over time.
Aortic valve gradient immediately after the TAVI procedure compared to valve gradient at the time of LCVE. Values inside the box indicates the mean from aortic mean valve gradients (mmHg). The line within the box indicates the median value. Top and bottom of the box are the 75th and 25th percentiles, respectively. Error bars (end of the whisker) indicate upper and lower adjacent values (the most extreme values within 1.5 interquartile range of the nearer quartile).

4.5.3. LCVE and clinical outcomes

Late stroke was disabling in 107 (69%) patients and associated with an in-hospital mortality rate of 29% (**Central Illustration 4.1**). Among patients with hemorrhagic stroke, disabling status and in-hospital mortality rates increased up to 79% and 66%,

respectively. After a median follow-up of 15 months (IQR: 1 to 34 months) following the LCVE, a total of 92 patients (48%) had died. The Kaplan-Meier curves for all cause mortality up to 4 years following the LCVE are shown in **Figure 4.4**.

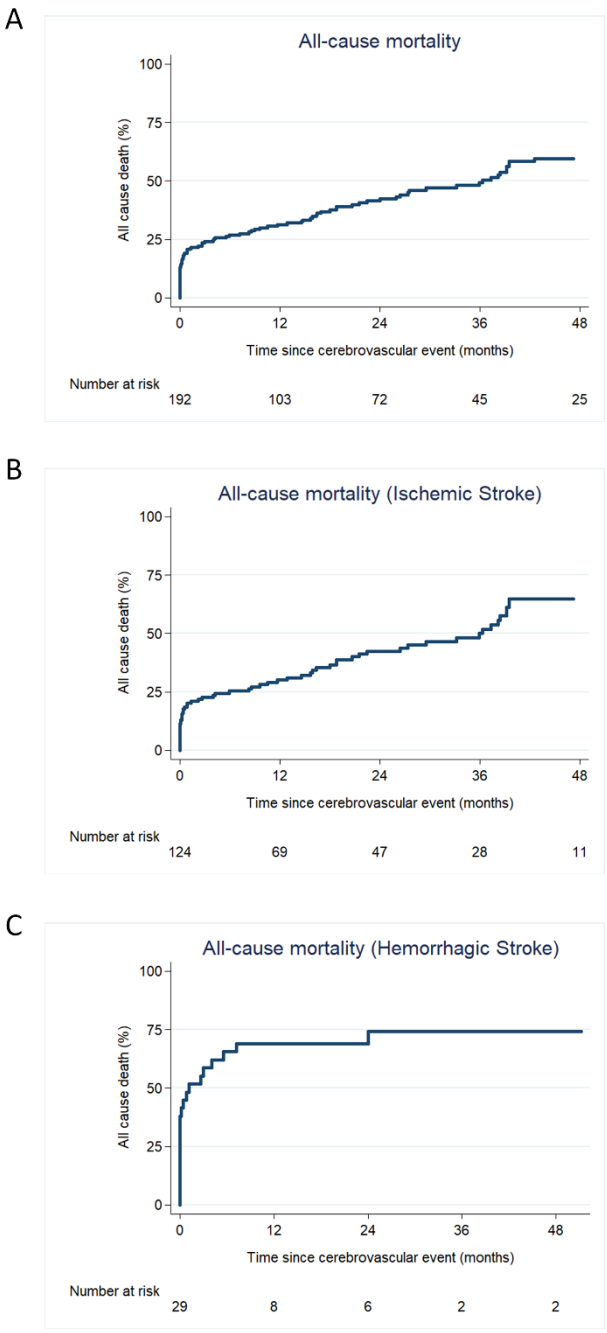


Figure 4. Kaplan-Meier curves for all-cause mortality post-LCVE.
A. Kaplan-Meier curve for all-cause death after LCVEs.
B. Kaplan-Meier curve for all-cause death after late ischemic stroke.
C. Kaplan-Meier curve for all-cause death after late hemorrhagic stroke.

The univariable and multivariable analyses of the factors associated with increased all-cause late (>30 days) mortality following TAVI (overall population) are

shown in **Table 4.3**. The occurrence of an LCVE was identified as an independent predictor of all-cause mortality following TAVI (HR: 1.34; 95% CI: 1.12 to 1.59; p ¼ 0.001). The Kaplan-Meier curves for all-cause mortality following TAVI according to the occurrence of LCVE are shown in **Figure 4.5**.

Table 4.3. Factors associated with all-cause mortality after TAVI.

	Univariable model		Multivariable model	
	HR (95%CI)	**p value**	**HR (95%CI)**	**p value**
Age, years	1.01 (1.01-1.02)	<0.001	1.02 (1.01-1.02)	<0.001
Female	0.78 (0.68-0.87)	<0.001	-	-
Diabetes	1.16 (1.08-1.24)	<0.001	-	-
History of smoking	1.14 (1.04-1.24)	0.004	-	-
COPD	1.48 (1.24-1.75)	<0.001	1.53 (1.27-1.83)	<0.001
Peripheral artery disease	1.38 (1.16-1.65)	<0.001	-	-
Coronary artery disease	1.15 (1.03-1.30)	0.017	-	-
Atrial fibrillation or flutter	1.42 (1.29-1.56)	<0.001	1.48 (1.29-1.70)	<0.001
Baseline LVEF, %	0.99 (0.99-0.99)	<0.001	0.99 (0.99-0.99)	<0.001
Transfemoral primary access	0.68 (0.56-0.83)	<0.001	0.69 (0.61-0.79)	<0.001
Acute renal failure post TAVI	1.64 (1.26-2.13)	<0.001	1.52 (1.19-1.95)	<0.001
Major vascular complication post TAVI	1.38 (1.15-1.66)	<0.001	-	-
LCVEs	1.26 (1.01-1.58)	0.047	1.34 (1.12-1.59)	0.001

Abbreviations as in Table 1

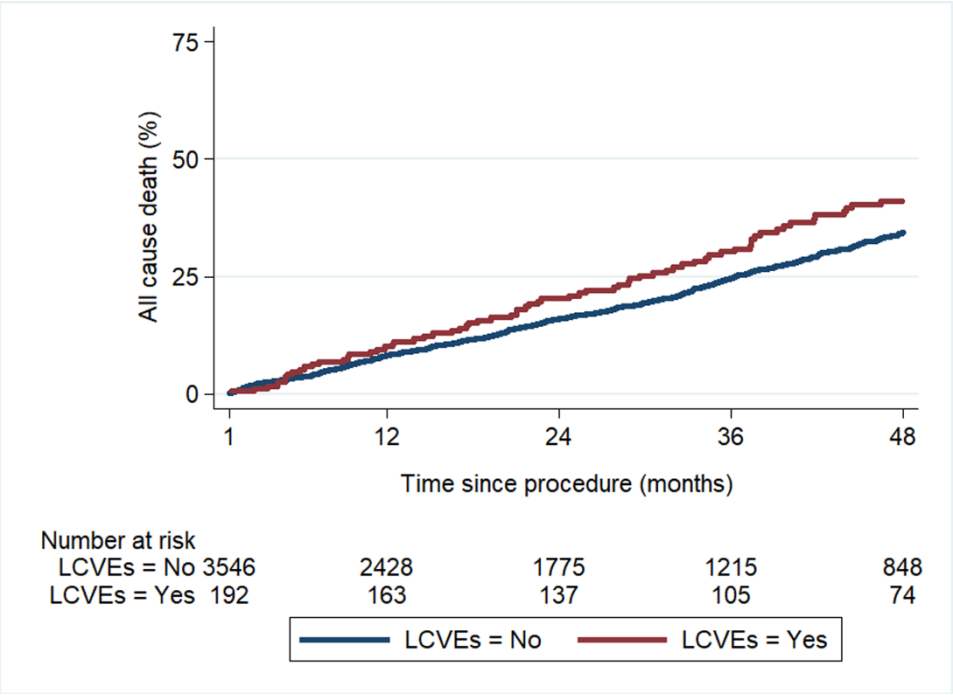


Figure 4.5. Kaplan-Meier curves for all-cause mortality according to the occurrence of LCVEs.

4.6. DISCUSSION

The main results of our study showed that LCVEs post-TAVI occurred in 5.1% of patients after a median follow up of 2 years post-TAVI, with an annual incidence of 1.5% to 2.1% over the 4 years following the procedure. Most LCVEs consisted of ischemic strokes, and older age, history of cerebrovascular disease, higher mean aortic gradient, periprocedural stroke at the time of the TAVI procedure, and the lack of anticoagulation (VKA or NOACs) therapy at hospital discharge (post-TAVI) were associated with an increased risk. However, one-half of patients suffering a hemorrhagic stroke were under anticoagulation therapy at the time of the event (a combination with antiplatelet therapy was present in one-third of them). The echocardiographic assessment at the time of the LCVE did not show signs of valve thrombosis and structural valve degeneration was detected in a minority (~3%) of patients. Two thirds of late strokes were disabling and associated with very high in-hospital (29%) and late (~50% at a median of 15 months) mortality rates. Clinical outcomes were particularly dreadful among patients with hemorrhagic stroke (disabling, 79%; in-hospital mortality, 66%).

The present study is the largest to date evaluating late neurological events in the TAVI setting. Kleiman et al. (136) reported 123 stroke events beyond the periprocedural TAVI period, but late stroke was defined as any episode occurring >10 days (instead of >30 days) after TAVI. The cumulative yearly incidence of LCVEs ranged between 1.5% and 2.1% (2.14 per 100 person-years), similar to the incidence reported in previous studies (134,136,356). Despite the use of antithrombotic therapy in most patients, this yearly cerebrovascular event rate seems to be higher than that reported in a general population of similar age (0.7 to 0.9 per 100 person-years in the 75 to 85 year old interval according to the ARIC [Atherosclerosis Risk In Communities] trial (357)]). This emphasizes the importance of identifying the factors associated with an increased risk of LCVEs in the TAVI population.

First, one may wonder whether the transcatheter aortic bioprosthesis per se may increase the risk of late stroke. The present study provides, for the first time, reassuring data regarding the echocardiographic findings at the time of the cerebrovascular event. Thus, no cases of clinically relevant valve thrombosis or endocarditis were detected, and the rate of possible or clinically relevant structural valve degeneration was low (3%), similar or even lower than that reported in previous TAVI studies with a similar follow-up period (79). Also, the rate of late stroke in PARTNER (Placement of AoRTic TraNscathetER Valve) and SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trials was similar in TAVI and SAVR patients (137,358), suggesting the lack of impact of transcatheter (vs. surgical) valves in LCVEs. Finally, TAVI candidates frequently exhibit a high atherosclerotic burden, and studies including elderly patients with coronary artery disease (non-TAVI) have reported similar rates of stroke at midterm follow-up, indirectly suggesting the lack of negative impact of the transcatheter valve on LCVEs (359).

Older age and a history of cerebrovascular disease were found to be independent predictors of ischemic LCVEs post-TAVI. These 2 factors have been associated with an increased risk of cerebrovascular events in the general population (357,360), and they have also been identified as risk factors of both early (periprocedural) and late stroke post-TAVI (134,358,361). A higher mean aortic gradient at baseline was also associated with late ischemic events. This suggests the presence of a more calcified aortic valve, a

condition that has already been associated with an increased risk of neurological events in the TAVI periprocedural period (354,358). A higher amount of aortic valve calcification may also reflect an increased atherosclerotic/inflammation burden that would indeed contribute to the risk of LCVEs (362).

Interestingly, the occurrence of periprocedural stroke was also associated with a 3-fold increased risk of LCVEs post-TAVI. Thus, in addition to mechanical factors leading to brain embolization during the TAVI procedure, periprocedural stroke seems to identify a group of patients at global risk of cerebrovascular events, and this may be considered in future studies for preventing subsequent events in these patients. Finally, the lack of anticoagulation therapy (NOACs or VKAs) at hospital discharge post-TAVI was associated with an increased risk of ischemic LCVEs. The occurrence of delayed episodes of atrial arrhythmias may partially explain such an association. In fact, the MARE trial (321), using an implantable cardiac monitoring device in TAVI recipients, showed that close to one-fifth of patients presented episodes of new-onset atrial fibrillation (most of them silent) within the months following the procedure. Identifying those patients with atrial arrhythmias could be useful to implement specific therapies as anticoagulation treatment. However, Chakravarty et al. (349) reported that subclinical leaflet thrombosis (as determined by 4-dimensional computed tomography [CT] scan) was associated with ischemic LCVEs (TIA or ischemic stroke) and anticoagulation seemed to be an effective preventive therapy. No CT data were available in the present study, but the echocardiographic data showing no significant changes in valve hemodynamics at the time of the ischemic event were not supportive of the role of valve thrombosis or structural degeneration on such events. Also, the median time of LCVEs (16 months post-TAVI) seems to be beyond the time period of subclinical transcatheter valve thrombosis, usually within the initial weeks/months post-TAVI (79).

Ongoing randomized studies will provide definite data on the potential relationship between subclinical valve thrombosis and neurological events, and on the potential role of anticoagulation post-TAVI (363,364). Meanwhile, it is important to consider that anticoagulation therapy increases the risk of bleeding events, including intracranial hemorrhage (365). In fact, the relative proportion of hemorrhagic stroke (18%) in our study population seems to be higher than that observed in the general stroke population (10% to 16%) (357,366,367), suggesting that TAVI recipients may be at

higher risk of intracranial bleeding. In fact, one-half of patients who had a hemorrhagic stroke in our study were receiving anticoagulants at the time of the event, and a significant proportion was under a combination of anticoagulant and antiplatelet drugs. Abdul-Jawad et al. (368) showed that combining anticoagulation and antiplatelet therapy in TAVI recipients increased late bleeding rates with no additional benefit with respect to ischemic events. Thus, current data along with the results from our study do not support the use of multiple antithrombotic drugs (particularly anticoagulation plus antiplatelet therapy) in TAVI and highlight the importance of implementing appropriate and evidence-based antithrombotic therapies, also considering the difficult balance between ischemic and hemorrhagic events in such patients (369,370). Finally, it should be noted that no supplemental benefit was observed in patients discharged under dual over single antiplatelet therapy regarding the occurrence of late ischemic events.

LCVEs post-TAVI had a major impact on clinical outcomes and were identified for the first time as an independent predictor of all-cause mortality among TAVI recipients. About two-thirds of stroke events were disabling and close to one-third and one-half of the patients died in-hospital and after a median follow-up of 15 months, respectively. Clinical outcomes were particularly dreadful among patients with hemorrhagic stroke, with extremely high disabling status (79%) and in-hospital mortality (66%) rates. Overall, the impact of late stroke among TAVI recipients seems to be similar to that observed in non-TAVI stroke cohorts of similar age (371). The high comorbidity burden and frequent frailty conditions in elderly individuals may likely contribute to such poor outcomes, but the possibility of elderly patients not receiving appropriate evidence-based therapies at the same level of their younger counterparts has also been pointed out as a contributing factor (372). Future studies need to determine the use of stroke evidence based therapies among TAVI recipients suffering a late stroke event.

4.6.1. Study Limitations

Although data were recorded prospectively, data analysis for this study was of retrospective nature. No event adjudication committee or echocardiographic core laboratory were available. No CT data were available for the evaluation of subclinical valve thrombosis. Finally, data on the specific treatment during the LCVE (i.e., thrombolysis or hospitalization in a specialized stroke unit) were not recorded.

4.7. CONCLUSIONS

LCVEs post-TAVI occurred at a rate of 2.14 per 100 person-years, which seems to be higher than the incidence reported in a general population of similar age. Most LCVEs were of ischemic origin and older age, prior stroke (before or during the TAVI procedure), a more severe aortic stenosis, and the lack of anticoagulation therapy post-TAVI were identified as independent risk factors. Importantly, echocardiographic studies at the time of the LCVE failed to identify valve thrombosis or degeneration as underlying factors. These data may be considered in further studies regarding potential preventive measures of LCVEs following TAVI. Most late stroke events were disabling and associated with very high early and late mortality rates, further highlighting the importance of future efforts to reduce their occurrence and implement the most appropriate therapies to improve outcomes.

4.8. CLINICAL PERSPECTIVES

What's known?

While the risk of cerebrovascular events post-TAVI peaks within the days following the procedure, very scarce data exist on late (>30 days) cerebrovascular events post-TAVI.

What's new?

LCVEs occurred in 5.1% of patients after a median follow-up of 2 years. Most LCVEs were ischemic, and older age, history of cerebrovascular disease, a higher mean aortic gradient, periprocedural stroke at the time of the TAVI procedure, and the lack of anticoagulation therapy at discharge were identified as independent predictors. Echocardiographic data did not show signs of thrombosis or degeneration in the vast majority of patients. LCVEs were associated with very high in-hospital and midterm mortality rates.

What's next?

These data may inform future studies to both reduce the occurrence of and implement the most appropriate therapies to improve outcomes following LCVEs in TAVI recipients.

4.9. ACKNOWLEDGMENTS

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4.10. SUPPLEMENTAL MATERIAL

Supplemental Table 4.1. Detailed treatment at discharge according to the presence of late ischemic events (TIA and late ischemic stroke).

		Overall (n=3750)	Late ischemic events (n=162)	Non- Late ischemic events (n=3588)	p Value
MAPT alone	**AAS**	460 (12.3)	17 (10.5)	443 (12.4)	0.482
	Clopidogrel	110 (2.93)	9 (5.56)	101 (2.81)	0.054
	Other	8 (0.22)	0 (0)	8 (0.21)	1
DAPT alone	**AAS+Clopidogrel**	1746 (45.56)	93 (57)	1653 (46.07)	0.005
	AAS+Ticagrelor/Prasugrel	6 (0.16)	0 (0)	6 (0.17)	1
Anticoagulation	**VKA**	1010 (26.9)	33 (20.37)	977 (27.23)	0.057
	NOACs	297 (7.9)	9 (5.6)	288 (8)	0.255
Anticoagulation + MAPT	**VKA + MAPT**	738 (19.7)	24 (14.8)	714 (19.9)	0.129
	NOACs + MAPT	139 (3.71)	2 (1.23)	137 (3.82)	0.089
Triple therapy (Anticoagulation + DAPT)		97 (2.6)	2 (1.23)	95 (2.65)	0.442

Values are n (%). MAPT: mono-antiplatelet therapy; DAPT: dual antiplatelet therapy; VKA: vitamin K antagonists; NOACs: novel oral anticoagulants.

Supplemental Table 4.2. Detailed treatment at discharge according to the presence of late hemorrhagic stroke

		Overall (n=3750)	Late hemorrhagic stroke (n=29)	Non- Late hemorrhagic stroke (n=3721)	p Value
MAPT alone	**AAS**	460 (12.3)	2 (6.9)	458 (12.31)	0.570
	Clopidogrel	110 (2.93)	0 (0)	110 (2.96)	1
	Other	8 (0.22)	0 (0)	8 (0.21)	1
DAPT alone	**AAS+Clopidogrel**	1746 (45.56)	9 (31)	1737 (45.68)	0.134
	AAS+Ticagrelor/Prasugrel	6 (0.16)	0 (0)	6 (0.16)	1
Anticoagulation	**VKA**	1010 (26.9)	16 (55.2)	994 (26.7)	0.001
	NOACs	297 (7.9)	2 (5.6)	295 (7.93)	0.255
Anticoagulation + MAPT	**VKA + MAPT**	738 (19.7)	13 (44.8)	725 (19.9)	0.129
	NOACs + MAPT	139 (3.71)	1 (3.5)	138 (3.7)	1
Triple therapy (Anticoagulation + DAPT)		97 (2.6)	3 (10.3)	94 (2.5)	0.038

Values are n (%). MAPT: mono-antiplatelet therapy; DAPT: dual antiplatelet therapy; VKA: vitamin K antagonists; NOACs: novel oral anticoagulants.

Supplemental Table 4.3. Baseline, procedural characteristics and in-hospital outcomes according to the presence of late ischemic events (TIA and late ischemic stroke).

	Overall (n=3750)	Late ischemic events (n=162)	Non- Late ischemic events (n=3588)	p Value
Baseline characteristics				
Age, years	80 +/-8	82 +/-7	80 +/-8	0.001
Female	1894 (50.53)	92(56.79)	1802 (50.25)	0.301
BMI, kg/m2	26.79(23.82-30.44)	26.82 (24.24-30.04)	26.78 (23.80-30.45)	0.9994
HTA	2999 (80.12)	133 (82.10)	2866 (80.03)	0.519
DM	1272 (33.94)	58 (35.80)	1214 (33.85)	0.608
History of smoking	712 (26.62)	26 (21.14)	686 (26.88)	0.159
COPD	859 (22.99)	36 (23.38)	823 (22.97)	0.906
Cerebrovascular disease	464 (12.41)	34 (20.99)	430 (12.02)	0.001
Peripheral artery disease	747 (19.95)	28 (17.28)	719 (20.07)	0.386
Coronary artery disease	1648 (44.05)	58 (36.02)	1590 (44.41)	0.036
Atrial fibrillation or flutter	1169 (31.24)	42 (26.09)	1127 (31.47)	0.149
Chronic renal disease (eGFR (<60 mL/min)	1986 (53.09)	87 (53.70)	1899 (53.06)	0.872
CHADS (mean)	3.17 +/-1.04	3.44+/-1.14	3.15+/-1.04	0.0007
STS-PROM	4.93(3.37-7.53)	4.8(3.16-8)	4.94(3.38-7.5)	0.8356
Echocardiography baseline findings				
LVEF, %	60(48-62)	60(55-65)	60(48-61)	0.0051
Mean aortic gradient, mmHg	45(37-55)	47(38-60)	45(36.85-55)	0.0299
Aortic valve area, cm^2	0.7(0.55-0.8)	0.65(0.5-0.8)	0.7(0.56-0.8)	0.0475
MR>2	493 (13.87)	20 (12.90)	473 (13.92)	0.721

Procedural and in-hospital outcomes				
Valve-in-Valve	190 (5.08)	7 (4.32)	183 (5.11)	0.653
Primary access, n (%)				
Transfemoral	2970 (80.51)	134 (82.72)	2836 (80.41)	0.468
Non-transfemoral	719 (19.49)	28 (17.28)	691 (19.59)	
Valve type, n(%)				
Balloon-Expandable	1699 (45.76)	67 (41.88)	1632 (45.93)	0.314
Self-Expandable	2014 (54.24)	93 (58.13)	1921 (54.07)	
Valve Embolization	28 (0.78)	3 (1.88)	25 (0.73)	0.110
Need 2nd valve	86 (2.42)	5 (3.18)	81 (2.38)	0.523
Acute renal failure	360 (9.96)	17 (10.83)	343 (9.92)	0.886
Major vascular complication	249 (6.65)	14 (8.64)	235 (6.56)	0.299
Stroke (Hospitalization)	74 (1.98)	10 (6.17)	64 (1.79)	< 0.001
New-onset atrial fibrillation	334 (12.84)	17 (13.60)	317 (12.80)	0.794
Echocardiography post procedure				
LVEF, %	60 (50-61)	60 (55-65)	60 (50-60)	0.0009
Mean valve gradient, mmHg	10 (7-13)	9 (7-12)	10 (7-13)	0.2978
Aortic valve area, cm^2	1.6 (1.3-1.9)	1.6(1.3-1.9)	1.6(1.3-1.9)	0.8102
AR >2	118 (3.34)	7 (4.70)	111 (3.28)	0.346
Treatment at discharge				
MAPT	578 (15.41)	26 (16.05)	552 (15.38)	0.819
DAPT	1752 (47.21)	93 (57.41)	1659 (46.75)	0.008
Anticoagulation	1299 (34.64)	42 (25.93)	1257 (35.03)	0.017

Values are mean ± SD, median and interquartile range or n (%). LCVEs: late cerebrovascular events; BMI: Body mass index; HTA: Hypertension; D.M. Diabetes mellitus; COPD: chronic obstructive pulmonary disease; CABG: Coronary artery bypass grafting; NYHA: New York heart association; eGFR: estimated glomerular filtration rate; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

MAPT: mono-antiplatelet therapy; DAPT: dual antiplatelet therapy; LVEF: Left ventricular ejection fraction; AR: Aortic regurgitation; MR: Mitral regurgitation; TR: Tricuspid regurgitation.

Supplemental Table 4.4. Baseline, procedural characteristics and in-hospital outcomes according to the presence of late hemorrhagic stroke.

	Overall (n=3750)	Late hemorrhagic stroke (n=29)	Non- Late hemorrhagic stroke (n=3721)	p Value
Baseline characteristics				
Age, years	80 +/-8	79 +/-8	80 +/-8	0.338
Female	1894 (50.53)	12 (41.38)	1882 (50.61)	0.322
BMI, kg/m2	26.79(23.82-30.44)	27.51 (24.24-30.11)	26.78 (23.81-30.44)	0.8085
HTA	2999 (80.12)	24 (82.76)	2975 (80.10)	0.721
DM	1272 (33.94)	16 (55.17)	1256 (33.77)	0.015
History of smoking	712 (26.62)	6 (26.09)	706 (26.62)	0.159
COPD	859 (22.99)	7 (24.14)	852 (22.98)	0.906
Cerebrovascular disease	464 (12.41)	6 (20.69)	458 (12.35)	0.175
Peripheral artery disease	747 (19.95)	10 (34.48)	737 (19.83)	0.049
Coronary artery disease	1648 (44.05)	58 (36.02)	1590 (44.41)	0.036
Atrial fibrillation or flutter	1169 (31.24)	14 (48.28)	1155 (31.11)	0.047
Chronic renal disease (eGFR (<60 mL/min)	1986 (53.09)	12 (41.38)	1974 (53.18)	0.0.205
CHADS (mean)	3.17 +/-1.04	3.34+/-1.37	3.16+/-1.04	0.3522
STS-PROM	4.93(3.37-7.53)	5.34(4.22-10.03)	4.92(3.36-7.5)	0.2586
Echocardiography baseline findings				
LVEF, %	60(48-62)	55(38-60)	60(48-62)	0.1791
Mean aortic gradient, mmHg	45(37-55)	47(40-52)	45(37-55.5)	0.8494
Aortic valve area, cm^2	0.7(0.55-0.8)	0.7(0.51-0.8)	0.7(0.55-0.8)	0.9603
MR>2	493 (13.87)	2 (8.33)	491 (13.91)	0.565
Procedural and in-hospital outcomes				
Valve-in-Valve	190 (5.08)	0(0))	190 (5.12)	0.4
Primary access, n (%)				

Transfemoral	2970 (80.51)	21 (72.41)	2949 (80.57)	0.269
Non-transfemoral	719 (19.49)	8 (27.59)	711 (19.43)	
Valve type, n(%)				
Balloon-Expandable	1699 (45.76)	20 (68.97)	1679 (45.58)	0.012
Self-Expandable	2014 (54.24)	9 (31.03)	2005 (54.42)	
Valve Embolization	28 (0.78)	0 (0)	28 (0.79)	1
Need 2nd valve	86 (2.42)	0(0)	86 (2.44)	1
Acute renal failure	360 (9.96)	2 (7.41)	358 (9.98)	0.656
Major vascular complication	249 (6.65)	0 (0)	249 (6.71)	0.258
Stroke (Hospitalization)	74 (1.98)	0 (0)	74 (2)	1
New-onset atrial fibrillation	334 (12.84)	3 (13.64)	331 (12.83)	0.794
Echocardiography post procedure				
LVEF, %	60 (50-61)	60 (46-61)	60 (50-61)	0.5964
Mean valve gradient, mmHg	10 (7-13)	10 (7.5-10.5)	10 (7-13)	0.7809
Aortic valve area, cm^2	1.6 (1.3-1.9)	1.7 (1.4-2)	1.6 (1.3-1.9)	0.9643
AR >2	118 (3.34)	4 (14.29)	114 (3.25)	0.013
Treatment at discharge				
MAPT	578 (15.41)	2 (6.90)	576 (15.48)	0.300
DAPT	1752 (47.21)	9 (31.03)	1743 (47.34)	0.080
Anticoagulation	1299 (34.64)	18 (62.07)	1281 (34.43)	0.002

Values are mean ± SD, median and interquartile range or n (%). LCVEs: late cerebrovascular events; BMI: Body mass index; HTA: Hypertension; D.M. Diabetes mellitus; COPD: chronic obstructive pulmonary disease; CABG: Coronary artery bypass grafting; NYHA: New York heart association; eGFR: estimated glomerular filtration rate; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

MAPT: mono-antiplatelet therapy; DAPT: dual antiplatelet therapy; LVEF: Left ventricular ejection fraction; AR: Aortic regurgitation; MR: Mitral regurgitation; TR: Tricuspid regurgitation.

Supplemental Table 4.5. Anticoagulation vs Non-anticoagulation according to type of stroke in the moment of stroke event.

	Ischemic stroke	Hemorrhagic stroke	p value
Anticoagulation	34 (27.4)	14 (48.3)	0.029
Non-Anticoagulation	90 (72.6)	15 (51.7)	

CHAPTER 5

Ambulatory Electrocardiographic Monitoring Following Minimalist Transcatheter Aortic Valve Implantation

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5.1. RÉSUMÉ

Étude prospective multicentrique incluant 459 patients TAVI sans stimulateur cardiaque. L'objectif était de déterminer l'impact du bloc auriculo-ventriculaire complet ou de haut degré tardif (BAC/BHD) en utilisant une approche minimaliste (séjour à l'hôpital : 2 [1-3] jours) suivie d'une surveillance ambulatoire par électrocardiogramme (SAE). La surveillance systématique pendant 2 semaines a détecté des épisodes de BAC/BHD dans ~5% des cas, sans mortalité à 1 mois. Alors que le BAC/BHD était rare chez les patients sans modification de l'électrocardiogramme après la procédure (2,2 %), les patients avec bloc de branche droite (13,6 %) et les patients avec troubles de conduction *de novo* (8,5 %) ont déterminé un risque accru. Ces résultats plaident en faveur d'une prise en charge individualisée post TAVI, en utilisant une surveillance continue après la sortie de l'hôpital et en évaluant des périodes d'hospitalisation plus longues chez les patients à haut risque de troubles du rythme tardifs.

5.2. ABSTRACT

Background: Little is known regarding the clinical impact of high-degree atrioventricular or complete heart block (HAVB/CHB) in the early period after discharge following transcatheter aortic valve implantation (TAVI).

Objectives: To determine the impact of delayed HAVB/CHB after TAVI using a minimalist approach followed by ambulatory electrocardiographic (AECG) monitoring.

Methods: Prospective, multicenter study including 459 consecutive TAVI patients without permanent pacemaker (PPM) who had continuous AECG monitoring for 14 days (hospital stay: 2 [1-3] days), using two devices (CardioSTAT and Zio AT). Primary endpoint: occurrence of HAVB/CHB. Patients were divided into 3 groups: I) No right bundle branch block (RBBB) and no electrocardiographic (ECG) changes; II) Baseline RBBB with no further changes; III) New-onset ECG conduction disturbances (ECG-CDs).

Results: Delayed HAVB/CHB episodes occurred in 21 (4.6%) patients (median: 5 [4-6] days post-procedure), leading to PPM in 17 (80.9%). HAVB/CHB events were rare in group I (7/315 [2.2%]), and its incidence increased in group II (5/38 [13.6%], $p<0.001$ vs group I) and III (9/106, [8.5%]; $p=0.007$ vs group I, $p=0.523$ vs group II). No episodes of sudden or all-cause death occurred at 30-day follow-up.

Conclusions: Systematic 2-week AECG monitoring following minimalist TAVI detected HAVB/CHB episodes in ~5% of cases, with no mortality at 1-month. Whereas HAVB/CHB was rare in patients without ECG changes post-TAVI, baseline RBBB and new-onset CDs (particularly new-onset first-degree atrioventricular block) determined an increased risk. These results would support a tailored management using AECG monitoring and the possibility of longer hospitalization periods in patients at higher risk of delayed HAVB/CHB.

5.3. INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of aortic stenosis. However, the occurrence of new-onset left bundle branch block (LBBB), high-degree atrioventricular block (HAVB), or complete heart block (CHB) leading to permanent pacemaker (PPM) implantation remains the most frequent drawback of the procedure (145), and its management is still under debate (296,297). Whereas periprocedural arrhythmic disorders have been largely studied, scarce data exist regarding delayed (>48 hours) events, particularly those occurring after hospital discharge. Also, the TAVI field has progressively evolved to a "minimalist" approach with a short length of stay (24-48 hours after the procedure or even same-day discharge) (126,127), which may be controversial regarding the occurrence of delayed arrhythmic disorders.

Ambulatory electrocardiographic (AECG) monitoring during the early postdischarge period has emerged as a tool for the early diagnosis and treatment of delayed arrhythmic events following TAVI (315). Furthermore, a recent scientific expert panel focusing on conduction disturbances (CDs) after TAVI proposed a tailored postprocedural management on the basis of baseline and post-TAVI electrocardiography, recommending the use of AECG monitoring in specific subsets such as patients with new electrocardiographic (ECG) CDs or baseline right bundle branch block (RBBB) (296). However, such a strategy lacks prospective validation. The objectives of this study using systematic AECG monitoring in consecutive TAVI recipients were to determine the incidence and clinical impact of delayed HAVB or CHB episodes in the overall TAVI population and according to the prespecified groups at risk (no RBBB or new-onset CDs, baseline RBBB, new-onset ECG CDs).

5.4 METHODS

5.4.1. Study design

This was a prospective study including consecutive transarterial TAVI patients. Exclusion criteria included previous or in-hospital PPM or implantable cardioverter-defibrillator, inhospital death, participation in other TAVI studies, and transaortic access. The study included 2 prospective cohorts from 2 centers that were pooled in a single

database. The first cohort was from a prospective trial (NCT04298593), and the second consisted of a prospective clinical implementation of a local protocol for AECG monitoring after TAVI. An AECG monitoring device (CardioSTAT [Icentia] or Zio AT Patch [iRhythm Technologies]) was implanted before hospital discharge (the day before or the same day of discharge) to perform AECG monitoring for 14 days. All types of arrhythmic events were recorded. Clinical follow-up was performed at 30 days. The study was performed in accordance with each local institutional ethics committees, and all patients provided signed informed consent for the procedures.

5.4.2. CardioSTAT Device

The CardioSTAT is a single-use, wire-free, wearable heart monitoring patch that provides continuous rhythm monitoring (single ECG trace lead) for 14 days (second-generation device). The device has shown an excellent correlation with standard Holter ECG monitoring in a clinical validation study (373). Patients reported symptoms potentially related to arrhythmic events (eg, palpitations, dizziness, dyspnea, exercise intolerance) by writing notes in a dedicated chart or pressing a symptom trigger button located on the front of the device. Once the monitoring period was complete, the patient returned the device personally or by mail. As soon as the patient returned the CardioSTAT, the data were analyzed by a certified technologist, and a report was sent electronically to a cardiac electrophysiologist for validation and final reporting. The time delay between the end of the monitoring and the initial data interpretation was no longer than 7 days. Patients with inadequate CardioSTAT signal (reported noise > 50%) were excluded.

5.4.3. Zio AT Device

The Zio AT device is a single-use, water-resistant patch that sticks to the patient's chest and monitors the heart rhythm for up to 14-days. The device integrates a symptom trigger button that can be pressed upon the occurrence of symptoms related to arrhythmias. The device has shown correlation with standard Holter ECG monitoring (374). Rhythm data were collected and analyzed when the device was received by the manufacturer. On the basis of a predefined notification criterion (**Supplemental Table**

5.1), events were reported to the prescribing provider while a call was placed to the patient's emergency contact. Individuals who met the predefined criteria were alerted and instructed to visit the emergency department. The final report was reviewed by a board-certified electrophysiologist.

5.4.4. Outcomes

The management of bradyarrhythmic events after the TAVI procedure followed the recommendations of a recent scientific expert consensus focusing on CDs post-TAVI (296), which divided TAVI recipients into several groups according to baseline and postprocedural ECG findings. In accordance with this expert consensus, arrhythmic and clinical events were analyzed according to 3 groups: 1) no changes between baseline and discharge electrocardiography in patients without baseline RBBB, irrespective of other baseline ECG CDs (group 1); 2) no changes between baseline and discharge electrocardiography, in patients with baseline RBBB (group 2); and 3) new-onset ECG CDs, which included new-onset LBBB, new-onset first-degree atrioventricular block (1-AVB), new large QRS (120 ms) without LBBB morphology, and significant ECG changes (increase in PR and/or QRS duration of ≥20 ms) in patients with preexisting ECG CDs (1-AVB, RBBB, LBBB, or nonspecific intraventricular conduction delay) (group 3) (**Figure 5.1**).

The primary outcome was the occurrence of HAVB or CHB during the 14-day AECG monitoring period, overall and according to the prespecified groups. Secondary outcomes were the occurrence of all type of arrhythmic events (tachyarrhythmias and bradyarrhythmias), bradyarrhythmic events leading to PPM implantation, global mortality, and sudden cardiac death at 30-day follow-up. HAVB was defined as any of the following: second-degree atrioventricular block type 2 (Mobitz II), 2:1 atrioventricular block, or ≥2 consecutive P waves that did not conduct to the ventricle. CHB was defined as P waves with a constant rate with dissociated ventricular rhythm or fixed slow ventricular rhythm in the presence of atrial fibrillation (173). A significant pause was defined as any pause lasting >4 seconds. Paroxysmal atrial fibrillation was defined as any irregular atrial rhythm with the absence of consistent P waves lasting at least 30 seconds (375). Nonsustained ventricular tachycardia was defined as runs of ≥3

ventricular beats at a heart rate of >100 beats/min lasting <30 seconds. When ventricular runs lasted ≥30 seconds, it was classified as sustained ventricular tachycardia (376).

Clinical events were defined according to the Valve Academic Research Consortium-2 criteria (326). Sudden cardiac death was defined as a death occurring within 1 hour of symptom onset if witnessed or within the previous 24 hours if unwitnessed (377).

5.4.5. Statistical analysis

Qualitative variables are expressed as percentages and numeric variables as mean (standard deviation) or median (interquartile range) according to variable distribution. Categorical variables were compared using the chi-square or Fisher exact test as appropriate. Numeric variables were compared using Student's t-test or the Wilcoxon test as appropriate. A 2-sided alpha level of 0.05 was used for all statistical testing. All statistical analyses were performed using Stata version 14.0 (StataCorp).

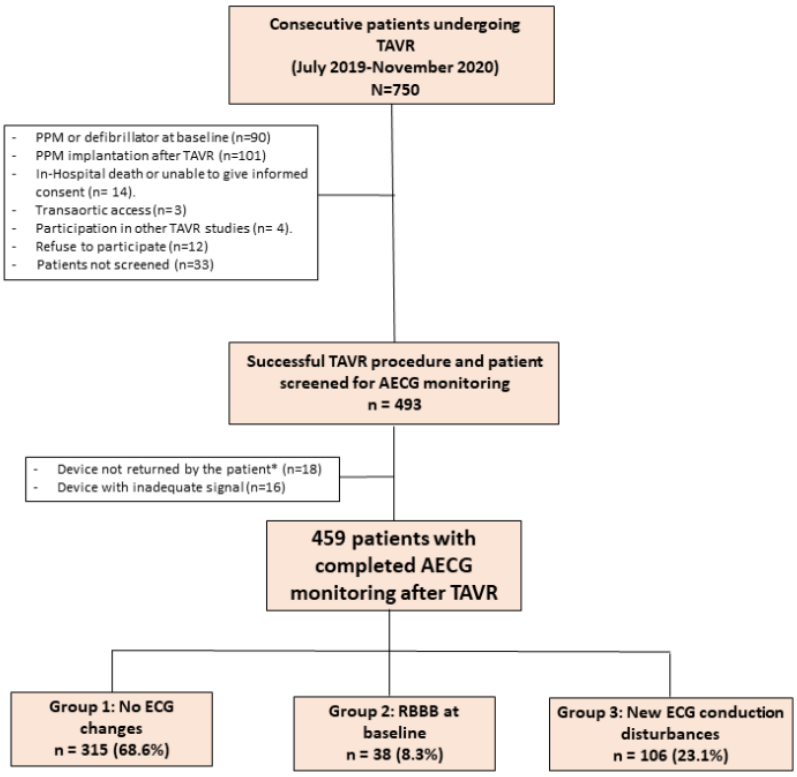


Figure 5.1. Flowchart of the study population.
AECG monitoring = Ambulatory ECG monitoring; ECG = Electrocardiogram; RBBB = Right bundle branch block; PPM = Permanent pacemaker; TAVI = Transcatheter aortic valve implantation.

*The reasons to not return the device were not related to medical conditions (patients forgot and/or did not correctly understand how to do it). No deaths or hospitalizations due to bradyarrhythmic events occurred in these patients.

5.5. RESULTS

Among 750 consecutive TAVI procedures performed between July 2019 and October 2020, 493 patients met the inclusion criteria and were screened for AECG monitoring (**Figure 5.1**). After the exclusion of ECG tracings with inadequate signal and lost devices (n = 34 [6.9%]; no mortality or hospitalization events due to bradyarrhythmias occurred in these patients), 459 patients completed the AECG monitoring, 211 (46%) and 248 (54%) with the CardioSTAT and Zio AT devices, respectively. **Table 5.1** depicts the clinical and procedural characteristics of the study population. The mean age was 79 +/- 8 years, 208 patients (45.3%) were women, and the mean Society of Thoracic Surgeons Predicted Risk of Mortality score was of 3.6% +/- 2.7%. A total of 126 patients (27%) had prior atrial fibrillation, and balloon- and self-expandable valves were used in 393 (85.6%) and 65 (14.2%) patients, respectively. The TAVI approach was transfemoral in 407 patients (88.7%), and the median hospitalization length was 2 days (interquartile range: 1-3 days).

Table 5.1. Clinical and procedural characteristics of the study population

Baseline characteristics	
Age	79 +/- 8
Women	208 (45.3)
Hypertension	422 (91.9)
Diabetes mellitus	196 (42.7)
Coronary artery disease	267 (58.3)
Atrial fibrillation or flutter*	126 (27.5)
STS-PROM	3.6 +/- 2.7
Baseline treatment	
Beta-blockers	186 (40.5)
Amiodarone	22 (4.8)
Anticoagulation	135 (29.4)
Echocardiography	
Left ventricular ejection fraction	57 +/-11
Mean gradient, mmHg	43 (35-52)
Aortic valve area	0.8 (0.6-0.9)
Procedure	
Valve type	
Sapien 3/Ultra	393 (85.6)
Evolut R/Pro	58 (12.6)
Acurate	6 (1.3)

Jenavalve	1 (0.2)
Lotus	1 (0.2)
Approach	
Transfemoral	407 (88.7)
Other (transcarotid, transubclavian)	52 (11.3)
Prosthesis size	
≤23 mm	174 (38.2)
>23 mm	282 (61.8)
Electrocardiogram at discharge	
Atrial fibrillation	51 (11.1)
PR interval, ms	183 +/- 34
QRS interval, ms	113 +/- 30
First-degree atrioventricular block*	80 (20)
Right bundle branch block	43 (9.4)
New-onset left bundle branch block	50 (10.9)
Medical treatment at discharge	
Beta-blockers	194 (42.3)
Amiodarone	21 (4.6)
Anticoagulation	143 (31.2)
Length of hospital stay, days	2 (1-3)

Values are mean +/- SD, n (%), or median (interquartile range).
STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.
*Permanent and paroxysmal.

The prespecified groups for the analysis of bradyarrhythmic events were distributed as follows: 315 patients (68.6%) in group 1, 38 (8.3%) in group 2, and 106 (23.1%) in group 3 (**Figure 5.1**). In group 1, 248 patients (79.0%) exhibited no significant ECG CDs (PR interval ≤ 200 ms if sinus rhythm and QRS duration < 120 ms), and 35 (11.2%) and 38 (12.1%) had 1-AVB and QRS duration > 120 ms, respectively (**Supplemental Table 5.2**). Among the 107 patients from group 3, new-onset 1-AVB and LBBB were found in 36 (33.6%) and 50 (46.7%) patients, respectively (**Supplemental Table 3**). Among the 36 patients with new-onset 1-AVB, 4 (11.1%), 7 (19.4%), and 2 (5.6%) had RBBB, LBBB, or nonspecific intraventricular conduction delay at baseline. The presence of PR and/or QRS enlargement in patients with baseline ECG CDs was found in 26 patients (24.3%) in group 3.

5.5.1. Bradyarrhythmic events

AECG monitoring revealed significant bradyarrhythmic events occurring within the 2-week period after hospital discharge in 36 patients (7.8%), 12 of them (33.3%)

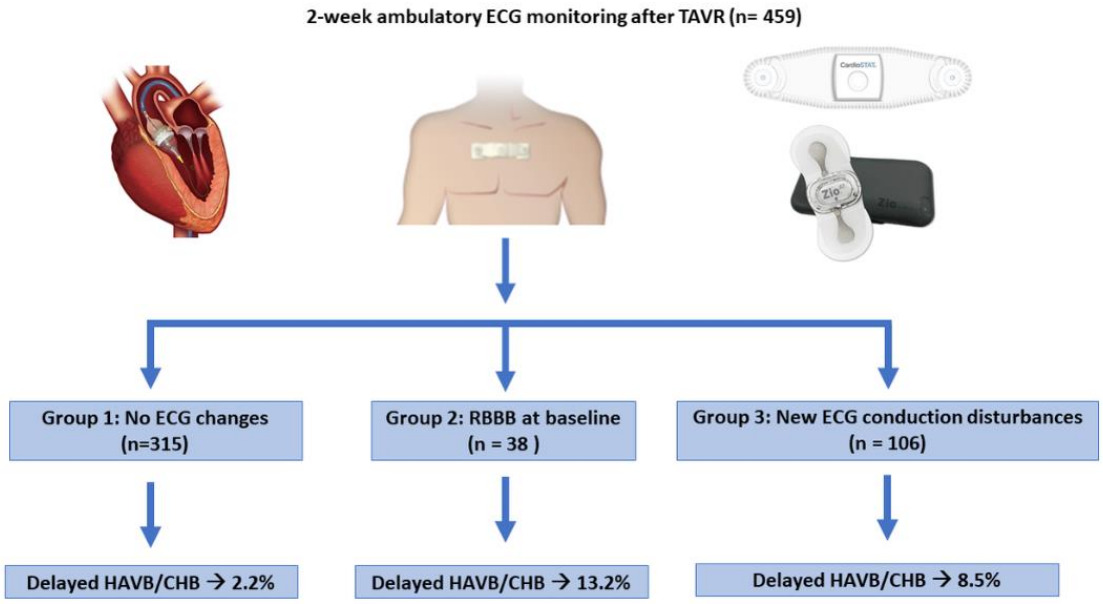
symptomatic (**Table 5.2**). HAVB or CHB and significant pause events occurred in 21 (4.6%) and 15 (3.3%) patients, respectively. PPM implantation because of AECG monitoring findings was performed in 19 TAVI recipients (4.1%) (**Table 5.2**).

Table 5.2. Bradyarrhythmic events

		Overall (n=459)	Group I (n=315)	Group II (n=38)	Group III (n=106)	P Value Global	Group I vs II	Group I vs III	Group II vs III
HAVB/CHB		21 (4.6)	7 (2.2)	5 (13.2)	9 (8.5)	0.001	<0.001	0.007	0.523
Time to HAVB/CHB		5 (5-6)	6 (4-8)	6 (5-6)	5 (5-6)	0.999	0.999	0.999	0.999
Significant pause (>4 sec)		15 (3.3)	9 (2.9)	2 (5.3)	4 (3.8)	0.519	0.336	0.745	0.654
Any bradyarrhythmia		36 (7.8)	16 (5.1)	7 (18.4)	13 (12.3)	0.002	0.002	0.024	0.346
Symptomatic	Overall	12 (2.6)	4 (1.3)	4 (10.5)	4 (3.8)	0.005	0.006	0.114	0.208
event	HAVB/CHB	11 (2.4)	4 (1.3)	4 (10.5)	3 (2.8)	0.007	0.006	0.375	0.079
	Significant pause	1 (0.2)	0 (0)	0 (0)	1 (0.9)	0.314	-	0.252	0.999
PPM	Overall	19 (4.1)	7 (2.2)	5 (13.2)	7 (6.6)	0.002	<0.001	0.053	0.302
implantation	HAVB/CHB	17 (3.7)	6 (1.9)	5 (13.2)	6 (5.7)	0.002	<0.001	0.083	0.159
	Significant pause	2 (0.4)	1 (0.3)	0 (0)	1 (0.9)	0.529	0.999	0.441	0.999

Values are n (%) or median (interquartile range).
Groups were defined according to baseline and discharge ECG. Group 1: No changes between baseline and discharge (irrespective of previous ECG-CDs); Group 2: RBBB at baseline; Group 3: New CDs after TAVR (new-onset LBBB, new 1-AVB, new wide QRS without LBBB morphology).
CDs: Conduction disturbances; ECG: Electrocardiogram; HAVB/CHB: High-degree atrioventricular block/Complete heart block; LBBB: Left bundle branch block; RBBB: Right bundle branch block; PPM: Permanent pacemaker implantation.

Significant differences were found in the incidence of HAVB or CHB according to the prespecified groups (**Table 5.2, Central Illustration 5.1**). The incidence of HAVB or CHB episodes was 2.2% in patients without changes between baseline and discharge electrocardiography (group 1), and all patients underwent PPM implantation (2.2%) (**Table 5.2, Figure 5.2**). Patients with RBBB at baseline and without further ECG changes (group 2) exhibited a 13.2% rate of both HAVB or CHB episodes and PPM implantation ($P < 0.001$ vs group 1). Patients with de novo ECG CDs (group 3) had incidence rates of 8.5% and 6.6% of HAVB or CHB events and PPM implantation, respectively (HAVB or CHB, $P = 0.007$ vs group 1 and $P = 0.523$ vs group 2; PPM implantation, $P = 0.053$ vs group 1 and $P = 0.302$ vs group 2).



Central Illustration 5.2. 2-week ambulatory ECG monitoring following TAVI.
Ambulatory ECG (AECG) monitoring was performed in consecutive patients without permanent pacemaker implantation following TAVI. Two patch-based devices were used, the CardioSTAT (Icentia Inc, Quebec, Canada) and the Zio AT (iRhythm Technologies, Inc., San Francisco, CA, USA) . The primary endpoint was the occurrence of HAVB/CHB. Groups were defined according to baseline and discharge ECG conduction disturbances (ECG-CDs). Group 1: No changes between baseline and discharge (irrespective of previous ECG-CDs); Group 2: RBBB at baseline; Group 3: New CDs after TAVI (new-onset LBBB, new 1-AVB, new wide QRS without LBBB morphology).
CHB: Complete heart block; ECG: Electrocardiogram; HAVB: High-degree atrioventricular block; RBBB: Right bundle branch block. TAVI: Transcatheter aortic valve implantation.

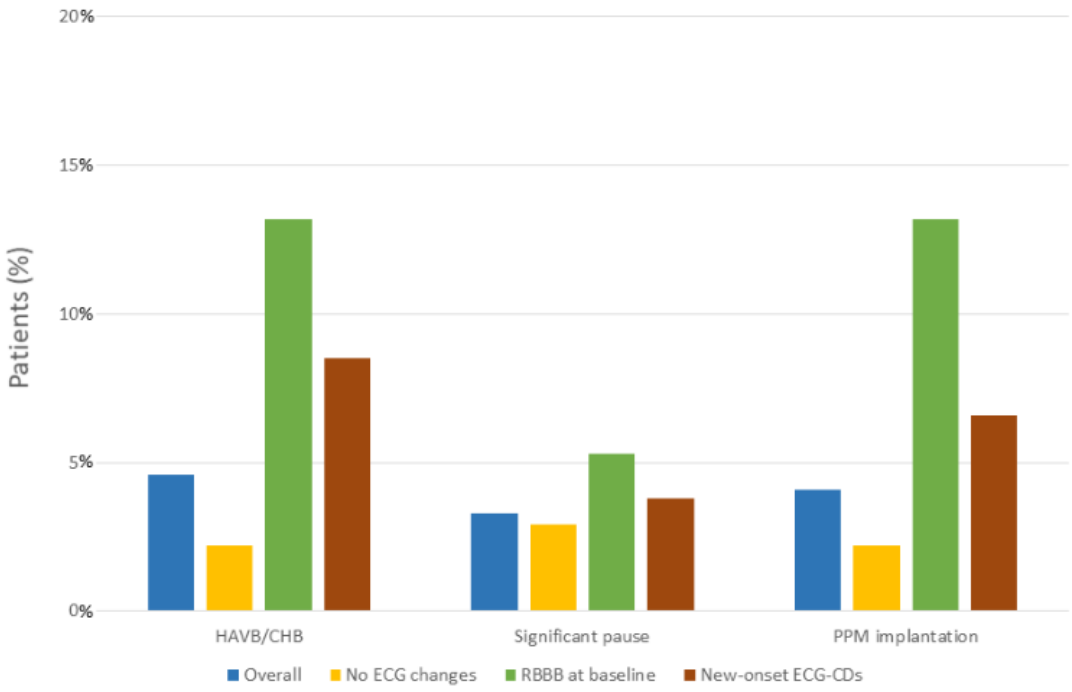


Figure 5.2. Bradyarrhythmic events and pacemaker implantation in the overall population and according to the prespecified groups.
ECG: Electrocardiogram; ECG-CDs: Electrocardiogram conduction disturbances; HAVB/CHB = High-degree atrioventricular block/Complete heart block; LBBB = left bundle branch block; RBBB = Right bundle branch block; PPM = Permanent pacemaker.

HAVB or SB events were symptomatic (temporal correlation between symptoms and the bradyarrhythmic event) in 12 of 459 patients (2.6%) (overall cohort), with significant differences between groups (10.5% in group 2 vs 1.3% and 3.8% in groups 1 [P < 0.001] and 3 [P = 0.079], respectively) (**Table 5.2**). The detailed individual characteristics of all patients with HAVB or CHB and/or PPM implantation due to AECG monitoring findings are described in **Supplemental Table 5.4**. Among the 11 of 21 patients (52.4%) with HAVB/CHB and symptomatic events, 2 patients had syncope, 1 had a presyncope episode, 6 experienced dizziness or light-headedness, and 2 had chest pain. All underwent PPM implantation. Regarding the 15 patients with significant pause episodes, the bradyarrhythmic event was symptomatic in 1 (6.7%), who did not undergo PPM implantation. Overall, PPM implantation was performed in 17 of 21 (80.9%) and 2 of 15 (13.3%) patients with HAVB or CHB and significant pauses, respectively (**Table 5.2, Supplemental Table 5.4**). Of note, PPM implantation in asymptomatic patients was performed in 6 and 2 patients with HAVB or CHB and significant pauses, respectively.

The overall median time from the TAVI procedure to the HAVB or CHB event was 5 days (interquartile range: 4-6 days) (4 days [interquartile range: 3-5 days] after hospital discharge), without significant differences among the prespecified groups (P = 0.999) (**Table 5.2**). A summary of the time from the procedure to HAVB or CHB episode in the overall cohort and according to the prespecified groups is shown in **Figure 5.3**. Overall, most (16 of 21 [76%]) events occurred within 3 to 6 days after the procedure, with similar timing patterns across the prespecified groups (**Figure 5.3**).

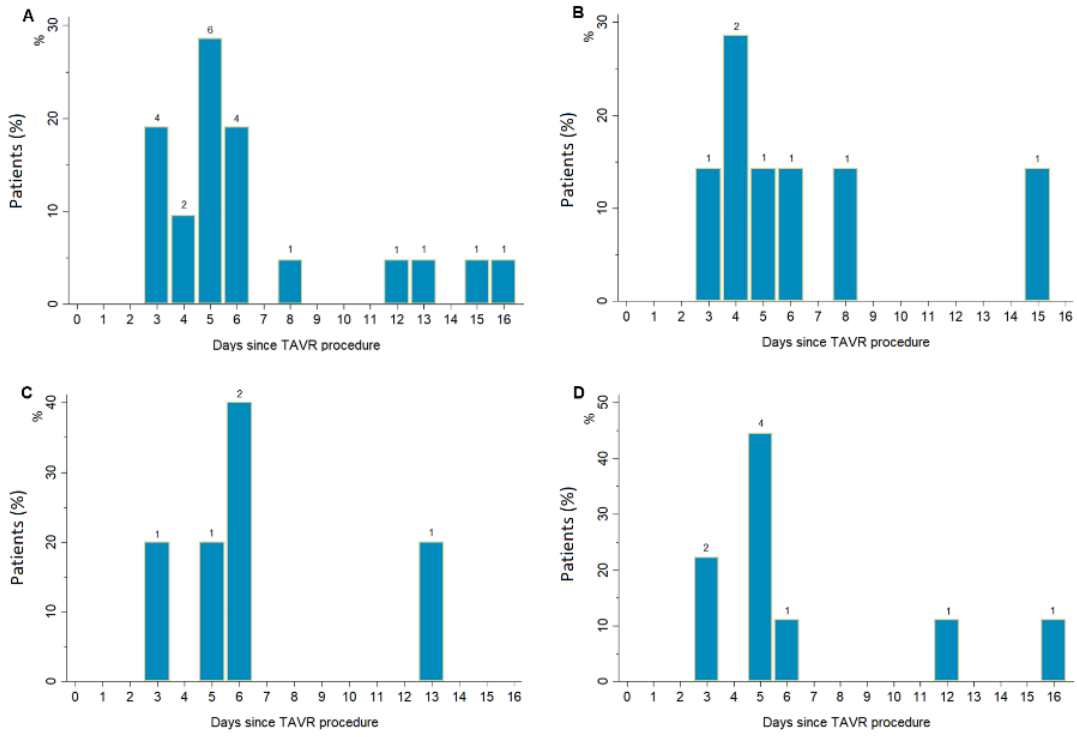


Figure 5.3. Time to HAVB/CHB event in the overall cohort and according to the prespecified groups.
A. Overall population.
B. Group I. No ECG changes in patients without RBBB at baseline.
C. Group II. RBBB at baseline, without further ECG changes.
D. Group III. New-onset ECG-CDs.
The y-axis shows the rate of patients with HAVB/CHB. The x-axis indicates the days since the TAVI procedure. The value at the top of each bar indicates the total number of patients with HAVB/CHB.
ECG: Electrocardiogram; ECG-CDs: Electrocardiogram conduction disturbances; HAVB/CHB: High-degree atrioventricular or complete heart block; RBBB: Right bundle branch block.

Figure 5.4 shows the incidence of HAVB or CHB events and the PPM implantation rate according to a more detailed subgroup classification. The lowest rate of HAVB or CHB events was found in patients in group 1 without significant baseline ECG

CDs (PR duration ≥200ms if sinus rhythm, QRS duration < 120 ms). In this group, 3 of 248 patients (1.2%) had HAVB or CHB episodes after hospital discharge (symptomatic in 1 or 248 [0.4%]), leading to PPM implantation in all of them. Patients with new-onset LBBB showed a rate of HAVB or CHB episodes of 4%, and the patients in group 1 and with ECG CDs at baseline had a rate of 6%. Finally, a higher incidence of HAVB or CHB was observed in patients with RBBB at baseline (13.2%) and in those with new-onset 1-AVB (13.9%). Among the 36 patients with new-onset 1-AVB, 5 experienced HAVB or CHB. HAVB/ CHB events were more frequent in those patients with new1-AVB and QRS duration>120ms at discharge (4 of 13 [30.8%]). The occurrence of bradyarrhythmic events according to valve type is shown in **Supplemental Table 5.5**. No significant differences were found between balloon-expandable and self-expandable valves.

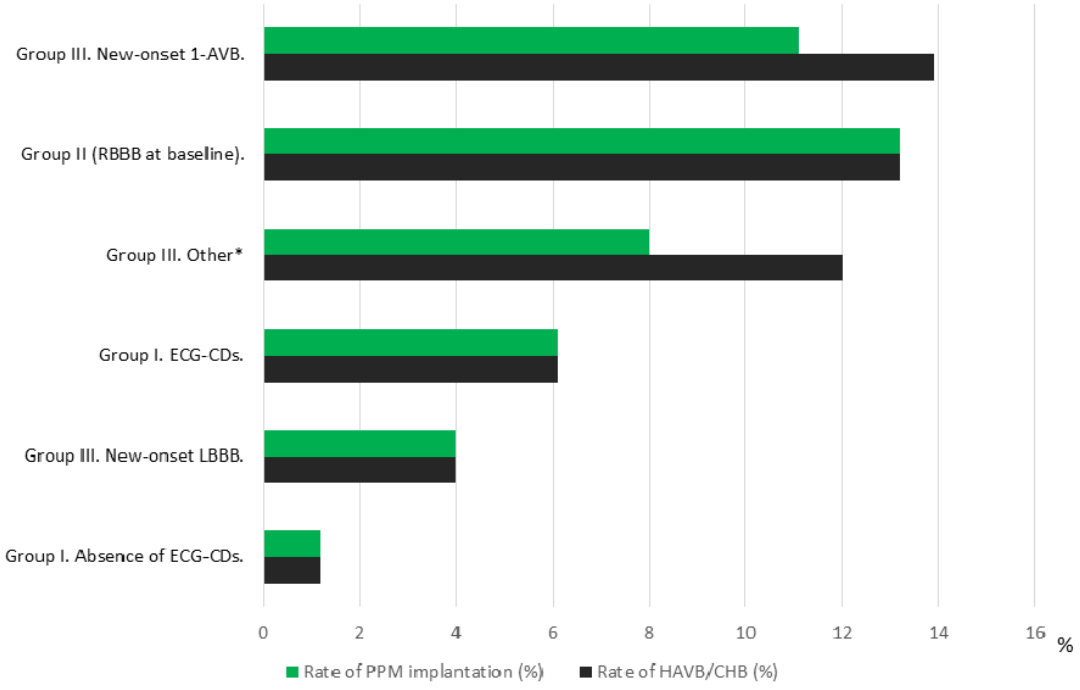


Figure 5.4. Rate of HAVB/CHB in specific subgroups.
1-AVB: First-degree atrioventricular block; ECG-CDs: Electrocardiogram conduction disturbances; LBBB: Left bundle branch block; PPM: Permanent pacemaker; RBBB: Right bundle branch block.
*ECG changes (persistent increase of PR or QRS duration ≥20 ms) in patients with pre-existing ECG-CDs, and new-onset QRS large (without LBBB morphology).

5.5.2. Tachyarrhythmic events

The incidence of tachyarrhythmic events is depicted in **Table 5.3**. Among patients with no history of atrial fibrillation (n = 333), 22 (6.6%) had at least 1 episode of new-

onset atrial fibrillation within the 2 weeks following hospital discharge. Regarding ventricular arrhythmias, about one third of the population had nonsustained events, and 1 patient (0.2%) had sustained ventricular tachycardia. No patient received an implantable cardiac defibrillator during the period of the study.

Table 5.3. Tachyarrhythmic events (n=459)

New-Onset AF*	22/333 (6.6)
Non-sustained ventricular tachycardia	167 (36.4)
Sustained ventricular tachycardia	1 (0.2)
Implantable cardiac defibrillator	0 (0)

Values are n (%). AF: Atrial fibrillation.
*Only patients without prior atrial fibrillation in the denominator for the %.

5.5.3. Thirty-day follow-up

All patients had clinical or remote 30-day visits, with no patient lost to follow-up. The 30-day clinical follow-up is outlined in **Table 5.4**. No episodes of sudden cardiac death or all-cause mortality occurred at 30 days. The global rate of hospitalization was 13%, without significant differences between groups.

Table 5.4. Clinical Outcomes at 30-day follow-up

	Overall (n=459)	**Group I (n=315)**	**Group II (n=38)**	**Group III (n=106)**	**P Value**
Symptomatic bradyarrhythmia	12 (2.6)	4 (1.3)	4 (10.5)	4 (3.8)	0.002
Pacemaker implantation	19 (4.1)	7 (2.2)	5 (13.2)	7 (6.6)	0.002
All-cause death	0 (0)	0 (0)	0 (0)	0 (0)	-
Sudden cardiac death	0 (0)	0 (0)	0 (0)	0 (0)	-

Values are n (%).Groups were defined as in Table 2.

5.6. DISCUSSION

This is the first multicenter study using systematic AECG monitoring in a large cohort of consecutive TAVI patients managed with a minimalist approach and following a nonvalidated scientific expert consensus for the management of CDs after TAVI (296).

The main results of the study can be summarized as follows: 1) Delayed HAVB or CHB events occurred in about 5% of patients, leading to PPM implantation in 81% of them. TAVI recipients without baseline RBBB and no ECG changes after the procedure exhibited a low risk for late events (2.2%; 1.2% in those patients without baseline ECG CDs), and the risk increased significantly in patients with new-onset CDs (8.5%) and in those with baseline RBBB (13.2%). 2) AECG monitoring after TAVI using a strategy of early discharge (median postoperative length of stay 2 days) was safe, with no mortality events between hospital discharge and 30-day follow-up.

A recent consensus focusing on CDs after TAVI recommended AECG monitoring in specific settings, such as patients with baseline RBBB and new-onset CDs (296). In contrast, early discharge (24 hours after the procedure) without AECG monitoring was recommended in those patients without ECG changes. This was based on previous publications (with clinical follow-up, no AECG monitoring) showing that a short postoperative length of stay would be safe in patients without significant ECG CDs after TAVI (231,232). However, although the evolution toward a minimalist procedure has led to a reduction of the postoperative length of stay in the global TAVI setting, the rate of readmissions for PPM implantation has increased in recent years (312). Also, the potential role of delayed CDs in the steep increase between in-hospital and 30- day mortality (from 1.5% to 2.6%) in contemporary TAVI registries remains to be elucidated (378). In this setting, AECG monitoring after discharge has emerged as a novel tool to enlighten the issue of delayed life-threatening bradyarrhythmias (315). To date, data using AECG monitoring in consecutive TAVI patients were limited to 2 small single-center studies (317,318). In this initial experience, the reported rate of HAVB or CHB events among patients without significant ECG abnormalities (QRS duration < 120 ms) at discharge was 4% (317,318). These results raised concerns about the applicability of a minimalist approach with short (24-48 hours) postprocedural hospital stay. The present study showed that after excluding patients with PPM during the periprocedural period and considering those with RBBB as an independent group, about 70% of TAVI recipients remained without significant ECG changes after the procedure. In this group, PPM implantation because of delayed HAVB or CHB events was about 2%, half of the rate reported in previous AECG monitoring studies (317,318). Indeed, the safety profile was even better in patients without significant baseline ECG abnormalities (PR duration ≤ 200 ms if sinus rhythm, QRS duration < 120 ms), who exhibited a very low rate of delayed HAVB or

CHB episodes (~1%; 0.4% when considering symptomatic events). These results would support early discharge without mandatory AECG monitoring in such cases. Conversely, the rate of HAVB or CHB episodes in patients with baseline ECG CDs (other than RBBB) and no further ECG changes post-TAVI increased to 6%. Thus, AECG monitoring at hospital discharge may be useful in these patients, in contrast to the recommendation from an expert consensus on CDs after TAVI (296). Also, a more prolonged hospitalization period may also be considered in this group of patients.

Baseline RBBB is present in about 10% of TAVI candidates and has been the most consistent risk factor for PPM implantation after the procedure (145). In addition, some evidence has shown an increased risk for mortality after hospital discharge in patients with RBBB (324). A recent study evaluated the timing of the occurrence of advanced CDs post-TAVI in patients with RBBB, showing that most CHB or HAVB episodes (98%) occur within the 3 days after the procedure (only 2% between 4 and 30 days) (379). In this context, a more prolonged hospital stay along with AECG monitoring after hospital discharge has been recommended in patients with RBBB (296). However, available data using AECG monitoring after discharge showed alarming results (317,318). Among the 15 patients with RBBB and AECG monitoring from 2 previous studies, 6 (40%) experienced delayed HAVB or CHB episodes (317,318). The present work included up to 38 patients with RBBB and no ECG changes after the procedure and confirmed the high-risk profile of patients with RBBB discharged without PPM implantation. The rate of HAVB or CHB events was 13.2%, and the episodes appeared to be more severe (more frequently symptomatic) compared with the other groups. More data are warranted to shed light on the management of this group of patients, and the possibility of prophylactic PPM implantation may be reasonable in those subgroups at higher risk (eg, associated 1-AVB at baseline) (379). In contrast, recent studies focusing on valve type and valve positioning have shown promising results regarding the rate of HAVB or CHB after TAVI, also including those patients with baseline RBBB (380,381). While waiting for additional data, AECG monitoring after discharge should probably be implemented in patients with RBBB and no PPM implantation following the procedure.

In the present work, patients with new-onset CDs after the procedure exhibited an 8.5% rate of HAVB or CHB events and therefore represent a subset of patients at higher risk for delayed CDs after TAVI. In the particular case of patients with new-onset LBBB,

a previous publication using long-term continuous monitoring with an implantable cardiac monitor (the 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) showed that up to 16% of patients had HAVB or CHB episodes at 2-year follow-up (leading to PPM implantation in two thirds of them), the majority occurring in the early phase post-TAVI (50% within the first month) (382). Our results confirm that AECG monitoring may be considered in the early period after discharge in those patients with new-onset CDs. Moreover, the present data showed that the subgroup of patients with new-onset 1-AVB had a high risk for bradyarrhythmic events, particularly in the presence of concomitant baseline ECG CDs. Accordingly, previous studies identified the delta PR length (each 10 ms of change between baseline and post-procedure electrocardiography) as an independent predictor of late HAVB or CHB events (230,231).

No sudden death or mortality events occurred between hospital discharge and 30 days in this study, and the use of AECG monitoring at hospital discharge may have contributed to such results. However, this was a nonrandomized study, and it remains unknown whether AECG monitoring could have prevented subsequent life-threatening episodes, including severe episodes of syncope or sudden cardiac death, in those patients with silent arrhythmias who received PPMs on the basis of AECG findings. In contrast, most HAVB and CHB events (~75%) occurred about 5 days after TAVI and could have been detected in the hospital with more prolonged hospitalization periods. In patients at high risk for delayed HAVB or CHB events, a strategy based on AECG monitoring at hospital discharge was safe even with a short postoperative length of stay. Therefore, AECG monitoring (especially those systems with real-time streaming transmission) with special focus on the first week after discharge could be considered in these groups (baseline RBBB, new-onset CDs post-TAVI) to increase global TAVI safety and improve clinical outcomes. In addition, a more prolonged hospitalization period may also be considered in these cases. Future large-scale prospective studies with standardized postprocedural management are needed to validate this strategy.

PPM implantation because of AECG monitoring findings in asymptomatic patients was performed in 6 and 2 patients with HAVB or CHB and significant pauses, respectively. The use of continuous AECG monitoring may have prevented further

symptomatic episodes in these patients. However, PPM implantation in TAVI patients with asymptomatic bradyarrhythmic events may also carry a potential risk for overtreatment in some cases (383). Thus, the indication for PPM implantation in asymptomatic patients after TAVI should probably be individualized (315). Nevertheless, current guidelines recommend PPM implantation in asymptomatic patients with infranodal atrioventricular block (173). Considering that the interaction between the TAVI device and the conduction system is usually infranodal (145), PPM implantation would probably be justified in most patients with HAVB or CHB episodes.

The use of balloon-expandable valves has been historically associated with a lower rate of periprocedural CDs (145). However, differences between valve types have been partially attenuated with the use of newer valve generation systems (296), and a recent randomized study failed to show significant differences in PPM implantation between the 2 most common newer generation self- and balloon-expandable valve systems (286). Previous data showed controversial results regarding the impact of valve type on delayed (>48 hours) arrhythmic events (230,232,321,384). The present study, using systematic AECG, failed to show differences between valve type and delayed arrhythmias, including HAVB or CHB. However, these results should be interpreted with caution because of both the nonrandomized nature of the study and the small proportion of patients who received a self-expandable valve system. Further studies using AECG and comparing different valve systems are warranted.

Scarce data exist regarding the incidence and clinical impact of silent tachyarrhythmias in the early period after TAVI. The diagnosis of atrial fibrillation may lead to the initiation of anticoagulation, with potential important clinical implications considering the high cardioembolic risk profile of TAVI recipients along with the dreadful prognosis of late cerebrovascular events in this population (348). The incidence of new-onset atrial fibrillation events at 30-day follow-up in the present study was close to 7%. Future larger studies focusing on the predictors of late new-onset atrial fibrillation are needed to identify those patients that could benefit from anticoagulation treatment.

5.6.1. Study limitations

Although all arrhythmic events were confirmed by an experienced electrophysiologist, no event adjudication committee or electrocardiography core laboratory was available in this study. Also, 2 different AECG monitoring systems were used, and some degree of variability between the 2 devices regarding the detection of the arrhythmic episodes cannot be excluded. On the other hand, the small number of TAVI recipients who had self-expandable valve systems (13.9%) hinders the extrapolation of the results to this subset of patients. Finally, the relatively low rate of events precluded the evaluation of independent predictive factors of late HAVB or CHB.

5.7. CONCLUSIONS

Systematic AECG monitoring in a large cohort of consecutive TAVI patients revealed the occurrence of delayed HAVB or CHB events in close to 5% of the patients, leading to PPM implantation in most of them. The use of AECG monitoring in a minimalist TAVI approach setting was safe, with no mortality events between hospital discharge and 30-day follow-up. Also, the results of this study would support a tailored management strategy post-TAVI, with 3 different groups of patients on the basis of baseline and postprocedural ECG findings, as recently recommended (296). A short hospitalization period without AECG monitoring after discharge may be applied to patients without ECG changes after the procedure (particularly in the absence of baseline ECG CDs). However, AECG monitoring along with the possibility of longer hospitalization periods may be recommended in those patients at higher risk, such as those with baseline RBBB or new onset CDs. Among the latter, patients with new-onset 1-AVB (particularly in the presence of concomitant ECG CDs) were the subgroup at highest risk for delayed HAVB or CHB. Future studies are warranted.

5.8. CLINICAL PERSPECTIVES

What is known?

- The evolution towards a minimalist TAVI procedure with a short post-procedural length of stay may be controversial regarding the occurrence of delayed arrhythmic disorders. Continuous ambulatory ECG monitoring following TAVI may be useful for the diagnosis and treatment of late arrhythmias.

What is new?

- In this minimalist TAVI cohort without PPM, late HAVB/CHB revealed by post-discharge AECG monitoring was seen in ~5% of patients. Whereas HAVB/CHB was rare in patients without ECG changes following the procedure, those patients with baseline RBBB and new-onset CDs had an increased risk.

What is next?

- A tailored approach based on pre- and post-procedural ECG findings and using AECG monitoring may improve the management of conduction disturbances after TAVI. Future, large-scale, prospective studies are warranted to validate such strategy.

5.9. FUNDING

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5.10. SUPPLEMENTAL MATERIAL

Supplemental Table 5.1: Criteria for notification of abnormal conduction abnormalities in patients discharged home with remote cardiac monitoring	
Criteria	
1	Wide QRS tachycardia ≥150bpm (sustained for ≥15 seconds) or ≥120 bpm (sustained for ≥30 seconds).
2	Complete heart block (6 beats or greater), Symptomatic 2nd degree AVB, Mobitz II.
3	Pauses ≥4 seconds. 5. Symptomatic Bradycardia ≤ 40bpm (sustained for ≥60 secs)
4	Atrial fibrillation/flutter (average heart rate ≤40 or ≥180 bpm, sustained for 60 seconds)
5	First documentation of Atrial fibrillation (sustained for 60 seconds)
6	Narrow QRS tachycardia ≥200bpm (sustained for 60 seconds
7	Ventricular fibrillation

Supplemental Table 5.2. Electrocardiogram characteristics at discharge in Group I (n=314)	
Atrial fibrillation	30 (9.6)
PR interval, ms	176 +/-27
QRS interval, ms	102 +/-20
First-degree atrioventricular block*	35 (11.2)
Left bundle branch block	27 (8.6)
QRS > 120 ms	38 (12.1)
No significant ECG-CDs**	248 (79.0)

*Patients in sinus rhythm.
**PR ≤200 ms (if sinus rhythm) and QRS <120 ms

Supplemental Table 5.3. Electrocardiogram characteristics at discharge in Group III (n=107)	
Atrial fibrillation	13 (12.2)
PR interval, ms	205 +/-43
QRS interval, ms	135 +/-37
New-onset first-degree atrioventricular block*	36 (33.6)
New-onset left bundle branch block	50 (46.7)
PR and/or QRS enlargement in patients with baseline ECG-CDs**	26 (24.3)

*Patients in sinus rhythm. RBBB, LBBB and NIVCD were found in 3 (8.3%), 7 (19.4%) and 3 (8.3%) patients, respectively.
**Patients with baseline first-degree atrioventricular block and/or RBBB, LBBB or NIVCD.
ECG-CDs: Electrocardiogram conduction disturbances; LBBB: Left bundle branch block; NIVCD: Nonspecific intraventricular conduction delay; RBBB: Right bundle branch block.

Supplemental Table 5.4. Individual Characteristics of the Patients with HAVB/CHB or with PPMI after discharge						
Age, yrs (Sex)	**Valve Type**	**Days after TAVI**	**Group**	**Discharge ECG**	**Clinical presentation**	**PPM implantation**
74 (female)	Evolut Pro	15	No changes.	Sinus rhythm. Normal PR. Normal QRS (86ms)	Isolated HAVB (Mobitz 2) episode. Asymptomatic.	No.
85 (female)	Acurate Neo	8	No changes.	Sinus rhythm. Normal PR. Normal QRS (66ms)	Several nocturnal HAVB episodes. Asymptomatic.	Yes.
78 (male)	Sapien 3	5	No changes.	Sinus rhythm. 1-AVB. Normal QRS (94ms)	Several nocturnal HAVB episodes. Asymptomatic.	Yes.
74 (male)	Sapien 3	16	New CDs. New-onset LBBB	Sinus rhythm. 1-AVB. LBBB (174 ms)	HAVB episode. Asymptomatic.	Yes.
79 (female)	Sapien 3	3	RBBB at baseline.	Sinus rhythm. RBBB + LAHB (138 ms)	HAVB episode. Symptomatic (pre-syncope).	Yes.
69 (female)	Evolut Pro	5	New CDs. New onset 1-AVB.	Sinus rhythm. 1-AVB. LBBB (138 ms)	CHB. Symptomatic (syncope).	Yes.
89 (male)	Sapien 3	3	New CDs. New onset 1-AVB	Sinus rhythm. 1-AVB. NIVCD (118 ms)	CHB. Asymptomatic.	Yes.
82 (male)	Sapien 3	3	No changes.	Atrial fibrillation. Normal QRS (90ms).	Significant pauses (6 sec) and episode of CHB. Symptomatic (dizziness).	Yes.
73 (male)	Sapien 3	6	No changes.	Atrial fibrillation. Incomplete LBBB (QRS 110ms).	Significant nocturnal pauses (9 sec), no CHB. Asymptomatic.	Yes.
96 (female)	Sapien 3	13	RBBB at baseline.	Sinus rhythm. RBBB (QRS 138 ms).	CHB. Symptomatic (dizziness).	Yes
83 (male)	Sapien 3	6	RBBB at baseline.	Sinus rhythm. RBBB (QRS 190 ms).	CHB. Symptomatic (lightheadedness).	Yes
86 (male)	Evolut Pro	3	New CDs. New onset 1-AVB	Sinus rhythm. 1-AVB. QRS 118 ms.	CHB. Symptomatic (chest pain).	No.

88 (male)	Sapien 3	4	No changes.	Sinus rhythm. QRS 110ms.	CHB. Symptomatic (lightheadedness).	Yes.
79 (male)	Sapien 3	5	New CDs. New onset 1-AVB	Sinus rhythm. 1-AVB. RBBB (132 ms)	CHB. Symptomatic (chest pain).	Yes.
82 (male)	Sapien 3	4	No changes.	Atrial fibrillation. LBBB (QRS 138 ns).	CHB. Symptomatic (syncope).	Yes.
78 (male)	Sapien 3	5	New CDs. New-onset 1-AVB and new-onset LBBB	Sinus rhythm. 1-AVB. LBBB (122 ms)	CHB. Symptomatic (dizziness).	Yes.
60 (male)	Sapien 3	5	New CDs PR enlargement (1-AVB at baseline).	Sinus rhythm. 1-AVB. NIVCD (122 ms)	CHB. Asymptomatic.	No.
82 (female)	Sapien 3	6	New CDs PR enlargement (1-AVB at baseline).	Sinus rhythm. 1-AVB. NIVCD (126 ms)	CHB. Asymptomatic.	No.
71 (male)	Sapien 3	6	No changes.	Atrial fibrillation. RBBB (QRS 172 ms).	CHB. Symptomatic (dizziness).	Yes.
87 (male)	Sapien 3	10	New CDs PR enlargement (1-AVB at baseline).	Sinus rhythm. 1-AVB QRS 100ms.	Pause. Asymptomatic.	Yes.
90 (male)	Sapien 3	12	New CDs. New-onset RBBB.	Sinus rhythm. RBBB (QRS 130 ns).	CHB. Asymptomatic.	Yes.
77 (male)	Sapien 3	5	RBBB at baseline.	Atrial fibrillation. RBBB (QRS 150 ms).	CHB. Asymptomatic.	Yes.
70 (male)	Sapien 3	6	No changes.	Sinus rhythm. 1-AVB. QRS 104ms.	CHB. Symptomatic (lightheadedness).	Yes.

Supplemental Table 5.5. Bradyarrhythmic events according to valve type.			
	BEv (n=393)	**SEv (n=65)**	**p Value**
HAVB/CHB	17 (4.3)	4 (6.2)	0.514
Significant pause (>4 sec)	14 (3.6)	1 (1.5)	0.706
Any bradyarrhythmia	31 (7.9)	5 (7.7)	0.999
Symptomatic event	10 (2.5)	1 (1.5)	0.999
Permanent pacemaker implantation	17 (4.3)	2 (3.1)	0.999

BEv: Balloon-expandable valve; HAVB/CHB: High-degree atrioventricular block/Complete heart block; SEv: Self-expandable valve.

DISCUSSION, CLINICAL PERSPECTIVES AND CONCLUSIONS

6.1. DISCUSSION

6.1.1. Long-Term Electrocardiographic changes and pacemaker implantation in TAVI recipients without new postprocedural conduction disturbances

Patients who undergo a TAVI procedure and do not experience significant ECG changes or rhythm disturbances during the periprocedural period may be discharged home without further measures or monitoring. This is stated in the two main consensus focusing on the management of post-TAVI rhythm disturbances (296,297). However, the evidence supporting these recommendations is based on previous data with follow-up limited to 30 days (231,232,323). Studies with longer-follow up focusing on this subset of patients are scarce (328). In this regard, to be able to demonstrate the long-term safety in relation to CDs of THVs devices in the era of the expansion to low-risk (younger) patients is of high importance.

The first aim of the current thesis was therefore to evaluate the long-term follow-up of these patients, including those with and without baseline ECG-CDs. This work was the first to provide data in this respect. After a median follow-up of 2 years, most patients without pre-existing CDs who remained with similar post-procedural ECG did not experience significant ECG changes. Also, the rate of PPM implantation was low (3.5% at 5-years, a rate of 1.1% per year). These findings provided reassuring data regarding the safety of THVs at long-term follow-up. Of note, the median time of advanced CDs leading to PPM was >2 years post-TAVI, suggesting no relation with the TAVI procedure. Thus, an age-related spontaneous progression of conduction abnormalities as the underlying mechanism may explain these results. On the other hand, the presence of pre-existing ECG-CD was associated with an increased risk of HAVB/CHB at follow-up (overall PPM rate at 5-year follow-up of 15.6%, 5.3% per year), higher than the expected rate in non-TAVI patients with bundle branch block (330,331). Interestingly, in this group the median time of PPM implantation after TAVI was 14 months, much earlier than the group without ECG-CDs. Finally, a higher risk of heart failure hospitalization at follow-up was found among TAVI recipients with pre-existing ECG-CDs. Thus, future studies may evaluate the efficacy of implementing systematic measures (i.e. continuous ECG monitoring devices, optimal medical/device HF therapies) to improve clinical outcomes in this subgroup of patients.

6.1.2. New-onset left bundle branch block following TAVI

As previously stated, the occurrence of new-onset LBBB appears in about 20% of TAVI patients after the procedure with the use of newer generation THV systems (167). Thus, new-onset LBBB may be considered as the most frequent drawback of TAVI, and its incidence has not decreased in low-risk populations (153). The management of new-onset LBBB patients is an unmet need in the TAVI field and its approach after the procedure has been largely debated since the beginning of the technique. Different strategies have been used in recent years (295), including clinical observation, prophylactic PPM implantation (173), AECG monitoring after discharge (296), or PPM implantation according to an electrophysiological study result (174). The recently published MARE study using an implantable cardiac monitor in 103 TAVI recipients provided data of high clinical relevance (321), showing an incidence of 10% of HAVB/CHB episodes leading to PPM implantation at 1-year follow-up. Furthermore, the MARE study reported a partial or complete recovery of the ECG abnormalities in one-third of patients at 1-year, in line with previous data (222). This underscores the clinical variability that occurs in this subset (from HAVB/CHB requiring PPM implantation to ECG normalization) and its challenging management. This thesis tried to evaluate two significant issues in the subset of new-onset LBBB after TAVI. The first work investigated the predictors of both regression and progression of the LBBB in TAVI recipients. The second article reported the two-year results of the MARE study.

In the first work, one-third of patients had LBBB recovery at one-year, in concordance with previous studies (222,321). On the other hand, 9% of the patients required PPM implantation. No variables were identified as a predictor of LBBB recovery at follow-up. This article confirmed that a high proportion of patients (nine out of ten) with LBBB will not suffer significant bradyarrhythmias leading to PPM implantation during the first year after TAVI, which discourages prophylactic PPM implantation before discharge. However, those with longer PR intervals or atrial fibrillation had an increased risk of PPM implantation at follow-up. In fact, previous data showed poorer outcomes (increased risk of HAVB and sudden death) in patients with new-onset LBBB and very long PR interval (>240ms) and/or wider QRS (>150-160 ms) (229,231,232). In these patients, a PPM implantation may be considered. As an alternative, the very recent European Guidelines propose the use of an electrophysiological study to guide the

decision for PPM implantation, being recommended if the HV interval is more than 70 milliseconds (174).

On the other hand, no variables were associated with LBBB recovery, further highlighting the challenging nature of this issue. LBBB recovery during follow-up is probably a multifactorial phenomenon. Also, some unmeasured factors may exist. In this line, previous anatomical data showed individual variability in the cardiac conduction system (e.g., the position at which the left bundle branch emerges from the deep ventricular septum and enters the superficial portion just under the endocardium may vary), which could have influenced our analysis (385).

The second article focusing on new-onset LBBB patients reported the 2-year results of the prospective, multicenter MARE study. This was the first work using long-term continuous AECG monitoring in the TAVI field in this subset of patients. The 2-year follow-up results showed that about two-thirds of the patients exhibited at least one arrhythmic episode, reflecting the very high arrhythmia burden in this group of patients. Of note, the episodes of significant bradyarrhythmias (HAVB/CHB leading to PPM implantation) were mainly limited to the initial months after the procedure. Hence, these results suggest the lack of significant delayed damage of the conduction system and do not support prophylactic permanent pacemaker implantation in these patients. However, the use of continuous AECG monitoring during the first weeks after the procedure might be evaluated, as recommended in some expert consensus and review articles (296,315).

Regarding tachyarrhythmias, close to one-third of the patients in the MARE trial exhibited NOAF episodes at 2-year follow-up, mostly asymptomatic. This is an important finding taking into account the clinical and therapeutic consequences of AF (e.g. risk of stroke, initiation of anticoagulant therapy). Interestingly, NOAF episodes had a homogeneous distribution over time, contrary to HAVB/CHB. The latter confirms that the risk of AF in TAVI candidates exceeds the periprocedural period. Previous data showed that the presence of silent AF in aged populations using continuous monitoring ranged from 1.5% to 15% (386). Furthermore, AF detection increased in populations comparable to TAVI cohorts (e.g. previous stroke, underlying heart disease) and it has been associated with poorer outcomes (387). In this line, two previous studies using

AECG monitoring before the TAVI procedure (duration of monitoring of 24h and 7 days, respectively) showed AF episodes in ~10% of the TAVI candidates (188,190). Of note, in the study of Urena et al, the occurrence of cerebrovascular events after TAVI was more frequent among the patients with atrial arrhythmias before the procedure (188). In the present work, AF episodes were of relatively short duration (median 1.5 min), which along with the relatively small number of patients included may partially explain the lack of association with cerebrovascular events. Further studies are needed to better identify patients at risk of late AF after TAVI, which may help both to improve the follow-up after the procedure (e.g. use of AECG monitoring in selected populations) and to decide on optimal antithrombotic treatment.

6.1.3. Anticoagulation after TAVI and its relation to ischemic late cerebrovascular events

The fourth work of the present thesis demonstrated the dreadful outcomes of patients with LCVEs after TAVI. LCVEs occurred in 5.1% of patients after a median follow-up of 2 years. Most LCVEs were ischemic, and older age, history of cerebrovascular disease, a higher mean aortic gradient, periprocedural stroke at the time of the TAVI procedure, and the lack of anticoagulation therapy at discharge were identified as independent predictors of ischemic LCVEs. LCVEs were associated with very high in-hospital and midterm significant disability and mortality rates.

As previously stated, the lack of anticoagulation therapy (NOACs or VKAs) at hospital discharge was an independent predictor of late ischemic LCVEs. Of note, the echocardiographic study performed at the time of the ischemic LCVE did not show significant changes in valve hemodynamics including signs of valve thrombosis. Hence, the occurrence of late ischemic LCVEs may be related to delayed episodes of atrial arrhythmias, which we demonstrated in the current thesis that are asymptomatic in most cases.

As discussed above, the two-year results of the MARE trial showed that close to one-third of patients presented episodes of new-onset AF (most of them silent) within the months following the procedure. The results of the MARE study are in line with a recent work that included 172 patients with PPM implantation following TAVI, which

demonstrated a rate of NOAF of 25% after a follow-up of 15 months (345). This rate of newly diagnosed AF is around 2-fold greater than reported with common follow-up without AECG monitoring or device interrogation (150,153).

As suggested, the initiation of anticoagulation treatment in those patients with late AF might have prevented ischemic LCVEs. However, the indication of anticoagulation therapy in asymptomatic short duration AF episodes is controversial, and a device-detected threshold of >5.5 hours has been proposed (386). However, previous studies showed an increased risk of ischemic stroke and major cardiovascular events with episodes of more than 5-6 minutes (346,388,389). In the TAVI setting, the integration of the baseline risk of stroke using validated scores (CHADS/CHA2DS2-VASc) may help in guiding the decision for initiation of anticoagulation therapy.

6.1.4. Ambulatory ECG monitoring.

The management of CDs after TAVI might be considered as the main concern after the procedure. Whereas the rate of the most feared complications has decreased in recent years due to successive iterations in THVs along with the increasing experience of TAVI operators, the occurrence of significant CDs remains high. Moreover, the TAVI field is evolving to a minimalist approach with a very short postprocedural length of stay, especially in the current era of expansion to patients at low surgical risk.

This thesis provides a significant piece of information in the setting of AECG monitoring after TAVI. Previous data using AECG monitoring are limited to studies with relatively small cohorts (317–319). Furthermore, the current work is the first using AECG monitoring in the setting of minimalist TAVI following a nonvalidated consensus for the management of CDs after the procedure (296). In summary, 459 consecutive TAVI patients (3 to 4 times more number of patients than in previous studies) without permanent pacemaker were included. The median hospital length of stay was of 2 (1-3) days. Systematic 2-week AECG monitoring detected HAVB/CHB episodes in ~5% of cases, with no mortality at 1-month. Whereas HAVB/CHB was rare in patients without ECG changes post-TAVI (2.2%), baseline RBBB (13.6%) and new-onset CDs (8.5%) determined an increased risk.

The occurrence of sudden cardiac death after TAVI is a dreadful complication and it may occur due to several causes including delayed bradyarrhythmic events. In contemporary registries, the mortality between discharge and 30-day follow-up is almost doubled (1.5% to 2.6%) (115). The present work adds valuable data in this context. No sudden death events occurred between hospital discharge and 30 days, reinforcing the implementation of AECG monitoring in some subsets of patients as recommended in a recent expert consensus document (296). AECG monitoring allowed the rapid implementation of therapeutic measures in patients with severe bradyarrhythmic events, which in turn may have prevented the occurrence of cardiac death at 30 days of follow-up. Future, large-scale studies are necessary to confirm these findings.

Patients with TAVI and no ECG changes may be discharged home early after the procedure and no further measures might be needed regarding the risk of delayed arrhythmic events (296). The fifth article of the present thesis provided new data in this context. We used AECG monitoring in a large cohort of consecutive TAVI patients, 315 of them without significant ECG changes after the procedure. Within this group, 248 patients had no ECG-CDs (normal PR interval if sinus rhythm and QRS < 120ms). Among them, 3 patients (1.2%) suffered delayed HAVB/CHB episodes, symptomatic in 1 patient. These findings are reassuring in the era of expanding TAVI treatment to most patients with AS, as low-risk patients tend to have fewer ECG-CDs. On the other hand and contrary to previous recommendations (296), patients with baseline ECG-CDs (excluding RBBB) and no changes after the procedure had an increased risk of post-discharge HAVB/CHB (6%). The presence of prior ECG-CDs may imply that mild conduction tissue damage is sufficient to cause HAVB/CHB events, and this could not be evident on the surface ECG after the procedure because of the presence of previous ECG-CDs itself. The latter may explain the higher event rate in this subgroup of patients.

Our work confirmed the high-profile risk of patients with RBBB, even if no changes occur after the procedure (13.2% of delayed HAVB/CHB). This underscores the urgent need to improve the post-procedural management of these patients. As previously discussed, prophylactic PPM implantation in selected cases (379), prolonged post-procedural length of stay (the “minimalist” TAVI concept may not apply in this subset of patients), and close monitoring (AECG using real-time alarm systems that may allow the implementation of rapid therapeutic measures) are options to be considered.

Finally, the group of patients with new-onset CDs (new-onset LBBB, new-onset 1-AVB, new large QRS without LBBB morphology, and significant ECG changes [increase in PR and/or QRS duration of ≥20 ms] in patients with preexisting ECG CDs) exhibited an 8.5% rate of HAVB/CHB events. Again, more studies are needed to confirm the safety and usefulness of AECG monitoring in this subset. TAVI operators may be aware that this is a largely varied group with multiple combinations of ECG-CDs. Case-by-case individualization will be necessary, integrating baseline risk (e.g. age, mean gradient, amount of calcification, baseline ECG), intra-procedural details (e.g. pre and post dilatation, THV type, prosthesis grade of oversizing, implantation depth), along with post-procedural clinical tools (e.g. electrophysiological study, AECG monitoring).

6.2. CLINICAL IMPLICATIONS

The studies included in this thesis provide novel insights with important clinical implications into the challenging conundrum of CDs after TAVI. The present work adds significant data to daily management and may contribute to improving the outcomes of TAVI recipients.

The first article demonstrated, for the first time, the good long-term clinical outcomes in terms of PPM implantation regarding patients without significant ECG changes post TAVI. This was even clearer in patients without significant baseline ECG-CDs, which did not exhibit higher PPM implantation rates compared to similar non-TAVI cohorts. The latter confirms that the mechanical interaction between THV and the conduction system leading to CDs may concentrate in the early stage after the procedure. Thus, our findings indicate that no specific measures beyond common clinical follow-up may be necessary for this group. On the contrary, a closer follow-up may be required in patients with baseline ECG-CDs, which had higher PPM implantation rates at follow-up.

Two articles focused on the follow-up of patients with new-onset LBBB after the procedure, a challenging subset whose management can be considered an unmet need in the TAVI field. First, although no predictors of LBBB regression were found, a closer follow-up might be necessary for patients with long PR interval or AF, as they were shown to have an increased risk of PPM implantation. Second, the two-year results of the

MARE study provided important clinical implications. Of note, we confirmed the good long-term follow-up of this subset of patients, as the risk of PPM implantation was anecdotal beyond the first year. HAVB/CHB episodes concentrated in the first weeks after the procedure, further supporting the potential use of AECG monitoring in this period.

The burden of late episodes of AF after TAVI is largely unknown and may lead to cerebrovascular events, which have dreadful outcomes as demonstrated in the fourth article. Moreover, the analysis of independent predictors suggested that AF may be linked to the occurrence of ischemic LCVEs. In addition, the two-year results of the MARE study showed that up to one-third of patients may develop late AF, and no data exist regarding its potential predictors. Thus, more studies are needed to better identify the patients at risk of late AF. Meanwhile, we consider that oral anticoagulation treatment may be initiated in those patients with daily AF of >5.5 h. Furthermore, it might be evaluated in patients with CHA2DS2-VASc score ≥3 and daily episodes of >6 min (315).

The last article of this thesis may represent an important step in the understanding of late TAVI-related arrhythmic disorders (with a special focus on HAVB/CHB) in the early period after discharge. Several significant clinical implications derived from this work could be translated to clinical practice. Overall, we confirmed the usefulness of tailored management of CDs after TAVI based on pre and post-procedural ECG (296). Also, the present data support a short post-procedural length of stay without mandatory AECG monitoring post-discharge in patients without significant ECG-CDs after the procedure. Conversely, AECG monitoring may be used in 3 specific subsets after TAVI: patients with baseline ECG-CDs and no further changes after the procedure, patients with baseline RBBB and no in-hospital PPM implantation, and patients with new-onset ECG-CDs. Finally, we suggest, for the first time, the possibility of a longer hospitalization stay in specific subsets, challenging the current trend of a very short post-procedural length of stay in the TAVI community.

6.3. FUTURE PERSPECTIVES

The management of CDs after TAVI will continue to evolve in the following years to improve TAVI outcomes. Regarding pre-procedural management that could impact late bradyarrhythmic events, future data may evaluate the use of prophylactic PPM implantation in specific subsets such as those patients with baseline RBBB. To date, a few relatively small, retrospective studies evaluated pre-procedural PPM implantation in this subset, which showed a lower rate of re-hospitalization after TAVI in the group of prophylactic PPM implantation, mainly due to late HAVB/CHB (390–392). Prospective data are needed to validate this strategy, either in all RBBB patients or in subgroups at higher risk of CHB after the procedure (379).

Regarding the TAVI procedure itself, recent data described a specific implantation technique that consists to isolate the non-coronary cusp (as result, the right and left cusps are overlapped) and place the THV as high as possible in this specific angiographic view. The "overlap cusp implantation technique" was first described in 2018 and may obtain a higher implantation depth and therefore less risk of CDs (393). The use of this novel technique is currently concentrated on self-expanding valves, and small retrospective data have shown a significant reduction in PPM implantation rates (394,395). The impact on late bradyarrhythmic events is unknown. The Optimize PRO Study (NCT04091048) is currently assessing this implanting technique in a large prospective cohort of TAVI recipients using the self-expanding Evolut Pro/Pro+ valve, and its results are highly expected. On the other hand, there is still room for improvement on the use of electrophysioligical studies before discharge to guide the management of patients with de novo ECG-CDs. In this line, the very recent European guidelines (174) recommend PPM implantation in new-onset LBBB patients with an HV interval of > 70ms, based on the results of relatively small studies (235,396,397). Large-scale, prospective data are needed.

Current data on the clinical use of AECG monitoring in the context of TAVI including the fifth article of this PhD research project have provided important insights into the high arrhythmic burden of TAVI patients after discharge. Also, promising results have been obtained on the clinical impact of AECG monitoring post-TAVI, with significant therapeutic changes such as PPM implantation or the initiation of

anticoagulation treatment. However, further data would be needed to confirm these findings and provide additional evidence on the usefulness and cost-effectiveness of AECG monitoring in TAVI recipients, which may entail a risk of overtreatment. Moreover, randomized studies using AECG monitoring would provide significant data to evaluate its clinical and economic impact (e.g., sudden cardiac death, unplanned hospitalization, length of stay). Currently, several ongoing studies using different AECG monitoring systems after discharge in the context of TAVI, which are summarized in **Table 7.1**.

Finally, the fifth article of this thesis using AECG monitoring followed the cited consensus of CDs after TAVI (296), which lacks prospective validation. In this line, the study called "Prospective Validation of a Pre-specified Algorithm for the Management of Conduction Disturbances Following Transcatheter Aortic Valve Replacement (PROMOTE)" (NCT04139616) will enroll 2000 patients that will follow the consensus. This large-scale, observational, prospective study will collect data from a large contemporary TAVI cohort that, for the first time, will follow a uniform post-procedure management including AECG monitoring. This upcoming study will provide significant data on periprocedural and late arrhythmic disorders along with important information regarding the role of AECG monitoring in the TAVI setting.

Table 7.1. Ongoing studies using ambulatory ECG monitoring in TAVI recipients

Study Acronym	Study Design and Timing	Intervention	n	Target population	Main Outcomes
Reveal (NCT02559011)	Observational. Prospective. Post procedure.	Medtronic Reveal ICM implantation	100	All TAVI patients.	Number of patients with NOAF and CHB. Time Frame: up to 12 months.
LBBB-TAVI (NCT02482844)	Observational. Prospective. Post procedure.	EP study with PPMI if HV >70ms and implantable holter monitoring if <70ms	200	New-onset LBBB.	Incidence of HAVB/CHB. Time frame: 12 months.
Clinical Monitoring Strategy vs. EP-Guided Algorithmic in LBBB Patients Post-TAVI (NCT03303612)	Randomized Prospective Post procedure.	Group 1: EP-based algorithmic approach Group 2: standard clinical follow-up with transcutaneous cardiac monitoring.	134	New-onset LBBB.	Hospitalization, syncope or death after TAVI. Time frame: 12 months.
Remote ECG Monitoring of TAVI Patients. (NCT03810820)	Observational Prospective. Pre and post procedure.	M-CARDS (MCT) pre and post TAVI	240	All TAVI patients.	New-onset conduction disturbances. Time frame: 30 days.
PAF-TAVI Trial (NCT03991754)	Randomized. Observational. Post procedure.	60-day Holter.: 1. Amiodarone group. 2. Non-Amiodarone group	120	All TAVI patients.	Incidence of NOAF.
SMART TAVR (NCT04454177)	Observational. Prospective. Post procedure.	Huawei smart watch	100	All TAVI patients.	Incidence of conduction disturbances and PPM implantation.

6.4. CONCLUSIONS

The TAVI therapy may soon become the treatment of choice for most patients with AS. In this context, the study of late rhythm disorders, especially significant bradyarrhythmias, will be of utmost importance. The present PhD research project provides new data that may help in the management of TAVI patients, and the main findings can be summarized as follows:

(i) Most patients without ECG changes in the post-procedural TAVI period remain with similar ECG findings at long-term follow-up. In patients without ECG-CDs, the incidence of advanced conduction disturbances leading to PPM implantation remains low over time. However, patients with ECG-CD exhibited a higher risk of advanced CDs.

(ii) New-onset LBBB following TAVI resolved in one-third of patients at 1-year follow-up, but no predictors were associated with LBBB recovery. A non-sinus rhythm at baseline and longer PR interval were associated with PPM implantation at follow-up.

(iii) In the 2-year results of the MARE study, about two-thirds of the patients exhibited at least one arrhythmic episode. HAVB events were mainly limited to the initial months after the procedure. Conversely, a high rate of AF episodes was found, with no significant decrease beyond 1 year.

(iv) Late cerebrovascular events (LCVEs) occurred in 5.1% of patients after a median follow-up of 2 years and were associated with a poor prognosis. The echocardiography at the time of the LCVE showed no evidence of valve degeneration. The absence of anticoagulation as an independent factor in ischemic LCVEs suggests a role for AF.

(v) Systematic AECG monitoring in consecutive TAVI patients using a minimalist approach showed delayed HAVB/CHB events in close to 5% of the patients, leading to PPM implantation in most of them. The use of AECG monitoring was safe, with no mortality at 30-day follow-up. The results support a short hospitalization period in patients without ECG changes after the procedure (particularly in the absence of baseline ECG CDs). However, AECG monitoring along with the possibility of longer hospitalization periods may be recommended in those patients at higher risk, such as those with baseline RBBB or new-onset CDs.

The success of the implementation of the TAVI therapy in most patients with AS in the following years will require an improvement in the management of arrhythmia disorders, especially CDs. Regarding the occurrence of late episodes, the present PhD research project incorporates new important evidence to this area. Overall, the management of late CDs may improve by implementing a tailored approach based on pre and post-procedural ECG and using AECG monitoring in selected patients. Future large-scale, prospective studies such as the ongoing PROMOTE study will provide insightful data to this challenging field.

REFERENCES

1. Moore KL, Agur AMR, Dalley AF. Clinically Oriented Anatomy. Philadelphia; 2013. 1134 p.

2. Betts JG, Desaix P, Johnson E, Johnson JE, Korol O, Kruse D, et al. Anatomy and Physiology. OpenStax, editor. 2013. 1381 p.

3. Hurst JW, Fuster V. Hurst's the heart, 13th Edition. New York: McGraw-Hill Medical; 2011.

4. Hall JE, Guyton AC. Guyton and Hall textbook of medical physiology. 12th ed. Philadelphia, Pa: Saunders/Elsevier; 2011. 1091 p.

5. Coffey S, Cairns BJ, Iung B. The modern epidemiology of heart valve disease. Heart. 2016 Jan;102(1):75–85.

6. Kasper, Dennis L.,, et al. Harrison's Principles of Internal Medicine. 19th edition. New York: McGraw Hill Education, 2015.

7. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. J Am Coll Cardiol. 1997 Mar 1;29(3):630–4.

8. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006 Sep 16;368(9540):1005–11.

9. Rhodes P, Guthrie DJ, Thomson WAR, Underwood EA, Richardson RG. Encyclopaedia Britannica online. 2021; 16 August.

10. Mesquita ET, Souza Júnior CV de, Ferreira TR. Andreas Vesalius 500 years--A Renaissance that revolutionized cardiovascular knowledge. Rev Bras Cir Cardiovasc. 2015 Apr;30(2):260–5.

11. Vaslef SN, Roberts WC. Early descriptions of aortic valve stenosis. Am Heart J. 1993 May;125(5 Pt 1):1465–74.

12. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. Nat Rev Cardiol. 2011 Mar;8(3):162–72.

13. Roberts WC. The structure of the aortic valve in clinically isolated aortic stenosis: an autopsy study of 162 patients over 15 years of age. Circulation. 1970 Jul;42(1):91–7.

14. Pawade TA, Newby DE, Dweck MR. Calcification in Aortic Stenosis: The Skeleton Key. J Am Coll Cardiol. 2015 Aug 4;66(5):561–77.

15. Otto CM. Calcific aortic stenosis--time to look more closely at the valve. N Engl J Med. 2008 Sep 25;359(13):1395–8.

16. von Knobelsdorff-Brenkenhoff F, Karunaharamoorthy A, Trauzeddel RF, Barker AJ, Blaszczyk E, Markl M, et al. Evaluation of Aortic Blood Flow and Wall Shear Stress in Aortic Stenosis and Its Association With Left Ventricular Remodeling. Circ Cardiovasc Imaging. 2016 Mar;9(3):e004038.

17. O'Brien KD, Kuusisto J, Reichenbach DD, Ferguson M, Giachelli C, Alpers CE, et al. Osteopontin is expressed in human aortic valvular lesions. Circulation. 1995 Oct 15;92(8):2163–8.

18. Marincheva-Savcheva G, Subramanian S, Qadir S, Figueroa A, Truong Q, Vijayakumar J, et al. Imaging of the aortic valve using fluorodeoxyglucose positron emission tomography increased valvular fluorodeoxyglucose uptake in aortic stenosis. J Am Coll Cardiol. 2011 Jun 21;57(25):2507–15.

19. Olsson M, Rosenqvist M, Nilsson J. Expression of HLA-DR antigen and smooth muscle cell differentiation markers by valvular fibroblasts in degenerative aortic stenosis. J Am Coll Cardiol. 1994 Dec;24(7):1664–71.

20. Olsson M, Thyberg J, Nilsson J. Presence of oxidized low density lipoprotein in nonrheumatic stenotic aortic valves. Arterioscler Thromb Vasc Biol. 1999 May;19(5):1218–22.

21. Rajamannan NM, Subramaniam M, Rickard D, Stock SR, Donovan J, Springett M, et al. Human aortic valve calcification is associated with an osteoblast phenotype. Circulation. 2003 May 6;107(17):2181–4.

22. O'Brien KD, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of "degenerative" valvular aortic stenosis. Arterioscler Thromb Vasc Biol. 1996 Apr;16(4):523–32.

23. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of "degenerative" valvular aortic stenosis. Histological and immunohistochemical studies. Circulation. 1994 Aug;90(2):844–53.

24. Kaden JJ, Dempfle CE, Grobholz R, Tran HT, Kiliç R, Sarikoç A, et al. Interleukin-1 beta promotes matrix metalloproteinase expression and cell proliferation in calcific aortic valve stenosis. Atherosclerosis. 2003 Oct;170(2):205–11.

25. Jian B, Narula N, Li Q yi, Mohler ER, Levy RJ. Progression of aortic valve stenosis: TGF-beta1 is present in calcified aortic valve cusps and promotes aortic valve interstitial cell calcification via apoptosis. Ann Thorac Surg. 2003 Feb;75(2):457–65; discussion 465-466.

26. Mohler ER, Adam LP, McClelland P, Graham L, Hathaway DR. Detection of osteopontin in calcified human aortic valves. Arterioscler Thromb Vasc Biol. 1997 Mar;17(3):547–52.

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

28. Ghaisas NK, Foley JB, O'Briain DS, Crean P, Kelleher D, Walsh M. Adhesion molecules in nonrheumatic aortic valve disease: endothelial expression, serum levels and effects of valve replacement. J Am Coll Cardiol. 2000 Dec;36(7):2257–62.

29. Jian B, Jones PL, Li Q, Mohler ER, Schoen FJ, Levy RJ. Matrix metalloproteinase-2 is associated with tenascin-C in calcific aortic stenosis. Am J Pathol. 2001 Jul;159(1):321–7.

30. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003 Jul;24(13):1231–43.

31. Osnabrugge RLJ, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013 Sep 10;62(11):1002–12.

32. Danielsen R, Aspelund T, Harris TB, Gudnason V. The prevalence of aortic stenosis in the elderly in Iceland and predictions for the coming decades: The AGES-Reykjavík study. Int J Cardiol. 2014 Oct 20;176(3):916–22.

33. Kong WKF, Regeer MV, Ng ACT, McCormack L, Poh KK, Yeo TC, et al. Sex Differences in Phenotypes of Bicuspid Aortic Valve and Aortopathy: Insights From a Large Multicenter, International Registry. Circ Cardiovasc Imaging. 2017 Mar;10(3):e005155.

34. Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. Circulation. 2000 Jul 25;102(4):470–9.

35. Kupari M, Turto H, Lommi J. Left ventricular hypertrophy in aortic valve stenosis: preventive or promotive of systolic dysfunction and heart failure? Eur Heart J. 2005 Sep;26(17):1790–6.

36. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol. 2012 Nov 6;60(19):1854–63.

37. Dweck MR, Joshi S, Murigu T, Gulati A, Alpendurada F, Jabbour A, et al. Left ventricular remodeling and hypertrophy in patients with aortic stenosis: insights from cardiovascular magnetic resonance. Journal of Cardiovascular Magnetic Resonance. 2012 Jul 28;14:50.

38. Ross J, Braunwald E. Aortic stenosis. Circulation. 1968 Jul;38(1 Suppl):61–7.

39. Green SJ, Pizzarello RA, Padmanabhan VT, Ong LY, Hall MH, Tortolani AJ. Relation of angina pectoris to coronary artery disease in aortic valve stenosis. Am J Cardiol. 1985 Apr 1;55(8):1063–5.

40. Vandeplas A, Willems JL, Piessens J, De Geest H. Frequency of angina pectoris and coronary artery disease in severe isolated valvular aortic stenosis. Am J Cardiol. 1988 Jul 1;62(1):117–20.

41. Julius BK, Spillmann M, Vassalli G, Villari B, Eberli FR, Hess OM. Angina pectoris in patients with aortic stenosis and normal coronary arteries. Mechanisms and pathophysiological concepts. Circulation. 1997 Feb 18;95(4):892–8.

42. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2017 Mar 1;18(3):254–75.

43. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Feb 2;143(5):e35–71.

44. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129(23):2440–92.

45. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, et al. Guidelines on

the management of valvular heart disease (version 2012). Eur Heart J. 2012 Oct;33(19):2451–96.

46. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):e57-185.

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

48. Annabi MS, Touboul E, Dahou A, Burwash IG, Bergler-Klein J, Enriquez-Sarano M, et al. Dobutamine Stress Echocardiography for Management of Low-Flow, Low-Gradient Aortic Stenosis. J Am Coll Cardiol. 2018 Feb 6;71(5):475–85.

49. Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. Eur Heart J. 2016 Sep 7;37(34):2645–57.

50. Dayan V, Vignolo G, Magne J, Clavel MA, Mohty D, Pibarot P. Outcome and Impact of Aortic Valve Replacement in Patients With Preserved LVEF and Low-Gradient Aortic Stenosis. J Am Coll Cardiol. 2015 Dec 15;66(23):2594–603.

51. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation. 2007 Jun 5;115(22):2856–64.

52. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Sénéchal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. J Am Coll Cardiol. 2012 Oct 2;60(14):1259–67.

53. Saikrishnan N, Kumar G, Sawaya FJ, Lerakis S, Yoganathan AP. Accurate assessment of aortic stenosis: a review of diagnostic modalities and hemodynamics. Circulation. 2014 Jan 14;129(2):244–53.

54. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2021 Aug 28;ehab395.

55. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. Circulation. 2004 May 18;109(19):2302–8.

56. Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW, et al. B-type natriuretic peptide clinical activation in aortic stenosis: impact on long-term survival. J Am Coll Cardiol. 2014 May 20;63(19):2016–25.

57. Chizner MA, Pearle DL, deLeon AC. The natural history of aortic stenosis in adults. Am Heart J. 1980 Apr;99(4):419–24.

58. Bach DS, Cimino N, Deeb GM. Unoperated patients with severe aortic stenosis. J Am Coll Cardiol. 2007 Nov 13;50(20):2018–9.

59. Borer JS, Sharma A. Drug Therapy for Heart Valve Diseases. Circulation. 2015 Sep 15;132(11):1038–45.

60. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008 Sep 25;359(13):1343–56.

61. Bull S, Loudon M, Francis JM, Joseph J, Gerry S, Karamitsos TD, et al. A prospective, double-blind, randomized controlled trial of the angiotensin-converting enzyme inhibitor Ramipril In Aortic Stenosis (RIAS trial). Eur Heart J Cardiovasc Imaging. 2015 Aug;16(8):834–41.

62. Ochiai T, Saito S, Yamanaka F, Shishido K, Tanaka Y, Yamabe T, et al. Renin-angiotensin system blockade therapy after transcatheter aortic valve implantation. Heart. 2018 Apr;104(8):644–51.

63. Dahl JS, Videbaek L, Poulsen MK, Pellikka PA, Veien K, Andersen LI, et al. Effect of candesartan treatment on left ventricular remodeling after aortic valve replacement for aortic stenosis. Am J Cardiol. 2010 Sep 1;106(5):713–9.

64. Rodriguez-Gabella T, Catalá P, Muñoz-García AJ, Nombela-Franco L, Del Valle R, Gutiérrez E, et al. Renin-Angiotensin System Inhibition Following Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2019 Aug 6;74(5):631–41.

65. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Aug 27;ehab368.

66. Cribier A, Savin T, Saoudi N, Rocha P, Berland J, Letac B. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? Lancet. 1986 Jan 11;1(8472):63–7.

67. Kennedy KD, Hauck AJ, Edwards WD, Holmes DR, Reeder GS, Nishimura RA. Mechanism of reduction of aortic valvular stenosis by percutaneous transluminal balloon valvuloplasty: report of five cases and review of literature. Mayo Clin Proc. 1988 Aug;63(8):769–76.

68. Hara H, Pedersen WR, Ladich E, Mooney M, Virmani R, Nakamura M, et al. Percutaneous Balloon Aortic Valvuloplasty Revisited. Circulation. 2007 Mar 27;115(12):e334–8.

69. Kuntz RE, Tosteson AN, Maitland LA, Gordon P, Leonard BM, McKay RG, et al. Immediate results and long-term follow-up after repeat balloon aortic valvuloplasty. Cathet Cardiovasc Diagn. 1992 Jan;25(1):4–9.

70. Otto CM, Mickel MC, Kennedy JW, Alderman EL, Bashore TM, Block PC, et al. Three-year outcome after balloon aortic valvuloplasty. Insights into prognosis of valvular aortic stenosis. Circulation. 1994 Feb;89(2):642–50.

71. Wang A, Harrison JK, Bashore TM. Balloon aortic valvuloplasty. Prog Cardiovasc Dis. 1997 Aug;40(1):27–36.

72. Ben-Dor I, Pichard AD, Satler LF, Goldstein SA, Syed AI, Gaglia MA, et al. Complications and outcome of balloon aortic valvuloplasty in high-risk or inoperable patients. JACC Cardiovasc Interv. 2010 Nov;3(11):1150–6.

73. Lieberman EB, Bashore TM, Hermiller JB, Wilson JS, Pieper KS, Keeler GP, et al. Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. J Am Coll Cardiol. 1995 Nov 15;26(6):1522–8.

74. Dall'Ara G, Tumscitz C, Grotti S, Santarelli A, Balducelli M, Tarantino F, et al. Contemporary balloon aortic valvuloplasty: Changing indications and refined technique. Catheterization and Cardiovascular Interventions. 2021;97(7):E1033–42.

75. Effler DB, Favaloro R, Groves LK. HEART VALVE REPLACEMENT. CLINICAL EXPERIENCE. Ann Thorac Surg. 1965 Jan;1:4–24.

76. Brown JM, O'Brien SM, Wu C, Sikora JAH, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg. 2009 Jan;137(1):82–90.

77. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation. 2009 Feb 24;119(7):1034–48.

78. Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, et al. Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. N Engl J Med. 2017 Nov 9;377(19):1847–57.

79. Rodriguez-Gabella T, Voisine P, Puri R, Pibarot P, Rodés-Cabau J. Aortic Bioprosthetic Valve Durability: Incidence, Mechanisms, Predictors, and Management of Surgical and Transcatheter Valve Degeneration. J Am Coll Cardiol. 2017 Aug 22;70(8):1013–28.

80. Paradis JM, Del Trigo M, Puri R, Rodés-Cabau J. Transcatheter Valve-in-Valve and Valve-in-Ring for Treating Aortic and Mitral Surgical Prosthetic Dysfunction. J Am Coll Cardiol. 2015 Nov 3;66(18):2019–37.

81. Dunning J, Graham RJ, Thambyrajah J, Stewart MJ, Kendall SWH, Hunter S. Stentless vs. stented aortic valve bioprostheses: a prospective randomized controlled trial. Eur Heart J. 2007 Oct;28(19):2369–74.

82. Karangelis D, Mazine A, Roubelakis A, Alexiou C, Fragoulis S, Mazer CD, et al. What is the role of sutureless aortic valves in today's armamentarium? Expert Rev Cardiovasc Ther. 2017 Feb;15(2):83–91.

83. Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. J Thorac Cardiovasc Surg. 2015 May;149(5):1262-1269.e3.

84. Ferrari E, Tozzi P, Hurni M, Ruchat P, Stumpe F, von Segesser LK. Primary isolated aortic valve surgery in octogenarians. Eur J Cardiothorac Surg. 2010 Aug;38(2):128–33.

85. Lindman BR, Bonow RO, Otto CM. Current management of calcific aortic stenosis. Circ Res. 2013 Jul 5;113(2):223–37.

86. Lauck SB, Baron SJ, Irish W, Borregaard B, Moore KA, Gunnarsson CL, et al. Temporal Changes in Mortality After Transcatheter and Surgical Aortic Valve Replacement: Retrospective Analysis of US Medicare Patients (2012-2019). J Am Heart Assoc. 2021 Sep 28;e021748.

87. Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012 Apr;41(4):734–44; discussion 744-745.

88. Puskas JD, Kilgo PD, Thourani VH, Lattouf OM, Chen E, Vega JD, et al. The society of thoracic surgeons 30-day predicted risk of mortality score also predicts long-term survival. Ann Thorac Surg. 2012 Jan;93(1):26–33; discussion 33-35.

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

90. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J. 2005 Dec;26(24):2714–20.

91. Charlson E, Legedza ATR, Hamel MB. Decision-making and outcomes in severe symptomatic aortic stenosis. J Heart Valve Dis. 2006 May;15(3):312–21.

92. Andersen HR, Knudsen LL, Hasenkam JM. Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs. Eur Heart J. 1992 May;13(5):704–8.

93. Cribier Alain, Eltchaninoff Helene, Bash Assaf, Borenstein Nicolas, Tron Christophe, Bauer Fabrice, et al. Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis. Circulation. 2002 Dec 10;106(24):3006–8.

94. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Nercolini D, et al. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. J Am Coll Cardiol. 2006 Mar 21;47(6):1214–23.

95. Webb JG, Chandavimol M, Thompson CR, Ricci DR, Carere RG, Munt BI, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. Circulation. 2006 Feb 14;113(6):842–50.

96. Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, et al. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation. 2007 Aug 14;116(7):755–63.

97. Lichtenstein SV, Cheung A, Ye J, Thompson CR, Carere RG, Pasupati S, et al. Transapical transcatheter aortic valve implantation in humans: initial clinical experience. Circulation. 2006 Aug 8;114(6):591–6.

98. Grube E, Laborde JC, Zickmann B, Gerckens U, Felderhoff T, Sauren B, et al. First report on a human percutaneous transluminal implantation of a self-

expanding valve prosthesis for interventional treatment of aortic valve stenosis. Catheter Cardiovasc Interv. 2005 Dec;66(4):465–9.

99. Laborde JC, Borenstein N, Behr L, Farah B, Fajadet J. Percutaneous implantation of an aortic valve prosthesis. Catheter Cardiovasc Interv. 2005 Jun;65(2):171–4; discussion 175.

100. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. Nat Rev Cardiol. 2011 Nov 15;9(1):15–29.

101. Butala NM, Chung M, Secemsky EA, Manandhar P, Marquis-Gravel G, Kosinski AS, et al. Conscious Sedation Versus General Anesthesia for Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2020 Jun 8;13(11):1277–87.

102. Binder RK, Rodés-Cabau J, Wood DA, Mok M, Leipsic J, De Larochellière R, et al. Transcatheter aortic valve replacement with the SAPIEN 3: a new balloon-expandable transcatheter heart valve. JACC Cardiovasc Interv. 2013 Mar;6(3):293–300.

103. Rheude T, Pellegrini C, Lutz J, Alvarez-Covarrubias HA, Lahmann AL, Mayr NP, et al. Transcatheter Aortic Valve Replacement With Balloon-Expandable Valves: Comparison of SAPIEN 3 Ultra Versus SAPIEN 3. JACC Cardiovasc Interv. 2020 Nov 23;13(22):2631–8.

104. Claessen BE, Tang GHL, Kini AS, Sharma SK. Considerations for Optimal Device Selection in Transcatheter Aortic Valve Replacement: A Review. JAMA Cardiol. 2021 Jan 1;6(1):102–12.

105. Blanke P, Weir-McCall JR, Achenbach S, Delgado V, Hausleiter J, Jilaihawi H, et al. Computed Tomography Imaging in the Context of Transcatheter Aortic Valve Implantation (TAVI)/Transcatheter Aortic Valve Replacement (TAVR): An Expert Consensus Document of the Society of Cardiovascular Computed Tomography. JACC Cardiovasc Imaging. 2019 Jan;12(1):1–24.

106. Faurie B, Souteyrand G, Staat P, Godin M, Caussin C, Van Belle E, et al. Left Ventricular Rapid Pacing Via the Valve Delivery Guidewire in Transcatheter

Aortic Valve Replacement. JACC Cardiovasc Interv. 2019 Dec 23;12(24):2449–59.

107. Mahtta D, Elgendy IY, Bavry AA. From CoreValve to Evolut PRO: Reviewing the Journey of Self-Expanding Transcatheter Aortic Valves. Cardiol Ther. 2017 Dec;6(2):183–92.

108. Kim WK, Pellegrini C, Ludwig S, Möllmann H, Leuschner F, Makkar R, et al. Feasibility of Coronary Access in Patients With Acute Coronary Syndrome and Previous TAVR. JACC Cardiovasc Interv. 2021 Jul 26;14(14):1578–90.

109. Faroux L, Guimaraes L, Wintzer-Wehekind J, Junquera L, Ferreira-Neto AN, Del Val D, et al. Coronary Artery Disease and Transcatheter Aortic Valve Replacement: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Jul 23;74(3):362–72.

110. Yudi MB, Sharma SK, Tang GHL, Kini A. Coronary Angiography and Percutaneous Coronary Intervention After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2018 Mar 27;71(12):1360–78.

111. Barbanti M, Costa G, Picci A, Criscione E, Reddavid C, Valvo R, et al. Coronary Cannulation After Transcatheter Aortic Valve Replacement: The RE-ACCESS Study. JACC Cardiovasc Interv. 2020 Nov 9;13(21):2542–55.

112. Möllmann H, Holzhey DM, Hilker M, Toggweiler S, Schäfer U, Treede H, et al. The ACURATE neo2 valve system for transcatheter aortic valve implantation: 30-day and 1-year outcomes. Clin Res Cardiol. 2021 Jun 20;

113. Søndergaard L, Rodés-Cabau J, Hans-Peter Linke A, Fichtlscherer S, Schäfer U, Kuck KH, et al. Transcatheter Aortic Valve Replacement With a Repositionable Self-Expanding Prosthesis: The PORTICO-I Trial 1-Year Outcomes. J Am Coll Cardiol. 2018 11;72(23 Pt A):2859–67.

114. Meredith Am IT, Walters DL, Dumonteil N, Worthley SG, Tchétché D, Manoharan G, et al. Transcatheter aortic valve replacement for severe symptomatic aortic stenosis using a repositionable valve system: 30-day primary

endpoint results from the REPRISE II study. J Am Coll Cardiol. 2014 Sep 30;64(13):1339–48.

115. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2020 Nov 24;76(21):2492–516.

116. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. Eur Heart J. 2019 Oct 7;40(38):3143–53.

117. Blackstone EH, Suri RM, Rajeswaran J, Babaliaros V, Douglas PS, Fearon WF, et al. Propensity-matched comparisons of clinical outcomes after transapical or transfemoral transcatheter aortic valve replacement: a placement of aortic transcatheter valves (PARTNER)-I trial substudy. Circulation. 2015 Jun 2;131(22):1989–2000.

118. Walther T, Falk V, Borger MA, Dewey T, Wimmer-Greinecker G, Schuler G, et al. Minimally invasive transapical beating heart aortic valve implantation--proof of concept. Eur J Cardiothorac Surg. 2007 Jan;31(1):9–15.

119. Junquera L, Kalavrouziotis D, Dumont E, Rodés-Cabau J, Mohammadi S. Paradigm shifts in alternative access for transcatheter aortic valve replacement: An update. J Thorac Cardiovasc Surg. 2021 May 3;S0022-5223(21)00760-1.

120. Cahill TJ, Chen M, Hayashida K, Latib A, Modine T, Piazza N, et al. Transcatheter aortic valve implantation: current status and future perspectives. Eur Heart J. 2018 Jul 21;39(28):2625–34.

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

122. Walther T, Hamm CW, Schuler G, Berkowitsch A, Kötting J, Mangner N, et al. Perioperative Results and Complications in 15,964 Transcatheter Aortic Valve

Replacements: Prospective Data From the GARY Registry. J Am Coll Cardiol. 2015 May 26;65(20):2173–80.

123. Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, et al. Impact of the Clinical Frailty Scale on Outcomes After Transcatheter Aortic Valve Replacement. Circulation. 2017 May 23;135(21):2013–24.

124. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, et al. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol. 2011 Jan 18;57(3):253–69.

125. VARC-3 WRITING COMMITTEE:, Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, et al. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. J Am Coll Cardiol. 2021 Jun 1;77(21):2717–46.

126. Wayangankar SA, Elgendy IY, Xiang Q, Jneid H, Vemulapalli S, Khachatryan T, et al. Length of Stay After Transfemoral Transcatheter Aortic Valve Replacement: An Analysis of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. JACC: Cardiovascular Interventions. 2019 Mar 11;12(5):422–30.

127. Perdoncin E, Greenbaum AB, Grubb KJ, Babaliaros VC, Keegan P, Ceretto-Clark B, et al. Safety of same-day discharge after uncomplicated, minimalist transcatheter aortic valve replacement in the COVID-19 era. Catheter Cardiovasc Interv. 2020 Dec 31;

128. Généreux P, Webb JG, Svensson LG, Kodali SK, Satler LF, Fearon WF, et al. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. J Am Coll Cardiol. 2012 Sep 18;60(12):1043–52.

129. Van Mieghem NM, Nuis RJ, Piazza N, Apostolos T, Ligthart J, Schultz C, et al. Vascular complications with transcatheter aortic valve implantation using the 18

Fr Medtronic CoreValve System: the Rotterdam experience. EuroIntervention. 2010 Jan;5(6):673–9.

130. Van Mieghem NM, Tchetche D, Chieffo A, Dumonteil N, Messika-Zeitoun D, van der Boon RMA, et al. Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation. Am J Cardiol. 2012 Nov 1;110(9):1361–7.

131. Mwipatayi BP, Picardo A, Masilonyane-Jones TV, Larbalestier R, Thomas S, Turner J, et al. Incidence and prognosis of vascular complications after transcatheter aortic valve implantation. J Vasc Surg. 2013 Oct;58(4):1028-1036.e1.

132. Barbanti M, Binder RK, Freeman M, Wood DA, Leipsic J, Cheung A, et al. Impact of low-profile sheaths on vascular complications during transfemoral transcatheter aortic valve replacement. EuroIntervention. 2013 Dec;9(8):929–35.

133. Sherwood MW, Xiang K, Matsouaka R, Li Z, Vemulapalli S, Vora AN, et al. Incidence, Temporal Trends, and Associated Outcomes of Vascular and Bleeding Complications in Patients Undergoing Transfemoral Transcatheter Aortic Valve Replacement: Insights From the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry. Circ Cardiovasc Interv. 2020 Jan;13(1):e008227.

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

135. Stortecky S, Windecker S, Pilgrim T, Heg D, Buellesfeld L, Khattab AA, et al. Cerebrovascular accidents complicating transcatheter aortic valve implantation: frequency, timing and impact on outcomes. EuroIntervention. 2012 May 15;8(1):62–70.

136. Kleiman NS, Maini BJ, Reardon MJ, Conte J, Katz S, Rajagopal V, et al. Neurological Events Following Transcatheter Aortic Valve Replacement and

Their Predictors: A Report From the CoreValve Trials. Circ Cardiovasc Interv. 2016;9(9).

137. Durko AP, Reardon MJ, Kleiman NS, Popma JJ, Van Mieghem NM, Gleason TG, et al. Neurological Complications After Transcatheter Versus Surgical Aortic Valve Replacement in Intermediate-Risk Patients. J Am Coll Cardiol. 2018 30;72(18):2109–19.

138. Holmes DR, Brennan JM, Rumsfeld JS, Dai D, O'Brien SM, Vemulapalli S, et al. Clinical outcomes at 1 year following transcatheter aortic valve replacement. JAMA. 2015 Mar 10;313(10):1019–28.

139. Sato Y, Kawakami R, Sakamoto A, Cornelissen A, Mori M, Kawai K, et al. Efficacy and safety of cerebral embolic protection systems during transcatheter aortic valve replacement: a review of current clinical findings. Expert Rev Cardiovasc Ther. 2021 Aug;19(8):725–37.

140. Capodanno D, Collet JP, Dangas G, Montalescot G, Ten Berg JM, Windecker S, et al. Antithrombotic Therapy After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2021 Aug 9;14(15):1688–703.

141. Saito Y, Nazif T, Baumbach A, Tchétché D, Latib A, Kaple R, et al. Adjunctive Antithrombotic Therapy for Patients With Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement. JAMA Cardiol. 2020 Jan 1;5(1):92–101.

142. Khalique OK, Hahn RT, Gada H, Nazif TM, Vahl TP, George I, et al. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilation after balloon-expandable transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2014 Aug;7(8):885–94.

143. Athappan G, Patvardhan E, Tuzcu EM, Svensson LG, Lemos PA, Fraccaro C, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol. 2013 Apr 16;61(15):1585–95.

144. Pibarot P, Hahn RT, Weissman NJ, Arsenault M, Beaudoin J, Bernier M, et al. Association of Paravalvular Regurgitation With 1-Year Outcomes After Transcatheter Aortic Valve Replacement With the SAPIEN 3 Valve. JAMA Cardiol. 2017 Nov 1;2(11):1208–16.

145. Auffret V, Puri R, Urena M, Chamandi C, Rodriguez-Gabella T, Philippon F, et al. Conduction Disturbances After Transcatheter Aortic Valve Replacement: Current Status and Future Perspectives. Circulation. 2017 Sep 12;136(11):1049–69.

146. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010 Oct 21;363(17):1597–607.

147. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011 Jun 9;364(23):2187–98.

148. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014 May 8;370(19):1790–8.

149. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol. 2014 May 20;63(19):1972–81.

150. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016 28;374(17):1609–20.

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

152. Siontis GCM, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for

treatment of severe aortic stenosis: a meta-analysis of randomized trials. Eur Heart J. 2016 Dec 14;37(47):3503–12.

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

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

155. Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, et al. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. Ann Thorac Surg. 2015 Jan;99(1):55–61.

156. Wu C, Vasseur B, Maisel W. The March of Transcatheter Aortic Valve Replacement Therapy-US Food and Drug Administration Perspectives on Device Approval for Patients at Low Surgical Risk. JAMA Cardiol. 2020 Jan 1;5(1):5–6.

157. Alperi A, Voisine P, Kalavrouziotis D, Dumont E, Dagenais F, Perron J, et al. Aortic Valve Replacement in Low-Risk Patients With Severe Aortic Stenosis Outside Randomized Trials. J Am Coll Cardiol. 2021 Jan 19;77(2):111–23.

158. Thyregod HGH, Ihlemann N, Jørgensen TH, Nissen H, Kjeldsen BJ, Petursson P, et al. Five-Year Clinical and Echocardiographic Outcomes From the NOTION Randomized Clinical Trial in Patients at Lower Surgical Risk. Circulation. 2019 Jun 11;139(24):2714–23.

159. Jørgensen TH, Thyregod HGH, Ihlemann N, Nissen H, Petursson P, Kjeldsen BJ, et al. Eight-year outcomes for patients with aortic valve stenosis at low surgical risk randomized to transcatheter vs. surgical aortic valve replacement. Eur Heart J. 2021 Aug 7;42(30):2912–9.

160. Anderson RH. The surgical anatomy of the aortic root. Multimed Man Cardiothorac Surg. 2007 Jan 1;2007(102):mmcts.2006.002527.

161. Piazza N, de Jaegere P, Schultz C, Becker AE, Serruys PW, Anderson RH. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. Circ Cardiovasc Interv. 2008 Aug;1(1):74–81.

162. Waller BF, Gering LE, Branyas NA, Slack JD. Anatomy, histology, and pathology of the cardiac conduction system--Part V. Clin Cardiol. 1993 Jul;16(7):565–9.

163. Sánchez-Quintana D, Yen Ho S. [Anatomy of cardiac nodes and atrioventricular specialized conduction system]. Rev Esp Cardiol. 2003 Nov;56(11):1085–92.

164. van der Boon RM, Nuis RJ, Van Mieghem NM, Jordaens L, Rodés-Cabau J, van Domburg RT, et al. New conduction abnormalities after TAVI--frequency and causes. Nat Rev Cardiol. 2012 May 1;9(8):454–63.

165. Cabrera JÁ, Anderson RH, Porta-Sánchez A, Macías Y, Cano Ó, Spicer DE, et al. The Atrioventricular Conduction Axis and its Implications for Permanent Pacing. Arrhythm Electrophysiol Rev. 2021 Oct;10(3):181–9.

166. Bagur R, Rodés-Cabau J, Gurvitch R, Dumont É, Velianou JL, Manazzoni J, 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 May;5(5):540–51.

167. Muntané-Carol G, Guimaraes L, Ferreira-Neto AN, Wintzer-Wehekind J, Junquera L, Del Val D, et al. How does new-onset left bundle branch block affect the outcomes of transcatheter aortic valve repair? Expert Rev Med Devices. 2019;16(7):589–602.

168. Moreno R, Dobarro D, López de Sá E, Prieto M, Morales C, Calvo Orbe L, et al. Cause of complete atrioventricular block after percutaneous aortic valve implantation: insights from a necropsy study. Circulation. 2009 Aug 4;120(5):e29-30.

169. Rubín JM, Avanzas P, del Valle R, Renilla A, Ríos E, Calvo D, et al. Atrioventricular conduction disturbance characterization in transcatheter aortic

valve implantation with the CoreValve prosthesis. Circ Cardiovasc Interv. 2011 Jun;4(3):280–6.

170. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009 Mar 17;53(11):976–81.

171. Auffret V, Martins RP, Daubert C, Leclercq C, Le Breton H, Mabo P, et al. Idiopathic/Iatrogenic Left Bundle Branch Block-Induced Reversible Left Ventricle Dysfunction: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018 Dec 18;72(24):3177–88.

172. Vogler J, Breithardt G, Eckardt L. Bradyarrhythmias and conduction blocks. Rev Esp Cardiol (Engl Ed). 2012 Jul;65(7):656–67.

173. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019 Aug 20;74(7):e51–156.

174. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021 Sep 14;42(35):3427–520.

175. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med. 2013 Apr 25;368(17):1585–93.

176. Shen L, Jhund PS, Docherty KF, Petrie MC, Anand IS, Carson PE, et al. Prior Pacemaker Implantation and Clinical Outcomes in Patients With Heart Failure and Preserved Ejection Fraction. JACC Heart Fail. 2019 May;7(5):418–27.

177. Elder DHJ, Lang CC, Choy AM. Pacing-induced heart disease: understanding the pathophysiology and improving outcomes. Expert Rev Cardiovasc Ther. 2011 Jul;9(7):877–86.

178. Yater WM. HEART BLOCK DUE TO CALCAREOUS LESIONS OF THE BUNDLE OF HIS: REVIEW AND REPORT OF A CASE WITH DETAILED HISTOPATHOLOGIC STUDY*. Ann Intern Med. 1935 Jan 1;8(7):777.

179. Mautner RK, Phillips JH. Atrioventricular and intraventricular conduction disturbances in aortic valvular disease. South Med J. 1980 May;73(5):572–8, 581.

180. Friedman HS, Zaman Q, Haft JI, Melendez S. Assessment of atrioventricular conduction in aortic valve disease. Br Heart J. 1978 Aug;40(8):911–7.

181. Wolfe RR, Driscoll DJ, Gersony WM, Hayes CJ, Keane JF, Kidd L, et al. Arrhythmias in patients with valvar aortic stenosis, valvar pulmonary stenosis, and ventricular septal defect. Results of 24-hour ECG monitoring. Circulation. 1993 Feb;87(2 Suppl):I89-101.

182. Marchandise B, Piette F, Chalant CH, Kremer R. [Conduction disorders in aortic valve diseases]. Acta Cardiol. 1975;30(2):111–28.

183. Thompson R, Mitchell A, Ahmed M, Towers M, Yacoub M. Conduction defects in aortic valve disease. Am Heart J. 1979 Jul;98(1):3–10.

184. Nair CK, Aronow WS, Stokke K, Mohiuddin SM, Thomson W, Sketch MH. Cardiac conduction defects in patients older than 60 years with aortic stenosis with and without mitral anular calcium. Am J Cardiol. 1984 Jan 1;53(1):169–72.

185. Rasmussen K, Thomsen PE, Bagger JP. HV interval in calcific aortic stenosis. Relation to left ventricular function and effect of valve replacement. Br Heart J. 1984 Jul;52(1):82–6.

186. MacMillan RM, Demorizi NM, Gessman LJ, Maranhao V. Correlates of prolonged HV conduction in aortic stenosis. Am Heart J. 1985 Jul;110(1 Pt 1):56–60.

187. Dhingra RC, Amat-y-Leon F, Pietras RJ, Wyndham C, Deedwania PC, Wu D, et al. Sites of conduction disease in aortic stenosis: significance of valve gradient and calcification. Ann Intern Med. 1977 Sep;87(3):275–80.

188. Urena M, Hayek S, Cheema AN, Serra V, Amat-Santos IJ, Nombela-Franco L, et al. Arrhythmia burden in elderly patients with severe aortic stenosis as determined by continuous electrocardiographic recording: toward a better understanding of arrhythmic events after transcatheter aortic valve replacement. Circulation. 2015 Feb 3;131(5):469–77.

189. Winter JL, Healey JS, Sheth TN, Velianou JL, Schwalm JD, Smith A, et al. Remote Ambulatory Cardiac Monitoring Before and After Transcatheter Aortic Valve Replacement. CJC open. 2020 Sep;2(5):416–9.

190. Asmarats L, Nault I, Ferreira-Neto AN, Muntané-Carol G, Del Val D, Junquera L, et al. Prolonged Continuous Electrocardiographic Monitoring Prior to Transcatheter Aortic Valve Replacement: The PARE Study. JACC Cardiovascular interventions. 2020 Aug 10;13(15):1763–73.

191. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013 Sep;34(35):2746–51.

192. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006 Jul 11;114(2):119–25.

193. Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978 Oct;28(10):973–7.

194. Lamassa M, Di Carlo A, Pracucci G, Basile AM, Trefoloni G, Vanni P, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke. 2001 Feb;32(2):392–8.

195. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA. 2011 May 25;305(20):2080–7.

196. Greve AM, Gerdts E, Boman K, Gohlke-Baerwolf C, Rossebø AB, Nienaber CA, et al. Prognostic importance of atrial fibrillation in asymptomatic aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis study. Int J Cardiol. 2013 Jun 5;166(1):72–6.

197. Fukuda T, Hawley RL, Edwards JE. Lesions of conduction tissue complicating aortic valvular replacement. Chest. 1976 May;69(5):605–14.

198. Thomas JL, Dickstein RA, Parker FB, Potts JL, Poirier RA, Fruehan CT, et al. Prognostic significance of the development of left bundle conduction defects following aortic valve replacement. J Thorac Cardiovasc Surg. 1982 Sep;84(3):382–6.

199. Fournial JF, Brodaty D, Chomette G, Tereau Y, Cabrol C, Acar J. [Conduction disorders after aortic valve replacement. Apropos of 200 cases]. Arch Mal Coeur Vaiss. 1979 Jan;72(1):4–11.

200. El-Khally Z, Thibault B, Staniloae C, Theroux P, Dubuc M, Roy D, et al. Prognostic significance of newly acquired bundle branch block after aortic valve replacement. Am J Cardiol. 2004 Oct 15;94(8):1008–11.

201. Dawkins S, Hobson AR, Kalra PR, Tang ATM, Monro JL, Dawkins KD. Permanent pacemaker implantation after isolated aortic valve replacement: incidence, indications, and predictors. Ann Thorac Surg. 2008 Jan;85(1):108–12.

202. Merin O, Ilan M, Oren A, Fink D, Deeb M, Bitran D, et al. Permanent pacemaker implantation following cardiac surgery: indications and long-term follow-up. Pacing Clin Electrophysiol. 2009 Jan;32(1):7–12.

203. Bagur R, Manazzoni JM, Dumont É, Doyle D, Perron J, Dagenais F, et al. Permanent pacemaker implantation following isolated aortic valve replacement in a large cohort of elderly patients with severe aortic stenosis. Heart. 2011 Oct;97(20):1687–94.

204. Matthews IG, Fazal IA, Bates MGD, Turley AJ. In patients undergoing aortic valve replacement, what factors predict the requirement for permanent pacemaker implantation? Interact Cardiovasc Thorac Surg. 2011 Mar;12(3):475–9.

205. De Torres-Alba F, Kaleschke G, Diller GP, Vormbrock J, Orwat S, Radke R, et al. Changes in the Pacemaker Rate After Transition From Edwards SAPIEN XT to SAPIEN 3 Transcatheter Aortic Valve Implantation: The Critical Role of Valve Implantation Height. JACC Cardiovasc Interv. 2016 Apr 25;9(8):805–13.

206. Husser O, Pellegrini C, Kessler T, Burgdorf C, Thaller H, Mayr NP, et al. Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve. JACC: Cardiovascular Interventions. 2016 Feb 8;9(3):244–54.

207. Schofer J, Colombo A, Klugmann S, Fajadet J, DeMarco F, Tchétché D, et al. Prospective multicenter evaluation of the direct flow medical transcatheter aortic valve. J Am Coll Cardiol. 2014 Mar 4;63(8):763–8.

208. Silaschi M, Treede H, Rastan AJ, Baumbach H, Beyersdorf F, Kappert U, et al. The JUPITER registry: 1-year results of transapical aortic valve implantation using a second-generation transcatheter heart valve in patients with aortic stenosis. Eur J Cardiothorac Surg. 2016 Nov;50(5):874–81.

209. Seiffert M, Conradi L, Kloth B, Koschyk D, Schirmer J, Schnabel RB, et al. Single-centre experience with next-generation devices for transapical aortic valve implantation. Eur J Cardiothorac Surg. 2015 Jan;47(1):39–45; discussion 45.

210. Jochheim D, Zadrozny M, Theiss H, Baquet M, Maimer-Rodrigues F, Bauer A, et al. Aortic regurgitation with second versus third-generation balloon-expandable prostheses in patients undergoing transcatheter aortic valve implantation. EuroIntervention. 2015 Jun;11(2):214–20.

211. Gonska B, Seeger J, Keßler M, von Keil A, Rottbauer W, Wöhrle J. Predictors for permanent pacemaker implantation in patients undergoing transfemoral aortic valve implantation with the Edwards Sapien 3 valve. Clin Res Cardiol. 2017 Aug;106(8):590–7.

212. Toggweiler S, Nissen H, Mogensen B, Cuculi F, Fallesen C, Veien KT, et al. Very low pacemaker rate following ACURATE neo transcatheter heart valve implantation. EuroIntervention. 2017 Dec 20;13(11):1273–80.

213. Schwerg M, Fulde F, Dreger H, Poller WC, Stangl K, Laule M. Optimized Implantation Height of the Edwards SAPIEN 3 Valve to Minimize Pacemaker Implantation After TAVI. J Interv Cardiol. 2016 Aug;29(4):370–4.

214. Webb J, Gerosa G, Lefèvre T, Leipsic J, Spence M, Thomas M, et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. J Am Coll Cardiol. 2014 Dec 2;64(21):2235–43.

215. Vahanian A, Urena M, Walther T, Treede H, Wendler O, Lefèvre T, et al. Thirty-day outcomes in patients at intermediate risk for surgery from the SAPIEN 3 European approval trial. EuroIntervention. 2016 Jun 12;12(2):e235-243.

216. Finkelstein A, Steinvil A, Rozenbaum Z, Halkin A, Banai S, Barbash I, et al. Efficacy and safety of new-generation transcatheter aortic valves: insights from the Israeli transcatheter aortic valve replacement registry. Clin Res Cardiol. 2019 Apr;108(4):430–7.

217. Rampat R, Khawaja MZ, Byrne J, MacCarthy P, Blackman DJ, Krishnamurthy A, et al. Transcatheter Aortic Valve Replacement Using the Repositionable LOTUS Valve: United Kingdom Experience. JACC Cardiovasc Interv. 2016 Feb 22;9(4):367–72.

218. Keßler M, Gonska B, Seeger J, Rottbauer W, Wöhrle J. Predictors of permanent pacemaker implantation after transfemoral aortic valve implantation with the Lotus valve. Am Heart J. 2017 Oct;192:57–63.

219. Zaman S, McCormick L, Gooley R, Rashid H, Ramkumar S, Jackson D, et al. Incidence and predictors of permanent pacemaker implantation following

treatment with the repositionable Lotus™ transcatheter aortic valve. Catheter Cardiovasc Interv. 2017 Jul;90(1):147–54.

220. Walther T, Manoharan G, Linke A, Möllmann H, Holzhey D, Worthley SG, et al. Incidence of new-onset left bundle branch block and predictors of new permanent pacemaker following transcatheter aortic valve replacement with the Portico™ valve. Eur J Cardiothorac Surg. 2018 01;54(3):467–74.

221. Zaid S, Sengupta A, Okoli K, Tsoi M, Khan A, Ahmad H, et al. Novel Anatomic Predictors of New Persistent Left Bundle Branch Block After Evolut Transcatheter Aortic Valve Implantation. Am J Cardiol. 2020 Apr 15;125(8):1222–9.

222. Houthuizen P, van der Boon RMA, Urena M, Van Mieghem N, Brueren GBR, Poels TT, et al. Occurrence, fate and consequences of ventricular conduction abnormalities after transcatheter aortic valve implantation. EuroIntervention. 2014 Feb;9(10):1142–50.

223. Massoullié G, Bordachar P, Ellenbogen KA, Souteyrand G, Jean F, Combaret N, et al. New-Onset Left Bundle Branch Block Induced by Transcutaneous Aortic Valve Implantation. Am J Cardiol. 2016 Mar 1;117(5):867–73.

224. Erkapic D, De Rosa S, Kelava A, Lehmann R, Fichtlscherer S, Hohnloser SH. Risk for permanent pacemaker after transcatheter aortic valve implantation: a comprehensive analysis of the literature. J Cardiovasc Electrophysiol. 2012 Apr;23(4):391–7.

225. Urena M, Webb JG, Cheema A, Serra V, Toggweiler S, Barbanti M, et al. 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. JACC Cardiovasc Interv. 2014 Feb;7(2):128–36.

226. Urena M, Mok M, Serra V, Dumont E, Nombela-Franco L, DeLarochellière R, et al. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol. 2012 Oct 30;60(18):1743–52.

227. Regueiro A, Abdul-Jawad Altisent O, Del Trigo M, Campelo-Parada F, Puri R, Urena M, et al. Impact of New-Onset Left Bundle Branch Block and Periprocedural Permanent Pacemaker Implantation on Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. Circ Cardiovasc Interv. 2016 May;9(5):e003635.

228. Ando T, Takagi H, ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. The Prognostic Impact of New-Onset Persistent Left Bundle Branch Block Following Transcatheter Aortic Valve Implantation: A Meta-analysis. Clin Cardiol. 2016 Sep;39(9):544–50.

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

230. Mangieri A, Lanzillo G, Bertoldi L, Jabbour RJ, Regazzoli D, Ancona MB, et al. Predictors of Advanced Conduction Disturbances Requiring a Late (≥48 H) Permanent Pacemaker Following Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2018 13;11(15):1519–26.

231. Jørgensen TH, De Backer O, Gerds TA, Bieliauskas G, Svendsen JH, Søndergaard L. Immediate Post-Procedural 12-Lead Electrocardiography as Predictor of Late Conduction Defects After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2018 13;11(15):1509–18.

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

233. Makki N, Dollery J, Jones D, Crestanello J, Lilly S. Conduction disturbances after TAVR: Electrophysiological studies and pacemaker dependency. Cardiovasc Revasc Med. 2017 Aug;18(5S1):S10–3.

234. Rogers T, Devraj M, Thomaides A, Steinvil A, Lipinski MJ, Buchanan KD, et al. Utility of Invasive Electrophysiology Studies in Patients With Severe Aortic

Stenosis Undergoing Transcatheter Aortic Valve Implantation. Am J Cardiol. 2018 01;121(11):1351–7.

235. Kostopoulou A, Karyofillis P, Livanis E, Thomopoulou S, Stefopoulos C, Doudoumis K, et al. Permanent pacing after transcatheter aortic valve implantation of a CoreValve prosthesis as determined by electrocardiographic and electrophysiological predictors: a single-centre experience. Europace. 2016 Jan;18(1):131–7.

236. Badenco N, Chong-Nguyen C, Maupain C, Himbert C, Duthoit G, Waintraub X, et al. Respective role of surface electrocardiogram and His bundle recordings to assess the risk of atrioventricular block after transcatheter aortic valve replacement. Int J Cardiol. 2017 Jun 1;236:216–20.

237. Carrabba N, Valenti R, Migliorini A, Marrani M, Cantini G, Parodi G, et al. Impact on Left Ventricular Function and Remodeling and on 1-Year Outcome in Patients With Left Bundle Branch Block After Transcatheter Aortic Valve Implantation. American Journal of Cardiology. 2015 Jul 1;116(1):125–31.

238. Schymik G, Tzamalis P, Bramlage P, Heimeshoff M, Würth A, Wondraschek R, et al. Clinical impact of a new left bundle branch block following TAVI implantation: 1-year results of the TAVIK cohort. Clin Res Cardiol. 2015 Apr;104(4):351–62.

239. Chamandi C, Barbanti M, Munoz-Garcia A, Latib A, Nombela-Franco L, Gutiérrez-Ibanez E, et al. Long-Term Outcomes in Patients With New-Onset Persistent Left Bundle Branch Block Following TAVR. JACC Cardiovasc Interv. 2019 Jun 24;12(12):1175–84.

240. Nazif TM, Chen S, George I, Dizon JM, Hahn RT, Crowley A, et al. New-onset left bundle branch block after transcatheter aortic valve replacement is associated with adverse long-term clinical outcomes in intermediate-risk patients: an analysis from the PARTNER II trial. Eur Heart J. 2019 Jul 14;40(27):2218–27.

241. Jørgensen TH, De Backer O, Gerds TA, Bieliauskas G, Svendsen JH, Søndergaard L. Mortality and Heart Failure Hospitalization in Patients With

Conduction Abnormalities After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2019 Jan 14;12(1):52–61.

242. Faroux L, Chen S, Muntané-Carol G, Regueiro A, Philippon F, Sondergaard L, et al. Clinical impact of conduction disturbances in transcatheter aortic valve replacement recipients: a systematic review and meta-analysis. Eur Heart J [Internet]. 2020 Feb 11 [cited 2020 Feb 11]; Available from: https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehz924/5695667

243. Reichenspurner H, Schaefer A, Schäfer U, Tchétché D, Linke A, Spence MS, et al. Self-Expanding Transcatheter Aortic Valve System for Symptomatic High-Risk Patients With Severe Aortic Stenosis. J Am Coll Cardiol. 2017 26;70(25):3127–36.

244. Maeno Y, Abramowitz Y, Kawamori H, Kazuno Y, Kubo S, Takahashi N, et al. A Highly Predictive Risk Model for Pacemaker Implantation After TAVR. JACC Cardiovasc Imaging. 2017;10(10 Pt A):1139–47.

245. Mauri V, Reimann A, Stern D, Scherner M, Kuhn E, Rudolph V, et al. Predictors of Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement With the SAPIEN 3. JACC Cardiovasc Interv. 2016 14;9(21):2200–9.

246. Abramowitz Y, Jilaihawi H, Chakravarty T, Maeno Y, Kawamori H, Kazuno Y, et al. Sapien 3 Transcatheter Aortic Valve Implantation With Moderate or Without Predilation. J Invasive Cardiol. 2016 Oct;28(10):421–6.

247. Ben-Shoshan J, Konigstein M, Zahler D, Margolis G, Chorin E, Steinvil A, et al. Comparison of the Edwards SAPIEN S3 Versus Medtronic Evolut-R Devices for Transcatheter Aortic Valve Implantation. Am J Cardiol. 2017 Jan 15;119(2):302–7.

248. Schulz E, Jabs A, Tamm A, Herz P, Schulz A, Gori T, et al. Comparison of transcatheter aortic valve implantation with the newest-generation Sapien 3 vs. Direct Flow Medical valve in a single center cohort. Int J Cardiol. 2017 Apr 1;232:186–91.

249. Sawaya FJ, Spaziano M, Lefèvre T, Roy A, Garot P, Hovasse T, et al. Comparison between the SAPIEN S3 and the SAPIEN XT transcatheter heart valves: A single-center experience. World J Cardiol. 2016 Dec 26;8(12):735–45.

250. Pilgrim T, Stortecky S, Nietlispach F, Heg D, Tueller D, Toggweiler S, et al. Repositionable Versus Balloon-Expandable Devices for Transcatheter Aortic Valve Implantation in Patients With Aortic Stenosis. J Am Heart Assoc. 2016 17;5(11).

251. Wendler O, Schymik G, Treede H, Baumgartner H, Dumonteil N, Ihlberg L, et al. SOURCE 3 Registry: Design and 30-Day Results of the European Postapproval Registry of the Latest Generation of the SAPIEN 3 Transcatheter Heart Valve. Circulation. 2017 Mar 21;135(12):1123–32.

252. Kodali S, Thourani VH, White J, Malaisrie SC, Lim S, Greason KL, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J. 2016 Jul 21;37(28):2252–62.

253. Rogers T, Steinvil A, Buchanan K, Alraies MC, Koifman E, Gai J, et al. Contemporary transcatheter aortic valve replacement with third-generation balloon-expandable versus self-expanding devices. J Interv Cardiol. 2017 Aug;30(4):356–61.

254. Seeger J, Gonska B, Rottbauer W, Wöhrle J. Outcome With the Repositionable and Retrievable Boston Scientific Lotus Valve Compared With the Balloon-Expandable Edwards Sapien 3 Valve in Patients Undergoing Transfemoral Aortic Valve Replacement. Circ Cardiovasc Interv. 2017 Jun;10(6).

255. Vendrik J, van Kesteren F, van Mourik MS, Piek JJ, Tijssen JG, Henriques JPS, et al. Procedural Outcome and Midterm Survival of Lower Risk Transfemoral Transcatheter Aortic Valve Implantation Patients Treated With the SAPIEN XT or SAPIEN 3 Device. Am J Cardiol. 2018 01;121(7):856–61.

256. Meyer A, Unbehaun A, Hamandi M, Sündermann SH, Buz S, Klein C, et al. Comparison of 1-Year Survival and Frequency of Paravalvular Leakage Using the Sapien 3 Versus the Sapien XT for Transcatheter Aortic Valve Implantation

for Aortic Stenosis. American Journal of Cardiology. 2017 Dec 15;120(12):2247–55.

257. Gomes B, Geis NA, Chorianopoulos E, Meder B, Leuschner F, Katus HA, et al. Improvements of Procedural Results With a New-Generation Self-Expanding Transfemoral Aortic Valve Prosthesis in Comparison to the Old-Generation Device. J Interv Cardiol. 2017 Feb;30(1):72–8.

258. Noble S, Stortecky S, Heg D, Tueller D, Jeger R, Toggweiler S, et al. Comparison of procedural and clinical outcomes with Evolut R versus Medtronic CoreValve: a Swiss TAVI registry analysis. EuroIntervention. 2017 Apr 7;12(18):e2170–6.

259. Sorajja P, Kodali S, Reardon MJ, Szeto WY, Chetcuti SJ, Hermiller J, et al. Outcomes for the Commercial Use of Self-Expanding Prostheses in Transcatheter Aortic Valve Replacement: A Report From the STS/ACC TVT Registry. JACC Cardiovasc Interv. 2017 23;10(20):2090–8.

260. Grube E, Van Mieghem NM, Bleiziffer S, Modine T, Bosmans J, Manoharan G, et al. Clinical Outcomes With a Repositionable Self-Expanding Transcatheter Aortic Valve Prosthesis: The International FORWARD Study. J Am Coll Cardiol. 2017 Aug 15;70(7):845–53.

261. Popma JJ, Reardon MJ, Khabbaz K, Harrison JK, Hughes GC, Kodali S, et al. Early Clinical Outcomes After Transcatheter Aortic Valve Replacement Using a Novel Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis Who Are Suboptimal for Surgery: Results of the Evolut R U.S. Study. JACC Cardiovasc Interv. 2017 13;10(3):268–75.

262. Kalra SS, Firoozi S, Yeh J, Blackman DJ, Rashid S, Davies S, et al. Initial Experience of a Second-Generation Self-Expanding Transcatheter Aortic Valve: The UK & Ireland Evolut R Implanters' Registry. JACC Cardiovasc Interv. 2017 13;10(3):276–82.

263. Hellhammer K, Piayda K, Afzal S, Kleinebrecht L, Makosch M, Hennig I, et al. The Latest Evolution of the Medtronic CoreValve System in the Era of

Transcatheter Aortic Valve Replacement: Matched Comparison of the Evolut PRO and Evolut R. JACC Cardiovasc Interv. 2018 26;11(22):2314–22.

264. Giannini C, De Carlo M, Tamburino C, Ettori F, Latib AM, Bedogni F, et al. Transcathether aortic valve implantation with the new repositionable self-expandable Evolut R versus CoreValve system: A case-matched comparison. Int J Cardiol. 2017 Sep 15;243:126–31.

265. Dumonteil N, Meredith IT, Blackman DJ, Tchétché D, Hildick-Smith D, Spence MS, et al. Insights into the need for permanent pacemaker following implantation of the repositionable LOTUS valve for transcatheter aortic valve replacement in 250 patients: results from the REPRISE II trial with extended cohort. EuroIntervention. 2017 Sep 20;13(7):796–803.

266. Montone RA, Testa L, Fraccaro C, Montorfano M, Castriota F, Nerla R, et al. Procedural and 30-day clinical outcomes following transcatheter aortic valve replacement with lotus valve: Results of the RELEVANT study. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2017;90(7):1206–11.

267. Falk V, Wöhrle J, Hildick-Smith D, Bleiziffer S, Blackman DJ, Abdel-Wahab M, et al. Safety and efficacy of a repositionable and fully retrievable aortic valve used in routine clinical practice: the RESPOND Study. Eur Heart J. 2017 Dec 1;38(45):3359–66.

268. De Backer O, Götberg M, Ihlberg L, Packer E, Savontaus M, Nielsen NE, et al. Efficacy and safety of the Lotus Valve System for treatment of patients with severe aortic valve stenosis and intermediate surgical risk: Results from the Nordic Lotus-TAVR registry. Int J Cardiol. 2016 Sep 15;219:92–7.

269. Meredith IT, Walters DL, Dumonteil N, Worthley SG, Tchétché D, Manoharan G, et al. 1-Year Outcomes With the Fully Repositionable and Retrievable Lotus Transcatheter Aortic Replacement Valve in 120 High-Risk Surgical Patients With Severe Aortic Stenosis: Results of the REPRISE II Study. JACC Cardiovasc Interv. 2016 Feb 22;9(4):376–84.

270. Möllmann H, Linke A, Holzhey DM, Walther T, Manoharan G, Schäfer U, et al. Implantation and 30-Day Follow-Up on All 4 Valve Sizes Within the Portico Transcatheter Aortic Bioprosthetic Family. JACC Cardiovasc Interv. 2017 14;10(15):1538–47.

271. Manoharan G, Linke A, Moellmann H, Redwood S, Frerker C, Kovac J, et al. Multicentre clinical study evaluating a novel resheathable annular functioning self-expanding transcatheter aortic valve system: safety and performance results at 30 days with the Portico system. EuroIntervention. 2016 Aug 20;12(6):768–74.

272. Mas-Peiro S, Vasa-Nicotera M, Weiler H, Papadopoulos N, De Rosa R, Zeiher AM, et al. Thirty-Day Outcomes in 100 Consecutive Patients Undergoing Transfemoral Aortic Valve Replacement With the Portico Valve on an All-Comer Basis. J Invasive Cardiol. 2017 Dec;29(12):431–6.

273. Søndergaard L, Rodés-Cabau J, Hans-Peter Linke A, Fichtlscherer S, Schäfer U, Kuck KH, et al. Transcatheter Aortic Valve Replacement With a Repositionable Self-Expanding Prosthesis: The PORTICO-I Trial 1-Year Outcomes. J Am Coll Cardiol. 2018 11;72(23 Pt A):2859–67.

274. Millan-Iturbe O, De Backer O, Bieliauskas G, Thonghong T, Chopra M, Ihlemann N, et al. Transcatheter aortic valve implantation with the self-expanding Portico valve system in an all-comers population: procedural and clinical outcomes. EuroIntervention. 2018 Aug 20;14(6):621–8.

275. Linke A, Holzhey D, Möllmann H, Manoharan G, Schäfer U, Frerker C, et al. Treatment of Aortic Stenosis With a Self-Expanding, Resheathable Transcatheter Valve: One-Year Results of the International Multicenter Portico Transcatheter Aortic Valve Implantation System Study. Circ Cardiovasc Interv. 2018;11(2):e005206.

276. Kim WK, Hengstenberg C, Hilker M, Kerber S, Schäfer U, Rudolph T, et al. The SAVI-TF Registry: 1-Year Outcomes of the European Post-Market Registry Using the ACURATE neo Transcatheter Heart Valve Under Real-World Conditions in 1,000 Patients. JACC: Cardiovascular Interventions. 2018 Jul 23;11(14):1368–74.

277. Börgermann J, Holzhey DM, Thielmann M, Girdauskas E, Schroefel H, Hofmann S, et al. Transcatheter aortic valve implantation using the ACURATE TA™ system: 1-year outcomes and comparison of 500 patients from the SAVI registries. Eur J Cardiothorac Surg. 2017 May 1;51(5):936–42.

278. Hamm K, Reents W, Zacher M, Kerber S, Diegeler A, Schieffer B, et al. Transcatheter aortic valve implantation using the ACURATE TA and ACURATE neo valves: a four-year single-centre experience [Internet]. EuroIntervention. [cited 2019 Nov 2]. Available from: https://eurointervention.pcronline.com/article/transcatheter-aortic-valve-implantation-using-the-acurate-ta-and-acurate-neo-valves-a-four-year-single-centre-experience

279. Kim WK, Möllmann H, Liebetrau C, Renker M, Rolf A, Simon P, et al. The ACURATE neo Transcatheter Heart Valve: A Comprehensive Analysis of Predictors of Procedural Outcome. JACC Cardiovasc Interv. 2018 10;11(17):1721–9.

280. Mauri V, Deuschl F, Frohn T, Schofer N, Linder M, Kuhn E, et al. Predictors of paravalvular regurgitation and permanent pacemaker implantation after TAVR with a next-generation self-expanding device. Clin Res Cardiol. 2018 Aug;107(8):688–97.

281. Kim U, Blanke P, Windecker S, Kasel AM, Schäfer U, Walters D, et al. Computed tomography-based oversizing and incidence of paravalvular aortic regurgitation and permanent pacemaker implantation with a new-generation self-expanding transcatheter heart valve. EuroIntervention. 2018 Aug 3;14(5):e511–8.

282. Lanz J, Kim WK, Walther T, Burgdorf C, Möllmann H, Linke A, et al. Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial. Lancet. 2019 Sep 26;

283. Ramirez Del Val F, Hirji SA, Carreras ET, Kolkailah AA, Chowdhury R, McGurk S, et al. Clinical Significance of Greater Implantation Height with SAPIEN 3 Transcatheter Heart Valve. J Heart Valve Dis. 2018 Jan;27(1):9–16.

284. Schaefer A, Neumann N, Linder M, Schofer N, Schneeberger Y, Deuschl F, et al. Outcomes with a latest generation self-expandable, intra-annular, re-sheathable transcatheter heart valve system: analysis of patients with impaired left ventricular function and determinants for pacemaker implantation. Clin Res Cardiol. 2018 Oct;107(10):914–23.

285. Guetta V, Goldenberg G, Segev A, Dvir D, Kornowski R, Finckelstein A, et al. Predictors and course of high-degree atrioventricular block after transcatheter aortic valve implantation using the CoreValve Revalving System. Am J Cardiol. 2011 Dec 1;108(11):1600–5.

286. Thiele H. A 2x2 randomized trial of self-expandable vs balloon-expandable valves and general vs local anesthesia in patients undergoing transcatheter aortic valve implantation. Presented at: TCT 2018. September 23, 2018. San Diego, CA.

287. Siontis GCM, Jüni P, Pilgrim T, Stortecky S, Büllesfeld L, Meier B, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. J Am Coll Cardiol. 2014 Jul 15;64(2):129–40.

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

289. Hamdan A, Guetta V, Klempfner R, Konen E, Raanani E, Glikson M, et al. Inverse Relationship Between Membranous Septal Length and the Risk of Atrioventricular Block in Patients Undergoing Transcatheter Aortic Valve Implantation. JACC Cardiovasc Interv. 2015 Aug 17;8(9):1218–28.

290. Hein-Rothweiler R, Jochheim D, Rizas K, Egger A, Theiss H, Bauer A, et al. Aortic annulus to left coronary distance as a predictor for persistent left bundle branch block after TAVI. Catheter Cardiovasc Interv. 2017 Mar 1;89(4):E162–8.

291. Junquera L, Freitas-Ferraz AB, Padrón R, Silva I, Nunes Ferreira-Neto A, Guimaraes L, et al. Intraprocedural high-degree atrioventricular block or

complete heart block in transcatheter aortic valve replacement recipients with no prior intraventricular conduction disturbances. Catheter Cardiovasc Interv. 2019 Apr 29;

292. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation. 2003 Jun 17;107(23):2932–7.

293. Fadahunsi OO, Olowoyeye A, Ukaigwe A, Li Z, Vora AN, Vemulapalli S, et al. Incidence, Predictors, and Outcomes of Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Replacement: Analysis From the U.S. Society of Thoracic Surgeons/American College of Cardiology TVT Registry. JACC Cardiovasc Interv. 2016 14;9(21):2189–99.

294. Rück A, Saleh N, Glaser N. Outcomes Following Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement: SWEDEHEART Observational Study. JACC Cardiovasc Interv. 2021 Oct 11;14(19):2173–81.

295. Cerrato E, Nombela-Franco L, Nazif TM, Eltchaninoff H, Søndergaard L, Ribeiro HB, et al. Evaluation of current practices in transcatheter aortic valve implantation: The WRITTEN (WoRldwIde TAVI ExperieNce) survey. Int J Cardiol. 2017 Feb 1;228:640–7.

296. Rodés-Cabau J, Ellenbogen KA, Krahn AD, Latib A, Mack M, Mittal S, et al. Management of Conduction Disturbances Associated With Transcatheter Aortic Valve Replacement: JACC Scientific Expert Panel. J Am Coll Cardiol. 2019 Aug 19;74(8):1086–106.

297. Lilly SM, Deshmukh AJ, Epstein AE, Ricciardi MJ, Shreenivas S, Velagapudi P, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Conduction Disturbances in Patients Undergoing Transcatheter Aortic Valve Replacement: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020 Nov 17;76(20):2391–411.

298. Vora AN, Dai D, Matsuoka R, Harrison JK, Hughes GC, Sherwood MW, et al. Incidence, Management, and Associated Clinical Outcomes of New-Onset Atrial Fibrillation Following Transcatheter Aortic Valve Replacement: An Analysis From the STS/ACC TVT Registry. JACC Cardiovasc Interv. 2018 Sep 10;11(17):1746–56.

299. Mok M, Urena M, Nombela-Franco L, Ribeiro HB, Allende R, Delarochellière R, et al. Clinical and prognostic implications of existing and new-onset atrial fibrillation in patients undergoing transcatheter aortic valve implantation. J Thromb Thrombolysis. 2013 May;35(4):450–5.

300. Motloch LJ, Reda S, Rottlaender D, Khatib R, Müller-Ehmsen J, Seck C, et al. Postprocedural atrial fibrillation after transcatheter aortic valve implantation versus surgical aortic valve replacement. Ann Thorac Surg. 2012 Jan;93(1):124–31.

301. Amat-Santos IJ, Rodés-Cabau J, Urena M, DeLarochellière R, Doyle D, Bagur R, et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. J Am Coll Cardiol. 2012 Jan 10;59(2):178–88.

302. Siontis GCM, Praz F, Lanz J, Vollenbroich R, Roten L, Stortecky S, et al. New-onset arrhythmias following transcatheter aortic valve implantation: a systematic review and meta-analysis. Heart. 2018 Jul 1;104(14):1208–15.

303. Stähli BE, Grünenfelder J, Jacobs S, Falk V, Landmesser U, Wischnewsky MB, et al. Assessment of inflammatory response to transfemoral transcatheter aortic valve implantation compared to transapical and surgical procedures: a pilot study. J Invasive Cardiol. 2012 Aug;24(8):407–11.

304. Tanawuttiwat T, O'Neill BP, Cohen MG, Chinthakanan O, Heldman AW, Martinez CA, et al. New-onset atrial fibrillation after aortic valve replacement: comparison of transfemoral, transapical, transaortic, and surgical approaches. J Am Coll Cardiol. 2014 Apr 22;63(15):1510–9.

305. Gargiulo G, Capodanno D, Sannino A, Barbanti M, Perrino C, Capranzano P, et al. New-onset atrial fibrillation and increased mortality after transcatheter aortic

valve implantation: A causal or spurious association? Int J Cardiol. 2016 Jan 15;203:264–6.

306. Biviano AB, Nazif T, Dizon J, Garan H, Fleitman J, Hassan D, et al. Atrial Fibrillation Is Associated With Increased Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement: Insights From the Placement of Aortic Transcatheter Valve (PARTNER) Trial. Circ Cardiovasc Interv. 2016 Jan;9(1):e002766.

307. Chopard R, Teiger E, Meneveau N, Chocron S, Gilard M, Laskar M, et al. Baseline Characteristics and Prognostic Implications of Pre-Existing and New-Onset Atrial Fibrillation After Transcatheter Aortic Valve Implantation: Results From the FRANCE-2 Registry. JACC Cardiovasc Interv. 2015 Aug 24;8(10):1346–55.

308. Tarantini G, Mojoli M, Windecker S, Wendler O, Lefèvre T, Saia F, et al. Prevalence and Impact of Atrial Fibrillation in Patients With Severe Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement: An Analysis From the SOURCE XT Prospective Multicenter Registry. JACC Cardiovasc Interv. 2016 09;9(9):937–46.

309. Papavasileiou LP, Halapas A, Chrisocheris M, Bellos K, Bouboulis N, Pattakos S, et al. Sudden Death After Transcatheter Aortic Valve Implantation. Are Bradyarrhythmias Always The Cause? J Atr Fibrillation. 2015 Nov;8(3):1108.

310. Tempio D, Pruiti GP, Conti S, Romano SA, Tavano E, Capodanno D, et al. Ventricular arrhythmias in aortic valve stenosis before and after transcatheter aortic valve implantation. Europace. 2015 Jul;17(7):1136–40.

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

312. Mazzella AJ, Hendrickson MJ, Arora S, Sanders M, Li Q, Vavalle JP, et al. Shifting Trends in Timing of Pacemaker Implantation After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2021 Jan 25;14(2):232–4.

313. Sana F, Isselbacher EM, Singh JP, Heist EK, Pathik B, Armoundas AA. Wearable Devices for Ambulatory Cardiac Monitoring: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2020 Apr 7;75(13):1582–92.

314. Steinberg JS, Varma N, Cygankiewicz I, Aziz P, Balsam P, Baranchuk A, et al. 2017 ISHNE-HRS expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry. Heart Rhythm. 2017;14(7):e55–96.

315. Muntané-Carol G, Philippon F, Nault I, Faroux L, Alperi A, Mittal S, et al. Ambulatory Electrocardiogram Monitoring in Patients Undergoing Transcatheter Aortic Valve Replacement: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021 Mar 16;77(10):1344–56.

316. Mittal S, Movsowitz C, Steinberg JS. Ambulatory external electrocardiographic monitoring: focus on atrial fibrillation. J Am Coll Cardiol. 2011 Oct 18;58(17):1741–9.

317. Ream K, Sandhu A, Valle J, Weber R, Kaizer A, Wiktor DM, et al. Ambulatory Rhythm Monitoring to Detect Late High-Grade Atrioventricular Block Following Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2019 May 28;73(20):2538–47.

318. Tian Y, Padmanabhan D, McLeod CJ, Zhang P, Xiao P, Sandhu GS, et al. Utility of 30-Day Continuous Ambulatory Monitoring to Identify Patients With Delayed Occurrence of Atrioventricular Block After Transcatheter Aortic Valve Replacement. Circ Cardiovasc Interv. 2019 Dec;12(12):e007635.

319. Tarakji KG, Patel D, Krishnaswamy A, Hussein A, Saliba W, Wilkoff BL, et al. Bradyarrhythmias Detected by Extended Rhythm Recording in Patients Undergoing Transcatheter Aortic Valve Replacement (BRADY-TAVR Study). Heart Rhythm. 2021 Nov 18;S1547-5271(21)02353-5.

320. Sandhu A, Tzou W, Ream K, Valle J, Tompkins C, Nguyen DT, et al. Heart Block After Discharge in Patients Undergoing TAVR With Latest-Generation Valves. J Am Coll Cardiol. 2018 Feb 6;71(5):577–8.

321. Rodés-Cabau J, Urena M, Nombela-Franco L, Amat-Santos I, Kleiman N, Munoz-Garcia A, et al. Arrhythmic Burden as Determined by Ambulatory Continuous Cardiac Monitoring in Patients With New-Onset Persistent Left Bundle Branch Block Following Transcatheter Aortic Valve Replacement: The MARE Study. JACC Cardiovasc Interv. 2018 Aug 13;11(15):1495–505.

322. Badertscher P, Knecht S, Zeljković I, Sticherling C, de Asmundis C, Conte G, et al. Management of conduction disorders after transcatheter aortic valve implantation: results of the EHRA survey. Europace. 2022 Jul 21;24(7):1179–85.

323. Takahashi M, Mouillet G, Deballon R, Sudre A, Lellouche N, Lim P, et al. Impact of QRS Duration on Decision of Early Removal of Pacing Catheter After Transcatheter Aortic Valve Replacement With CoreValve Device. Am J Cardiol. 2017 Sep 1;120(5):838–43.

324. Auffret V, Webb JG, Eltchaninoff H, Muñoz-García AJ, Himbert D, Tamburino C, et al. Clinical Impact of Baseline Right Bundle Branch Block in Patients Undergoing Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2017 14;10(15):1564–74.

325. Fischer Q, Himbert D, Webb JG, Eltchaninoff H, Muñoz-García AJ, Tamburino C, et al. Impact of Preexisting Left Bundle Branch Block in Transcatheter Aortic Valve Replacement Recipients. Circ Cardiovasc Interv. 2018;11(11):e006927.

326. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012 Oct 9;60(15):1438–54.

327. Bradshaw PJ, Stobie P, Knuiman MW, Briffa TG, Hobbs MST. Trends in the incidence and prevalence of cardiac pacemaker insertions in an ageing population. Open Heart. 2014;1(1):e000177.

328. Mouillet G, Lellouche N, Lim P, Meguro K, Yamamoto M, Deux JF, et al. Patients without prolonged QRS after TAVI with CoreValve device do not experience high-degree atrio-ventricular block. Catheter Cardiovasc Interv. 2013 Apr;81(5):882–7.

329. Nazif TM, Williams MR, Hahn RT, Kapadia S, Babaliaros V, Rodés-Cabau J, et al. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. Eur Heart J. 2014 Jun 21;35(24):1599–607.

330. McAnulty JH, Rahimtoola SH, Murphy E, DeMots H, Ritzmann L, Kanarek PE, et al. Natural history of "high-risk" bundle-branch block: final report of a prospective study. N Engl J Med. 1982 Jul 15;307(3):137–43.

331. Peters RW, Scheinman MM, Modin G, O'Young J, Somelofski CA, Mies C. Prophylactic permanent pacemakers for patients with chronic bundle branch block. The American Journal of Medicine. 1979 Jun 1;66(6):978–85.

332. Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. Am Heart J. 2002 Mar;143(3):398–405.

333. Vaillant C, Martins RP, Donal E, Leclercq C, Thébault C, Behar N, et al. Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy. J Am Coll Cardiol. 2013 Mar 12;61(10):1089–95.

334. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.

335. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special

contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129–200.

336. Puri R, Chamandi C, Rodriguez-Gabella T, Rodés-Cabau J. Future of transcatheter aortic valve implantation - evolving clinical indications. Nat Rev Cardiol. 2018 Jan;15(1):57–65.

337. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation. 1989 Apr;79(4):845–53.

338. Verbeek XAAM, Vernooy K, Peschar M, Van Der Nagel T, Van Hunnik A, Prinzen FW. Quantification of interventricular asynchrony during LBBB and ventricular pacing. Am J Physiol Heart Circ Physiol. 2002 Oct;283(4):H1370-1378.

339. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol. 2005 Dec 20;46(12):2183–92.

340. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013 Aug;34(29):2281–329.

341. Kawashima T, Sasaki H. A macroscopic anatomical investigation of atrioventricular bundle locational variation relative to the membranous part of the ventricular septum in elderly human hearts. Surg Radiol Anat. 2005 Aug;27(3):206–13.

342. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013 Jan 22;61(3):e6-75.

343. Muntané-Carol G, Alméndarez M, Junquera L, Wintzer-Wehekind J, Del Val D, Faroux L, et al. Long-Term Electrocardiographic Changes and Clinical Outcomes of Transcatheter Aortic Valve Implantation Recipients Without New Postprocedural Conduction Disturbances. Am J Cardiol. 2020 Jan 1;125(1):107–13.

344. Oh JK, Little SH, Abdelmoneim SS, Reardon MJ, Kleiman NS, Lin G, et al. Regression of Paravalvular Aortic Regurgitation and Remodeling of Self-Expanding Transcatheter Aortic Valve: An Observation From the CoreValve U.S. Pivotal Trial. JACC Cardiovasc Imaging. 2015 Dec;8(12):1364–75.

345. Megaly M, Garcia S, Anzia LE, Morley P, Garberich R, Gornick CC, et al. Detection of Atrial Fibrillation and Atrial Flutter by Pacemaker Device Interrogation After Transcatheter Aortic Valve Replacement (TAVR): Implications for Management. J Invasive Cardiol. 2019 Jul;31(7):E177–83.

346. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012 Jan 12;366(2):120–9.

347. Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, et al. Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk Population: The REVEAL AF Study. JAMA Cardiol. 2017 Oct 1;2(10):1120–7.

348. Muntané-Carol G, Urena M, Munoz-Garcia A, Padrón R, Gutiérrez E, Regueiro A, et al. Late Cerebrovascular Events Following Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2020 Apr 13;13(7):872–81.

349. Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet. 2017 Jun 17;389(10087):2383–92.

350. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, et al. A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement. New England Journal of Medicine. 2020 Jan 9;382(2):120–9.

351. Auffret V, Regueiro A, Del Trigo M, Abdul-Jawad Altisent O, Campelo-Parada F, Chiche O, et al. Predictors of Early Cerebrovascular Events in Patients With Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016 16;68(7):673–84.

352. Muralidharan A, Thiagarajan K, Van Ham R, Gleason TG, Mulukutla S, Schindler JT, et al. Meta-Analysis of Perioperative Stroke and Mortality in Transcatheter Aortic Valve Implantation. The American Journal of Cardiology. 2016 Oct 1;118(7):1031–45.

353. Abdul-Jawad Altisent O, Puri R, Rodés-Cabau J. Embolic Protection Devices During TAVI: Current Evidence and Uncertainties. Rev Esp Cardiol (Engl Ed). 2016 Oct;69(10):962–72.

354. Kapadia SR, Huded CP, Kodali SK, Svensson LG, Tuzcu EM, Baron SJ, et al. Stroke After Surgical Versus Transfemoral Transcatheter Aortic Valve Replacement in the PARTNER Trial. J Am Coll Cardiol. 2018 Nov 13;72(20):2415–26.

355. Lansky AJ, Messé SR, Brickman AM, Dwyer M, van der Worp HB, Lazar RM, et al. Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative. J Am Coll Cardiol. 2017 Feb 14;69(6):679–91.

356. Gilard M, Eltchaninoff H, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, et al. Late Outcomes of Transcatheter Aortic Valve Replacement in High-Risk Patients: The FRANCE-2 Registry. J Am Coll Cardiol. 2016 11;68(15):1637–47.

357. Koton S, Schneider ALC, Rosamond WD, Shahar E, Sang Y, Gottesman RF, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA. 2014 Jul 16;312(3):259–68.

358. Miller DC, Blackstone EH, Mack MJ, Svensson LG, Kodali SK, Kapadia S, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. J Thorac Cardiovasc Surg. 2012 Apr;143(4):832-843.e13.

359. Tegn N, Abdelnoor M, Aaberge L, Endresen K, Smith P, Aakhus S, et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet. 2016 Mar 12;387(10023):1057–65.

360. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke. 2011 May;42(5):1489–94.

361. Vlastra W, Chandrasekhar J, Muñoz-Garcia AJ, Tchétché D, de Brito FS, Barbanti M, et al. Comparison of balloon-expandable vs. self-expandable valves in patients undergoing transfemoral transcatheter aortic valve implantation: from the CENTER-collaboration. European Heart Journal. 2019 Feb 1;40(5):456–65.

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

363. Collet JP, Berti S, Cequier A, Van Belle E, Lefevre T, Leprince P, et al. Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: The randomized ATLANTIS trial. Am Heart J. 2018;200:44–50.

364. Nijenhuis VJ, Bennaghmouch N, Hassell M, Baan J, van Kuijk JP, Agostoni P, et al. Rationale and design of POPular-TAVI: antiPlatelet therapy fOr Patients undergoing Transcatheter Aortic Valve Implantation. Am Heart J. 2016 Mar;173:77–85.

365. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology. 2007 Jan 9;68(2):116–21.

366. Longstreth WT, Gasca NC, Gottesman RF, Pearce JB, Sacco RL. Adjudication of Transient Ischemic Attack and Stroke in the Multi-Ethnic Study of Atherosclerosis. Neuroepidemiology. 2018;50(1–2):23–8.

367. Krishnamurthi RV, Barker-Collo S, Parag V, Parmar P, Witt E, Jones A, et al. Stroke Incidence by Major Pathological Type and Ischemic Subtypes in the Auckland Regional Community Stroke Studies: Changes Between 2002 and 2011. Stroke. 2018 Jan;49(1):3–10.

368. Abdul-Jawad Altisent O, Durand E, Muñoz-García AJ, Nombela-Franco L, Cheema A, Kefer J, et al. Warfarin and Antiplatelet Therapy Versus Warfarin Alone for Treating Patients With Atrial Fibrillation Undergoing Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2016 Aug 22;9(16):1706–17.

369. Vilalta V, Asmarats L, Ferreira-Neto AN, Maes F, de Freitas Campos Guimarães L, Couture T, et al. Incidence, Clinical Characteristics, and Impact of Acute Coronary Syndrome Following Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2018 Dec 24;11(24):2523–33.

370. Rodés-Cabau J, Dauerman HL, Cohen MG, Mehran R, Small EM, Smyth SS, et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. J Am Coll Cardiol. 2013 Dec 24;62(25):2349–59.

371. Sanossian N, Apibunyopas KC, Liebeskind DS, Starkman S, Burgos AM, Conwit R, et al. Characteristics and Outcomes of Very Elderly Enrolled in a Prehospital Stroke Research Study. Stroke. 2016 Nov;47(11):2737–41.

372. Sanossian N, Ovbiagele B. Prevention and management of stroke in very elderly patients. Lancet Neurol. 2009 Nov;8(11):1031–41.

373. Nault I, André P, Plourde B, Leclerc F, Sarrazin JF, Philippon F, et al. Validation of a novel single lead ambulatory ECG monitor - Cardiostat^{TM} - Compared to a standard ECG Holter monitoring. J Electrocardiol. 2019 Apr;53:57–63.

374. Rosenberg MA, Samuel M, Thosani A, Zimetbaum PJ. Use of a noninvasive continuous monitoring device in the management of atrial fibrillation: a pilot study. Pacing Clin Electrophysiol. 2013 Mar;36(3):328–33.

375. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021 Feb 1;42(5):373–498.

376. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2018 Sep 25;138(13):e210–71.

377. Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, et al. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010 Nov 30;122(22):2335–48.

378. Bavaria JE. TAVR Update: New Insights and Perspectives from the U.S. National STS/ACC TVT Registry. :98.

379. Muntané-Carol G, Del Val D, Junquera L, Faroux L, Delarochellière R, Paradis JM, et al. Timing and evolution of advanced conduction disturbances in patients with right bundle branch block undergoing transcatheter aortic valve replacement. Europace. 2020 Oct 1;22(10):1537–46.

380. Husser O, Pellegrini C, Kim WK, Holzamer A, Pilgrim T, Toggweiler S, et al. Transcatheter Valve SELECTion in Patients With Right Bundle Branch Block and Impact on Pacemaker Implantations. JACC Cardiovasc Interv. 2019 Sep 23;12(18):1781–93.

381. Jilaihawi H, Zhao Z, Du R, Staniloae C, Saric M, Neuburger PJ, et al. Minimizing Permanent Pacemaker Following Repositionable Self-Expanding Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2019 Sep 23;12(18):1796–807.

382. Muntané-Carol G, Urena M, Nombela-Franco L, Amat-Santos I, Kleiman N, Munoz-Garcia A, et al. Arrhythmic burden in patients with new-onset persistent

left bundle branch block after transcatheter aortic valve replacement: 2-year results of the MARE study. Europace. 2020 Oct 21;

383. Irles D, Salerno F, Cassagneau R, Eschalier R, Maupain C, Dupuis JM, et al. Evolution of high-grade atrioventricular conduction disorders after transcatheter aortic valve implantation in patients who underwent implantation of a pacemaker with specific mode-that minimizes ventricular pacing-activated. J Cardiovasc Electrophysiol. 2021 May;32(5):1376–84.

384. Kooistra NHM, van Mourik MS, Rodríguez-Olivares R, Maass AH, Nijenhuis VJ, van der Werf R, et al. Late onset of new conduction disturbances requiring permanent pacemaker implantation following TAVI. Heart (British Cardiac Society). 2020 Aug;106(16):1244–51.

385. Kawashima T, Sato F. Visualizing anatomical evidences on atrioventricular conduction system for TAVI. Int J Cardiol. 2014 Jun 1;174(1):1–6.

386. Gorenek B, Bax J, Boriani G, Chen SA, Dagres N, Glotzer TV, et al. Device-detected subclinical atrial tachyarrhythmias: definition, implications and management-an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology: Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology. 2017 01;19(9):1556–78.

387. Potpara TS, Polovina MM, Marinkovic JM, Lip GYH. A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: the Belgrade Atrial Fibrillation Study. International Journal of Cardiology. 2013 Oct 12;168(5):4744–9.

388. Mahajan R, Perera T, Elliott AD, Twomey DJ, Kumar S, Munwar DA, et al. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. Eur Heart J. 2018 Apr 21;39(16):1407–15.

389. Pastori D, Miyazawa K, Li Y, Székely O, Shahid F, Farcomeni A, et al. Atrial high-rate episodes and risk of major adverse cardiovascular events in patients with cardiac implantable electronic devices. Clin Res Cardiol. 2020 Jan;109(1):96–102.

390. Tovia-Brodie O, Letourneau-Shesaf S, Hochstadt A, Steinvil A, Rosso R, Finkelstein A, et al. The Utility of Prophylactic Pacemaker Implantation in Right Bundle Branch Block Patients Pre-Transcatheter Aortic Valve Implantation. Isr Med Assoc J. 2019 Dec;21(12):790–5.

391. Fukutomi M, Hokken T, Wong I, Bieliauskas G, Daemen J, de Jaegere P, et al. Prophylactic permanent pacemaker strategy in patients with right bundle branch block undergoing transcatheter aortic valve replacement. Catheter Cardiovasc Interv. 2021 Aug 14;

392. Fukutomi M, Hokken T, Wong I, Bieliauskas G, Daemen J, de Jaegere P, et al. Prophylactic Permanent Pacemaker Implantation in Patients With Right Bundle Branch Block Undergoing TAVR. JACC Cardiovasc Interv. 2021 Jun 14;14(11):1272–4.

393. Tang GHL, Zaid S, Michev I, Ahmad H, Kaple R, Undemir C, et al. "Cusp-Overlap" View Simplifies Fluoroscopy-Guided Implantation of Self-Expanding Valve in Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2018 Aug 27;11(16):1663–5.

394. Mendiz OA, Noč M, Fava CM, Gutiérrez Jaikel LA, Sztejfman M, Pleskovič A, et al. Impact of Cusp-Overlap View for TAVR with Self-Expandable Valves on 30-Day Conduction Disturbances. J Interv Cardiol. 2021;2021:9991528.

395. Pascual I, Almendárez M, Avanzas P, Álvarez R, Arboine LA, Del Valle R, et al. Cusp-overlapping TAVI technique with a self-expanding device optimizes implantation depth and reduces permanent pacemaker requirement. Rev Esp Cardiol (Engl Ed). 2021 Jul 2;S1885-5857(21)00176-6.

396. Tovia-Brodie O, Ben-Haim Y, Joffe E, Finkelstein A, Glick A, Rosso R, et al. The value of electrophysiologic study in decision-making regarding the need for

pacemaker implantation after TAVI. J Interv Card Electrophysiol. 2017 Mar;48(2):121–30.

397. Rivard L, Schram G, Asgar A, Khairy P, Andrade JG, Bonan R, et al. Electrocardiographic and electrophysiological predictors of atrioventricular block after transcatheter aortic valve replacement. Heart Rhythm. 2015 Feb;12(2):321–9.