Rates of and predictors for the need of permanent pacemaker and its long-term utilization in patients undergoing surgical or transcatheter aortic valve replacement

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Abstract

Rates of and predictors for the need of permanent pacemaker and its long-term utilization in patients undergoing surgical or transcatheter aortic valve replacement

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Introduction: Complete atrioventricular block (AVB) leading to permanent pacemaker (PPM) requirement is a common complication of both surgical and transcatheter aortic valve replacement (SAVR and TAVR) but more frequently in TAVR. The primary aim of this study was to compare SAVR and TAVR cohorts with regard to rates and independent risk factors for PPM placement, as well as assess rates of AVB recovery and independent risk factors for long term PPM dependency.

Methods: The study included patients without prior PPM and infective endocarditis that underwent SAVR and TAVR at the Yale New Haven Hospital from 2012 to 2016. PPM dependency was defined as any ventricular pacing without resolution of AVB.

Results: Of the initial 1102 patients, 199 were excluded, 122 of those for prior PPM. Of those 903 remaining, 499 underwent SAVR and 404 TAVR. Rates of PPM were 4.6% and 14.4% for SAVR and TAVR respectively ($p < 0.001$). Right bundle branch block (RBBB) was identified as an individual risk factor for PPM following TAVR (odds ratio (OR): 7.86, 95% confidence interval (CI): 4.16 – 14.97, $p < 0.001$) while no specific risk factor was independently associated with PPM following SAVR. Of the 62 patients that required PPM for AVB following either SAVR or TAVR, 37.1% recovered within a mean of 31.2±44.5 days. Pre-operative Ca^{+2} channel blocker (CCB) therapy (OR: 14.91, 95% CI: 2.25 – 300.75, $p = 0.018$) and peripheral vascular disease (PVD) (OR: 5.91, 95% CI: 1.61 – 25.81, $p = 0.011$) were identified as independent risk factors for long-term PPM dependency.

Conclusions: The rate of PPM implantation was higher after TAVR compared to SAVR. RBBB was an independent risk factor for PPM placement following TAVR. A large portion of patients with AVB indication for PPM placement became independent of their PPM a short time after implantation. Pre-operative CCB therapy and PVD were independent risk factors for long-term PPM dependency.

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Contents

Figures

Tables

Abbreviations

AF	Atrial fibrillation
AFL	Atrial flutter
AR	Aortic valve regurgitation
AS	Aortic valve stenosis
AVB I, II and III	First, second and third degree atrioventricular block
AVC	Aortic valve calcification
AVR	Aortic valve replacement
BAV	Bicuspid aortic valve
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCB	Ca^{+2} channel blocker
CI	Confidence interval
ECG	Electrocardiogram
IVS	Interventricular septum
LAHB	Left anterior hemiblock
LBBB	Left bundle branch block
LVEDD	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end systolic diameter
LV	Left ventricle
MAC	Mitral annular calcification
MI	Myocardial infarction
PPM	Permanent pacemaker
PVD	Peripheral vascular disease
RBBB	Right bundle branch block
SAVR	Surgical aortic valve replacement
SSS	Sick sinus syndrome
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiogram
TTE	Transthoracic echocardiogram
VP	Ventricular pacing
YNHH	Yale New Haven Hospital

1 Introduction

In an aging population, prevalence of aortic valve disease is on the rise.(1) It is estimated that in the US, over 110,000 aortic valve replacements are performed each year and is expected to increase consistently over the following years.(2)

1.1 The Aortic Valve

The aortic valve anatomically and functionally separates the left ventricle (LV) and the aorta, restricting back flow of blood from the latter into the ventricle.(3) The aortic valve is similar to the pulmonic valve in some attributes, it is made up of three semilunar cusps that originate at the aortic annulus and project superiorly into the lumen of the aorta (figure1). The cavities separating each semilunar cusp from the aortic wall are called the aortic sinuses. These sinuses are named the right, left and posterior sinuses according to their anatomical position with reference to the human body. The coronary arteries originate from these sinuses with left and right coronary arteries arising from their corresponding coronary sinus. Coronary ostia arising from each corresponding coronary sinus enable blood to flow from the sinus to the artery. The posterior sinus is also known as the non-coronary sinus since it does not give rise to any coronary arteries. The aortic valve opens during systole allowing pressurized blood from the ventricle to flow into the aorta. Once the ventricle starts relaxing, the aortic valve closes and the blood recoiling in the diastolic phase fills the coronary sinus and flows into the coronary arteries, thereby perfusing the heart. The most common pathologies of the aortic valve are aortic valve-stenosis (AS) and regurgitation (AR).

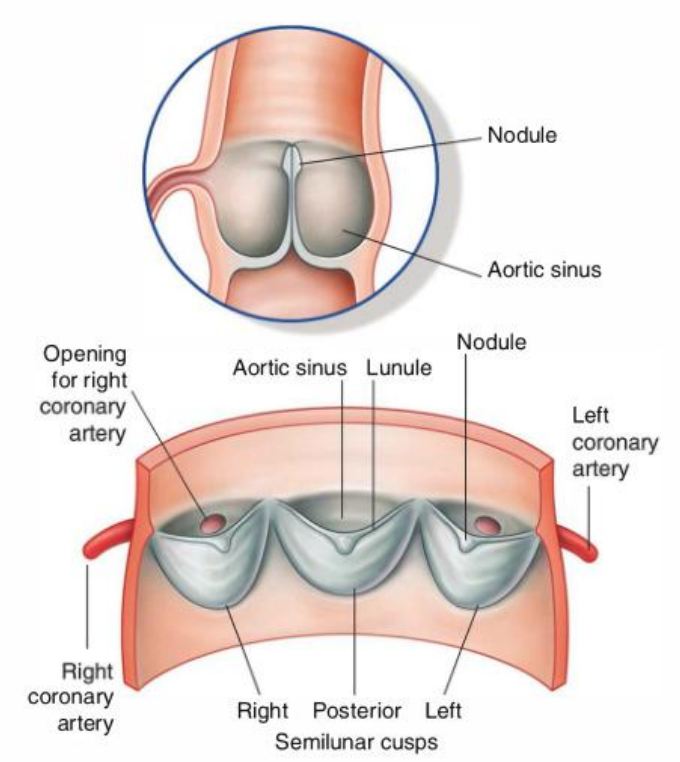

Figure 1. The anatomy of the aortic valve.(3)

1.2 Aortic Stenosis

1.2.1 Epidemiology

Aortic stenosis is the third most common cardiovascular disease after hypertension and coronary artery disease and the most common form of valvular heart disease. The prevelance of AS is 2% to 7% in patients older than 65 years.(4) The disease has a slow progression but once symptoms develop it has a 3-year mortality averaging 75% for patients who do not get an aortic valve replacement.(5)

1.2.2 Etiology and pathophysiology

Aortic stenosis (AS) involves obstruction in outflow of blood from the LV to the aorta. Because of the outflow obstruction and increased afterload, AS leads to LV hypertrophy as the cardiac muscle fibres adapt to the increasing pressure. When the disease progresses the LV end-diastolic pressure increases resulting in cardiomyopathy and LV dilatation. The three most common primary causes of AS are calcification of a trileaflet valve, congenital bicuspid aortic valve (BAV) and rheumatic valvular disease. (4)

Calcific aortic valve disease is the most common cause of AS with 80% of AS cases in the west originating due to senile calcification.(6) Today calcified AS is recognized as an inflammatory disease similar to atherosclerosis rather than age related wear and tear. Accordingly, there are similar risk factors associated with AS and atherosclerosis including older age, male sex, smoking, hypertension, diabetes, low density lipoprotein cholesterol, lipoprotein and C-reactive protein.(7) The primary pathogenesis is endothelial damage that leads to subendothelial inflammation and acummulation of oxidized low density lipoproteins.(8) From aortic sclerosis, defined as thickened leaflets without obstruction, to severe AS, calcific aortic stenosis is a spectrum of progressively reduced aortic valve orifice.(4)

After calcific AS, congenital BAV is the second most common cause of AS in western countries.(4) Typically, BAV presents at a younger age than calcific AS because of abnormal, non laminar flow through the malformed valve, leading to accelerated formation of calcific aortic valve plaques. Other conditions often associated with BAV aortopathy are AR, dilated aortic root and rarely, aortic dissection.(4) There is evidence that BAV can be genetically inherited and is one of the most common genetic cardiovascular variations in the human anatomy.(9)

The third most common cause of AS is rheumatic valve disease. It is relatively uncommon in the western world as treatment has improved but is still a significant cause of AS in third world countries. (4) Other diseases that accelerate AS progression include chronic kidney disease, Paget‘s disease, radiation exposure and familial homozygous hypercholesterolemia.(4)

1.2.3 Symptoms

AS has three classic symptoms: angina, syncope and heart failure. Angina results from increased oxygen demand of the LV due to the hypertrophic muscle mass and insufficient blood supply due to maladaptation of the aortic valve apparatus. Insufficient blood supply is caused by the hypertrophic

myocardium outgrowing the capillary bed and increased LV end-diastolic pressure which in turn limits blood perfusion by the coronary arteries.(10) Because of the limited opening of the aortic valve in AS there is decreased ability to augment cardiac output during exertion which results in decreased cerebral perfusion and syncope.(11) Other mechanisms for syncope include inappropriate LV baroreceptor reflex vasodilation in response to a severe increase in intracavitary pressure and ventricular tachycardia, usually associated with a coexisting coronary artery disease (CAD). Heart failure results from pulmonary edema caused by diastolic dysfunction of the left atria.(4)

1.2.4 Associated medical conditions

For AS patients the overlapping risk factors of CAD make them a common mutually existing medical condition. Patients with BAV present with co-existing aortic dilation and coarctation of the aorta in up to 50% and 6% of the cases respectively.(12) AS can be associated with Heyde‘s syndrome through acquired Von Willebrand deficiency.(13) AS can also be associated with conduction system abnormalities following annular calcification which affects the AV node conduction. Heart block occurs more commonly after an aortic valve replacement (AVR) as discussed later.(4)

1.2.5 Diagnosis

The initial manifestation of AS may be a presence of a systolic murmur which radiates to the carotid arteries. Electrocardiogram (ECG) findings are nonspecific but abnormal in >90% of patients with AS.(4) Aortic valve calcification, cardiomegaly and aortic aneurysm may be seen on a chest X-ray but those findings are neither specific nor sensitive. The gold standard in AS diagnosis and evaluation is transthoracic echocardiography (TTE).(14) Transvalvular velocity, aortic valve area and mean pressure gradient over the valve are the most important measurements that a TTE can provide to assess the severity of AS. If TTE findings aren‘t adequate for diagnosis and/or evaluation, cardiac catheterization or transesophageal echocardiography (TEE) should be performed.(4) The criteria for severe aortic stenosis are AVA < 1.0 cm^2, mean gradient > 40 mm Hg and transvalvular velocity > 4.0 m/sec. (15)

1.2.6 Medical treatment

No medical treatment has been validated to be successful in improving survival rates in AS patients. Statins have been shown to slow progression in some studies but there is equally contradicting evidence and their use is not recommended for AS.(16, 17) Statins are only indicated in cases of AS if the patients have a risk of developing CAD, not for treating the AS.(4) Hypertension should be tightly controlled in patients with AS since it increases the load on the LV.(4) Other medication used in patients with AS are diuretics and intravenous sodium nitroprusside in case of cardiogenic shock. Beta blockers should be avoided in patients with severe AS.(4)

1.3 Aortic regurgitation

1.3.1 Etiology and epidemiology

Aortic regurgitation (AR) or insufficiency is the leaking of the aortic valve that causes blood to leak back in the reverse direction from the aorta into the LV during diastole. The causes of AR can be a primary disease of the aortic valve or perivalvular abnormalities. The most common causes of AR are calcification of the aortic valve, congenital BAV and rheumatic heart disease.(18) Other causes of AR are complications of balloon valvuloplasty and transcatheter aortic valve replacement (TAVR), infective endocarditis and rupture of the ascending aorta.(19) In the Framingham study, AR prevalence was 4.9% in total and 0.5% for moderate and severe AR.(20) AR is classified into acute and chronic where acute AR causes a rapid hemodynamic collapse while chronic AR results in compensatory adjustment of the LV. Chronic AR can be asymptomatic for a long time but progresses to produce general symptoms of heart failure.(19)

1.3.2 Diagnosis

In diagnosis and evaluation of AR severity an echogardiogram is most commonly used. Often, cardiac magnetic resonance imaging can be a more precise method of evaluating AR severity.(21) In chronic AR, imaging data is required to evaluate timing of surgical intervention. Staging of chronic AR involves assessing valve anatomy, valve hemodynamics, hemodynamic consequences and patient symptoms. (19)

1.3.3 Treatment

There is currently no medical therapy that has been shown to prevent disease progression in AR patients.(19) Medical therapy for AR involves improving hemodynamic functions. For acute AR and symptomatic severe chronic AR, AVR is the recommended treatment.(22)

1.4 Aortic valve replacement

1.4.1 Surgical aortic valve replacement

The only validated, standard treatment for AS is aortic valve replacement (AVR).(4) A balloon valvuloplasty has been used as a palliative option, where a catheter with an expandable balloon is used to inflate the aortic valve open and reduce the stenosis, but it hasn‘t been shown to improve long-term mortality and is associated with numerous complications.(23) Surgical AVR (SAVR) is the gold standard treatment for AS as it has shown an overall mortality rate of 2.6% and gives patients near-normal life expectancy.(24, 25) SAVR requires a sternotomy where the patient is put on cardiopulmonary bypass and the heart put in cardioplegic arrest while the dysfunctional valve is removed surgically and a new one placed instead.(4) Currently, up to 30% of patients with AS have too high operative risk assessment to undergo the surgery.(26) However, in recent years there has been a surge in referrals of those high risk patients to transcatheter AVR (TAVR) with comparable outcomes to those of SAVR. (4)

1.4.2 Transcatheter aortic valve replacement

The TAVR procedure is less invasive where a new valve and a stent is deployed with a balloon expandable catheter. The catheter enters either through the femoral artery or transapically through the thoracic wall. The two major types of valves used in TAVR are Medtronic's CoreValve and Edwards Sapien valve. There are considerable differences in the build of these two valves (figure 2).

	Size (width x height)	For annulus diameter	Height of skirt
Edward SAPIEN™	23 x 14.5 mm	18-22 mm	10.1 and 7.74 mm
	26 x 16 mm	21-25 mm	11.4 and 8.67 mm
CoreValve Revalving™	26 x 53 mm	20-23 mm	12 mm
	29 x 55 mm	23-27 mm	12 mm

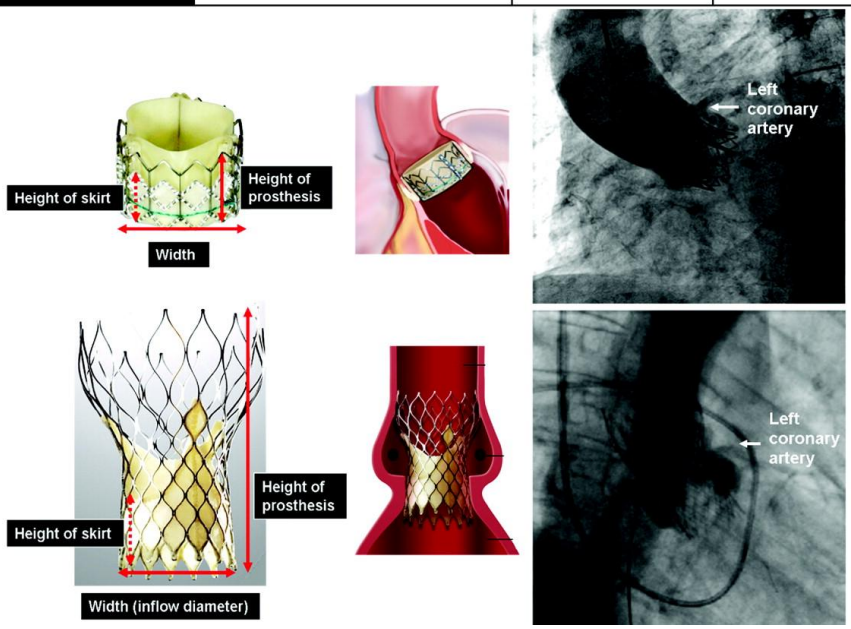

Figure 2. Description of the Edward SAPIEN valve and CoreValve (upper and bottom row of figures respectively). A summary of the dimensions is seen in the table.(27)

1.4.3 SAVR vs TAVR: High surgical risk patients

In the PARTNER 1 cohort B trial, comparing standard therapy to TAVR in inoperable patients, there was a significant improvement in 1 year survival rates for the TAVR group but high rates of stroke and vascular events were a concern. In the PARTNER 1 cohort A which compared TAVR to SAVR in high risk but operable patients the criteria for noninferiority were met. Major strokes and vascular complications were significantly higher in the TAVR group with new-onset atrial fibrillation (AF) and major bleeding significantly higher in the SAVR group.(28, 29)

1.4.4 SAVR vs TAVR: Intermediate surgical risk patients

With TAVR being established as non inferior to SAVR for high risk patients there has been interest in expanding the indication to indermediate and low risk patients. The Partner 2 cohort A trial compared TAVR to SAVR in intermediate risk patients. The primary endpoints, all-cause death and disabling stroke were evaluated at 2 years and TAVR was proven to be non-inferior to SAVR in those regards. Paravalvular regurgitation and major vascular complications were more frequent in the TAVR group while life-threatening bleeding, acute kidney injury and new-onset AF were less frequent compared to the SAVR group.(30) The SURTAVI trial demonstrated similar results and concluded non-inferiority of TAVR compared to SAVR in intermediate risk patients.(31) There is still an ongoing debate if TAVR should be considered for intermediate and low risk patients.(32, 33) Long-term results of the TAVR procedure are yet to be defined.(34)

1.5 Pacemaker

A cardiac pacemaker is a device that consists of an impulse generator and conducting leads that carry the impulse to the patient‘s heart.(35) Permanent pacemakers (PPM) are subcutaneously implanted devices with leads going transvenously and, to a lesser extent, epicardially to the heart chambers. PPMs come in different modes including single- and dual chamber, having biventricular, unipolar and bipolar modules for sensing the presence of rhythm and generating a response if it is inadequate according to the settings fed into the pacemaker.(35) All pacemaker modes are coded with the North American Society of Pacing and Electrophysiology (NASPE)/British Pacing and Electrophysiology Group (BPEG) Generic Pacemaker Code.(36)

Table 1. Explanation for each character in The Revised NASPE/BPEG Generic Code for Antibradycardia Pacing.

Position	**I**	**II**	**III**	**IV**	**V**
Category	Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate Modulation	Multisite pacing
Code	O = None A = Atrium V = Ventricle D = Dual (A + V)	O = None A = Atrium V = Ventricle D = Dual (A + V)	O = None T = Triggered I = Inhibited D = Dual (T + I)	O = None R = Rate Modulation	O = None A = Atrium V = Ventricle D = Dual (A + V)

In the dual setting, the pacemaker provides atrioventricular synchrony by ensuring that a ventricular pacing follows atrial. The inhibit setting serves as an inhibitor for pacing if adequate electrical activity is sensed. Triggered means the pacemaker will only pace in response to sensing.(35)

1.5.1 Indications

According to ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities there are five categories of indications for a pacemaker implant. (37)

1. Bradycardia due to sinus and atrioventricular node dysfunction.
2. Pacing for specific conditions e.g. cardiac transplant, neuromuscular disease etc.
3. Pacing to prevent and terminate arrhythmias.
4. Pacing for hemodynamic indications.
5. Pacing in children, adolecents and patients with congenital heart disease.

Following an AVR, common indications of PPM are third and advanced second degree AV block that are not expected to recover and arrhythmias e.g. long-QT syndrome, sick sinus syndrome and atrial fibrillation.(37) Following a pacemaker implantation, careful follow-up is required. The pacemaker should be interrogated frequently either in clinic or remotely to have all programmed parameters reviewed.(37)

1.6 Rates, risk factors and long term utilization of PPM following SAVR and TAVR

For many early/mid-term outcomes and end-points in high risk patients, including survival, TAVR has been proven to be a non-inferior alternative to SAVR.(38-40) One contrasting outcome consistently defined when comparing TAVR to SAVR is higher rates of post-operative permanent pacemaker (PPM) implantation for TAVR. The need for PPM after SAVR is thought to be related to surgical trauma or ischemia to the atrioventricular node while the conduction abnormalities after TAVR are more related to mechanical trauma of the stented prosthesis as well as annular and valvular calcifications.(41)

1.6.1 Rates

According to three different meta-analysis, the rates of PPM post SAVR are 5.9%, 3.0% and 7.5% and by contrast 12.1%, 13.2% and 21.6% for TAVR.(42-44) Significant differences have been described between the TAVR prosthesis, Edwards Sapien valve and the Medtronic CoreValve with reported rates of PPM 5.9% and 24.5%, respectively.(42) A comparison of isolated SAVR to SAVR plus a coronary artery bypass graft (CABG) reveiled PPM rates of 4.8% and 4.6%, respectively.(45) In a systematic review of long-term outcomes of TAVR in non-surgical candidates or high-risk patients, post-operative requirement for PPM was 13.4%.(34) Post-operative PPM rates following TAVR and SAVR in low-risk patients were 12.7% and 2.9%, respectively.(33)

1.6.2 Risk factors

Independent risk factors for PPM following SAVR have been highlighted in a meta analysis by Matthews, et al. which included 2557 patients from 7 different studies.(46) Conduction abnormalities like left bundle branch block (LBBB), right bundle branch block (RBBB), left anterior hemiblock (LAHB) and first degree atrioventricular block (AVBI) were identified most consistently as independent risk factors for requirement of PPM.(46) Individual studies demonstrated preoperative MI and AR as

individual risk factors.(47-49) Septal hypertrophy, greater left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF) <35%, pulmonary hypertension, aortic annular calcification, BAV and female sex were also identified as factors defining a trend for PPM placement.(46) A meta-analysis assessing risk factors for PPM following TAVR by Siontis, et al. identified conduction abnormalities such as RBBB, LAHB, AVBI and intraprocedural AVB to be high risk rhythm abnormalities leading to permanent pacemaker implantation.(50) When comparing CoreValve to Sapien the study also found CoreValve to be a significant risk factor for PPM requirement.(50) However, neither of these meta-analyses assessed long-term utilization of PPM since there was rarely any comment on such in the individual studies being reported.

1.6.3 Long term utilization

Long term utilization of PPM following aortic valve replacement is an emerging topic of interest. Previously described rates of long term PPM dependency are inconsistent. Varying definitions of PPM dependence and follow up time demonstrate a lack of agreement on this topic. The rates of independence from PPM range from 10% to 51% (51, 52) and 6% to 78% after SAVR and TAVR procedures respectively.(41, 53)

2 Study aim

The primary aim of this study was to analyze the rates of, and identify independent risk factors for PPM placement, characterize the long-term utilization of PPM and assess if return of atrioventricular conduction is different between SAVR and TAVR cohorts.

3 Methods and materials

3.1 Patients and study design

This was a single center retrospective review of patients who underwent an aortic valve replacement (SAVR or TAVR) consecutively from 2012 to 2016 at the Yale New Haven Hospital (YNHH). This study was approved by the Yale Institutional Review Board (IRB) according to IRB#: 2000022005. Initially, records of 1102 patients were found according to our inclusion critera, of these patients, 122 were excluded on the basis of having a PPM at the time of surgery, 31 with infective endocarditis, 43 with inadequate or missing data and 3 who had a redo AVR after a short period of time (figure 3). The remaining 904 patients were then stratified into two groups, comprising of 499 SAVR patients and 405 TAVR patients. Twelve different surgeons performed the SAVR‘s and nine different surgeons/cardiologists performed the TAVR procedures. The TAVR patient‘s either received a Sapien Valve from Edward‘s Life Science or a CoreValve from Medtronic.

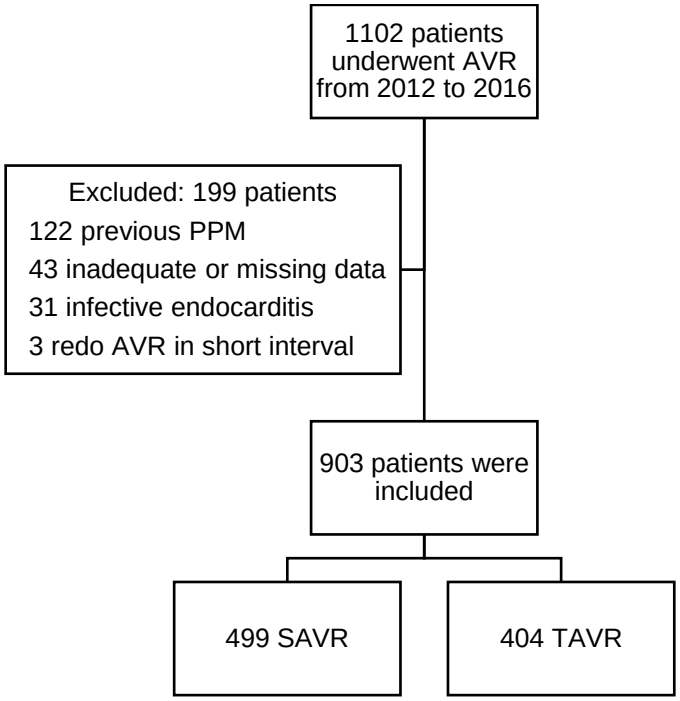

Figure 3. Exclusions from the initial study group

3.2 Patient data

General demographic information on the patients was retrieved from the institutional database at the YNHH. Most of the data on SAVR was acquired from the Society of Thoracic Surgery adult institutional database whereas TAVR procedural information was retrieved from a separate TAVR database. Information on type and size of valve used was reported from the respective operative notes in the Yale electronic health records.

The SAVR and TAVR groups were compared with regard to general demographics, echocardiographic parameters, arrhythmias and surgical specifics to assess the compatability of the groups. Then we compared the pacemaker and non-pacemaker groups within the SAVR and TAVR

groups for analysis of potential risk factors. It was decided to include patients that had a PPM implanted within two months of surgery in the PPM cohort.

At last we specifically looked at the group of patients that had a PPM implanted for analysis of long-term utilization. For the purpose of this study we excluded from that group those patients that had other indications for PPM than AVB resulting from the surgical intervention for further analysis. This was done to limit the group instances of direct surgical trauma to the conduction system that lead to PPM placement and to be able to analyze the recovery rate of those patients. Patient‘s that did not require long-term pacemaker usage were compared with the ones that did, both descriptively and analytically. To establish long term pacemaker dependency, device interrogation reports and electrophysiologist notes were reviewed with regard to percentage of ventricular pacing (VP) and underlying rhythm. PPM independency was defined as either VP < 1% or resolution of AVB based on an electrophysiologists review of the report.

3.2.1 Echocardiographic data

Echocardiographic reports were obtained from electronic patient records. Left ventricular ejection fraction (LVEF), bicuspid aortic valve (BAV), end-diastolic and end-systolic left ventricular diameter (LVEDD and LVESD) and interventricular septum (IVS) thickness was retrieved from pre-operative echocardiographic reports. Mitral annular calcification (MAC) and aortic valve calcification (AVC) was quantified from descriptions in echocardiographic reports where moderate and severe were coded as calcified and mild or none not calcified. If there was no mention of calcification it was assumed that there was none.

3.2.2 Electrocardiogram data

Cardiologist notes on preoperative electrocardiograms (ECG) were used to assess the state of arrhythmias. In cases where no cardiologist note was available, automatic ECG reports were used. Arrhythmias included in the study were atrial fibrillation- and flutter (AF and AFL) and conduction disorders, including first degree atrioventricular block (AVBI), right and left bundle branch block (RBBB and LBBB) and left anterior hemiblock (LAHB).

3.3 Statistical analysis

All statistical analysis was done using the statistical software R. Categorical variables were presented as percentages and compared between groups using Fisher‘s exact test. Continuous variables were presented as mean ± standard deviation and compared using Welch‘s t-test. To identify individual risk factors a multivariable regression model was built and included those factors that had a P-value of less than 0.1 in the univariate analysis or were considered important to identify a causal relationship. P-values less than 0.05 were considered significant.

4 Results

4.1 Study cohort

A total of 903 patients underwent aortic valve replacement from 2012-2016. This group comprised of 499 and 404 patients who underwent SAVR and TAVR respectively. Table 2 shows the general and clinical demographics of the patients. A majority of the patients identified as caucasian, or 94.2%, 3.7% identified as black and 0.6% asian. While 270 (30.1%) patients had a conduction abnormality prior to surgery a total of 81 patients (8.8%) required a PPM implant within 50 days after surgery in a mean of 5.2±9.3 days.

4.2 SAVR vs TAVR

The social and demographic factors for the SAVR and TAVR cohorts differed considerably (table 2). TAVR patients were 11.5 years older on average (SAVR: 70.5±11.3 years, TAVR: 82.0±8.8 years, p = <0.001). One year mortality was higher for TAVR patients than SAVR (12.1% vs. 4.4%, p < 0.001). However the SAVR patients had a higher BMI value on average (30.0±6.5 vs. 28.0±6.1, p < 0.001). The TAVR cohort had a significantly higher ratio of patients with peripheral vascular disease (33.2% vs. 10.2%, p < 0.001), previous cerebral vascular accident (CVA) (10.1% vs. 5.4%, p = 0.008), previous CABG surgery (26.9% vs. 6.6%, p < 0.001) and previous myocardial infarction (MI) (23.4% vs. 13.2%, p < 0.001). Rates of preoperative AF/AFL (p < 0.001), first degree AVB (AVBI) (p = 0.002), RBBB (p < 0.001), LBBB (p = 0.002) and conduction abnormalities in general (p < 0.001) were significantly higher among TAVR patients. The TAVR cohort had higher rates of AVC and MAC (p < 0.001 and p < 0.001), fewer BAV then SAVR (0.3% versus 10.9%, p < 0.001), a smaller LVEF (p = 0.004) and smaller LVESD (p < 0.001). Rates of PPM implants following SAVR and TAVR were 4.6% and 14.4% respectively (p < 0.001). Average time from surgery to PPM placement by any indication was significantly lower in the TAVR group at a mean of 3.84±9.0 days while SAVR patients waited for a mean of 9.5±8.7 days before getting a PPM (p = 0.012).

Table 2. Comparison of demographic and clinical variables between SAVR and TAVR

Variable	All patients (n = 903)	SAVR patients (n = 499)	TAVR patients (n = 404)	P-value
PPM (any indication)	81 (8.8%)	23 (4.6%)	58 (14.4%)	< 0.001
Days from surgery to PPM	5.2±9.3	9.5±8.7	3.84±9.0	0.012
General demographics				
Age (years)	75.6±11.7	70.5±11.3	82.0±8.8	< 0.001
Female gender	397 (44.0%)	215 (43.1%)	182 (45.0%)	0.590
30 day mortality	17 (1.9%)	6 (1.2%)	11 (2.7%)	0.138
1 year mortality	71 (7.9%)	22 (4.4%)	49 (12.1%)	< 0.001
BMI	29.1±6.4	30.0±6.5	28.0±6.1	< 0.001
Asian	5 (0.6%)	4 (0.8%)	1 (0.2%)	0.386
Black	33 (3.7%)	19 (3.8%)	14 (3.5%)	0.859
Caucasian	848 (94.2%)	462 (93.1%)	386 (93.7)	0.151
Diabetes	298 (33.0%)	158 (31.7%)	140 (34.7%)	0.355

Hypertension	750 (83.1%)	417 (83.6%)	333 (82.4%)	0.657
PVD	185 (20.5%)	51 (10.2%)	134 (33.2%)	< 0.001
Previous CVA	68 (7.5%)	27 (5.4%)	41 (10.1%)	0.008
Previous CABG	141 (15.6%)	33 (6.6%)	108 (26.9%)	< 0.001
Pevious MI	160 (17.8%)	66 (13.2%)	94 (23.4%)	< 0.001
Arrhythmias				
AF/AFL	113 (12.6%)	29 (5.9%)	84 (20.7%)	< 0.001
Conduction Abnormalities	270 (30.2%)	113 (23.0%)	157 (39.1%)	< 0.001
- **AVBI**	106 (11.8%)	43 (8.7%)	63 (15.6%)	0.002
- **RBBB**	105 (11.7%)	41 (8.3%)	64 (15.9%)	< 0.001
- **LBBB**	68 (7.6%)	25 (5.1%)	43 (10.7%)	0.002
- **LAHB**	57 (6.4%)	31 (6.3%)	26 (6.5%)	1.000
Echocardiographic parameters				
AVC	632 (78.4%)	295 (71.8%)	337 (85.3%)	< 0.001
MAC	263 (32.6%)	107 (26.0%)	156 (39.6%)	< 0.001
BAV	47 (5.8%)	46 (10.9%)	1 (0.3%)	< 0.001
LVEF (%)	58.8±12.0	59.9±11.0	57.5±12.9	0.004
LVEDD (mm)	47.1±8.1	48.1±8.3	46.1±7.6	< 0.001
LVESD (mm)	31.9±8.7	32.0±8.8	31.8±8.5	0.675
IVS thickness (mm)	12.3±2.4	12.3±2.5	12.3±2.3	0.772
Surgical aspects				
Prosthetic Size (mm)	24.5±3.4	22.2±2.1	27.2±2.7	< 0.001
Redo/ Valve in valve	46 (5.1%)	22 (4.4%)	24 (5.9%)	0.362
CoreValve	NA	NA	220 (54.7%)	
Bypass time	NA	88.3±24.8	NA	
Cross-clamp time	NA	67.8±17.7	NA	

AF = atrial fibrillation, AFL = atrial flutter, AVBI = first degree atrioventricular block, AVC = aortic valve calcification, BAV = bicuspid aortic valve, BMI = body mass index, CABG = coronary artery bypass graft, CVA = cerebral vascular accident, IVS = interventricular septum, LAHB = left anterior hemiblock, LBBB = left bundle branch block, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, MAC = mitral annular calcification, MI = myocardial infarct, PPM = permanent pacemaker, PVD = peripheral vascular disease, RBBB = right bundle branch block, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.

4.3 Evolution of PPM rates

Overall rates of PPM implants following AVR for each year included in the study remained relatively steady as can be seen in figure 4. Rates of PPM following TAVR varied from 11.1% – 28% by year, with the highest rate in 2012 and the lowest in 2014. On the other hand the SAVR group‘s lowest rate is in 2013 (3.2%) and the highest in 2015 (6.3%).

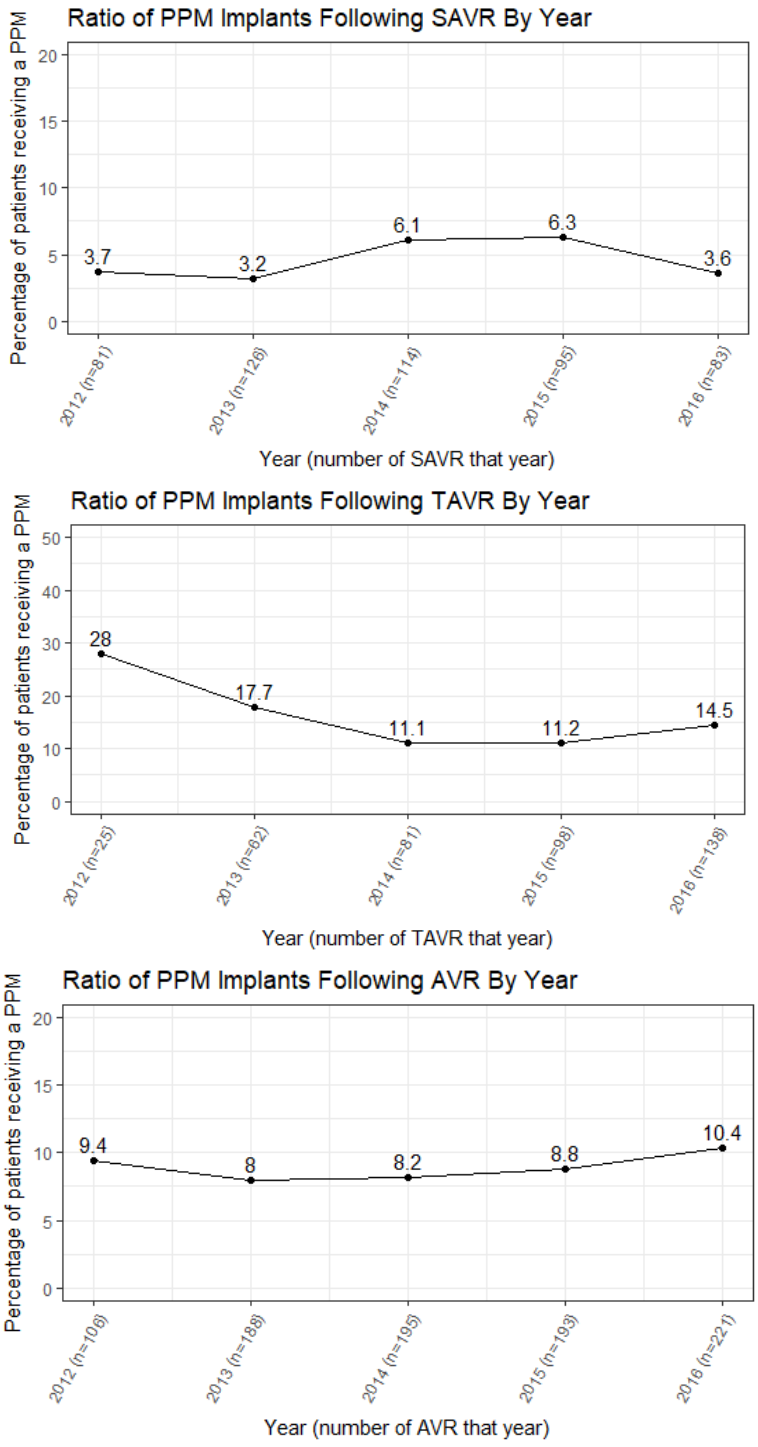

Figure 4. The evolution of PPM rates following SAVR (top figure), TAVR (middle figure) and both combined (bottom figure) from 2012 to 2016.

4.4 TAVR patients

No significant differences in general demographics were found between the PPM and control groups within the TAVR cohort as seen in table 3. Rates of pre-operative conduction abnormalities were significantly higher in the pacemaker group ($p < 0.001$). Within those, first degree AVB (AVBI) ($p = 0.030$) and RBBB ($p < 0.001$) were individually predictive of PPM implant. Pre-operative AF/AFL rates were similar between the groups. Post-dilation ballooning was not predictive of higher rates of PPM. No significant differences were found in rates of PPM implants between individual surgeons and cardiologists. When grouped together, surgeons had a slightly lower rate of PPM (14.0%) than cardiologists (16.1%) but non-significantly ($p = 0.609$) (table 4). The PPM group had a higher ratio of CoreValve implants than the control group (69.0% vs 52.3%, $p = 0.022$). Patients that had a CoreValve implant had a PPM rate of 18.2% versus 9.9% of the patients that had a Sapien implant ($p = 0.022$). Lastly, a larger prosthetic valve was associated with a higher likelihood of requiring a PPM (0.005). A valve-in-valve procedure was inversely associated with PPM implantation ($p = 0.034$).

Table 3. Predictors of PPM requirement following TAVR.

Variable	Control group (n = 346)	PPM group (n = 58)	P value
General demographics			
Age	81.8±8.8	82.7±8.8	0.503
Female gender	155 (44.8%)	27 (45.8%)	0.887
30 day mortality	9 (2.6%)	2 (3.4%)	0.663
1 year mortality	38 (11.0%)	11 (19.0%)	0.125
BMI	27.9±6.0	28.2±6.8	0.772
Diabetes	120 (34.7%)	20 (34.5%)	1.000
Hypertension	290 (83.8%)	43 (74.1%)	0.092
PVD	110 (31.8%)	24 (41.4%)	0.175
Previous CVA	38 (11.0%)	3 (5.2%)	0.240
Previous CABG	90 (26.2%)	18 (31.0%)	0.428
Pevious MI	81 (23.5%)	13 (22.4%)	1.000
Arrhythmias			
AF/AFL	71 (20.5%)	13 (22.4%)	0.729
Conduction Abnormalities	117 (34.0%)	40 (69.0%)	< 0.001
- **AVBI**	48 (13.9%)	15 (25.9%)	0.030
- **RBBB**	37 (10.8%)	27 (46.6%)	< 0.001
- **LBBB**	39 (11.3%)	4 (6.9%)	0.489
- **LAHB**	20 (5.8%)	6 (10.3%)	0.242
Echocardiographic parameters			
AVC	288 (84.7%)	49 (89.1%)	0.538
MAC	141 (41.6%)	15 (27.3%)	0.053
BAV	1 (0.3%)	0	1.000
LVEF (%)	57.4±13.0	58.2±12.0	0.627
LVEDD (mm)	46.1±7.7	46.1±7.4	0.988
LVESD (mm)	31.9±8.5	31.0±8.6	0.464
IVS thickness (mm)	12.2±2.2	12.5±2.6	0.517
Surgical aspects			
Corevalve	180 (52.3%)	40 (69.0%)	0.022
Prosthetic Size (mm)	27.1±2.7	28.2±2.7	0.005
Balloon post-dilation	64 (18.6%)	9 (15.5%)	0.713
Valve in valve	24 (6.9%)	0	0.034

AF = atrial fibrillation, AFL = atrial flutter, AVBI = first degree atrioventricular block, AVC = aortic valve calcification, BAV = bicuspid aortic valve, BMI = body mass index, CABG = coronary artery bypass graft, CVA = cerebral vascular accident, IVS = interventricular septum, LAHB = left anterior hemiblock, LBBB = left bundle branch block, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, MAC = mitral annular calcification, MI = myocardial infarct, PPM = permanent pacemaker, PVD = peripheral vascular disease, RBBB = right bundle branch block, TAVR = transcatheter aortic valve replacement.

Table 4. Comparison of surgeons and cardiologists with regard to PPM rates following TAVR

	Surgeons (n = 314)	Cardiologists (n = 87)	P value
PPM implants	44 (14.0%)	14 (16.1%)	0.609

PPM = permanent pacemaker, TAVR = transcatheter aortic valve replacement.

4.4.1 Risk factors for PPM following TAVR

Four variables were significantly higher in the PPM group upon univariate analysis, pre-operative AVBI and RBBB, prosthetic size and CoreValve implant type. Table 5 shows the outcomes of a multivariate logistic regression analysis on these variables which found RBBB to be an independent risk factor for PPM following TAVR (OR = 7.86, 95% CI: 4.16 – 14.97, p = <0.001).

Table 5. Multivariate logistic regression analysis for identification of independent risk factors of PPM requirement following TAVR.

Variable	Odds Ratio	95% Confidence Interval	P-value
AVBI	1.78	0.90 – 3.81	0.073
RBBB	7.86	4.16 – 14.97	< 0.001
Prosthetic size	1.12	0.98 – 1.30	0.126
CoreValve	1.75	0.75 – 3.43	0.153

AVBI = first degree atrioventricular block, PPM = permanent pacemaker, RBBB = right bundle branch block, TAVR = transcatheter aortic valve replacement.

4.5 SAVR patients

As seen in table 6, general demographics did not differ significantly between the PPM and control groups within the SAVR cohort, except for the higher rate of diabetes within the PPM group (52.2% vs. 30.7%, p = 0.039). Rates of PPM did non differ significantly between individual surgeons (p = 0.231). No significant differenses were found between the two groups with regard to arrhythmias. However there were some significant differences in the echocardiographic variables, specificly AVC, LVESD and IVS thickness. Increased IVS thickness was observed in the PPM group (13.2±1.8 mm vs. 12.3±2.5 mm, p = 0.048) as well as a smaller LVESD (28.2±6.6 mm vs. 32.3±8.9 mm, p = 0.020). AVC was inversely associated with PPM placement (p = 0.033).

Table 6. Predictors of PPM requirement following SAVR.

Variable	Control group (n = 476)	PPM group (n = 23)	P-value
General demographics			
Age	70.5±11.2	70.3±12.4	0.9371
Female gender	207 (43.5%)	8 (34.8%)	0.519
30 day mortality	5 (1.1%)	1 (4.3%)	0.248
1 year mortality	21 (4.4%)	1 (4.3%)	1.000
BMI	30.0±6.5	30.0±6.1	0.980
Diabetes	146 (30.7%)	12 (52.2%)	0.039
Hypertension	398 (83.6%)	19 (82.6%)	0.780
PVD	48 (10.1%)	3 (13.0%)	0.720
Previous CVA	26 (5.5%)	1 (4.3%)	1.000
Previous CABG	32 (6.7%)	1 (4.3%)	1.000
Pevious MI	62 (13.0%)	4 (17.4%)	0.528
Arrhythmias			
AF/AFL	26 (5.6%)	3 (13.0%)	0.148
Conduction abnormalities	109 (23.2%)	4 (17.4%)	0.620
- **AVBI**	41 (8.7%)	2 (8.7%)	1.000
- **RBBB**	40 (8.5%)	1 (4.3%)	0.710
- **LBBB**	24 (5.1%)	1 (4.3%)	1.000
- **LAHB**	30 (6.4%)	1 (4.3%)	1.000
Echocardiographic parameters			
AVC	286 (73.0%)	9 (47.4%)	0.033
MAC	289 (26.5%)	3 (15.8%)	0.424
BAV	45 (11.1%)	1 (5.3%)	0.708
LVEF (%)	59.7±11.1	62.2±10.6	0.293
LVEDD (mm)	48.2±8.3	46.4±8.8	0.378
LVESD (mm)	32.3±8.9	28.2±6.6	0.020
IVS thickness (mm)	12.3±2.5	13.2±1.8	0.048
Surgical aspects			
Prosthetic Size (mm)	22.2±2.0	22.1±2.5	0.840
Redo SAVR	20 (4.2%)	2 (8.7%)	0.269
Bypass time (min)	67.4±24.8	95.2±25.0	0.103
Cross-clamp time (min)	67.4±17.5	75.1±21.3	0.189

AF = atrial fibrillation, AFL = atrial flutter, AVBI = first degree atrioventricular block, AVC = aortic valve calcification, BAV = bicuspid aortic valve, BMI = body mass index, CABG = coronary artery bypass graft, CVA = cerebral vascular accident, IVS = interventricular septum, LAHB = left anterior hemiblock, LBBB = left bundle branch block, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, MAC = mitral annular calcification, MI = myocardial infarct, PPM = permanent pacemaker, PVD = peripheral vascular disease, RBBB = right bundle branch block, SAVR = surgical aortic valve replacement.

4.5.1 Risk factors for PPM following SAVR

To analyse potential individual risk factors for PPM placement following SAVR, Diabetes, AF/AFL, IVS thickness and LVESD were included in a multivariate logistic regression analysis (table 7). No statistically significant individual risk factors for PPM placement following SAVR were identified. A smaller LVESD came close (OR: 0.93, 95% CI: 0.86 – 1.00, p = 0.062).

Table 7. Multivariate logistic regression analysis for identifying individual risk factors for PPM placement following SAVR.

Variable	Odds Ratio	95% Confidence Interval	P value
Diabetes	2.13	0.80 – 5.71	0.125
AF/AFL	1.93	0.28 – 7.90	0.417
IVS thickness	1.11	0.93 – 1.31	0.232
LVESD	0.93	0.86 – 1.00	0.062

AF = atrial fibrillation, AFL = atrial flutter, IVS = interventricular septum, LVESD = left ventricular end-systolic diameter.

4.6 PPM patients

4.6.1 Patient characteristics

A total of 81 patients required a PPM implantation following surgery, 23 in the SAVR cohort and 58 in the TAVR cohort. As seen in table 8, and schematically in figure 5, a majority of those had AVB as an indication for PPM implantation or 76.5%. Excluded from the long-term utilization analysis were sick sinus syndrome (SSS) which was the indication in 8.6% of cases and other indications 13.6%. AVB as an indication was more common with the TAVR patients (p < 0.001) and SSS was more common with the SAVR group (p = 0.006). Other indications did not differ significantly between groups.

Table 8. All indications for PPM ipmlantation following both SAVR and TAVR.

Indication	All patients (n = 81)	SAVR patients (n = 23)	TAVR patients (n = 58)	P value
AVB	62 (76.5%)	11 (47.8%)	51 (87.9%)	< 0.001
Other	11 (13.6%)	6 (26.1%)	5 (8.6%)	0.067
SSS	8 (8.6%)	6 (26.1%)	2 (3.4%)	0.006

AVB = atrioventricular block, PPM = permanent pacemaker, SAVR = surgical aortic valve replacement, SSS = sick sinus syndrome, TAVR = transcatheter aortic valve replacement.

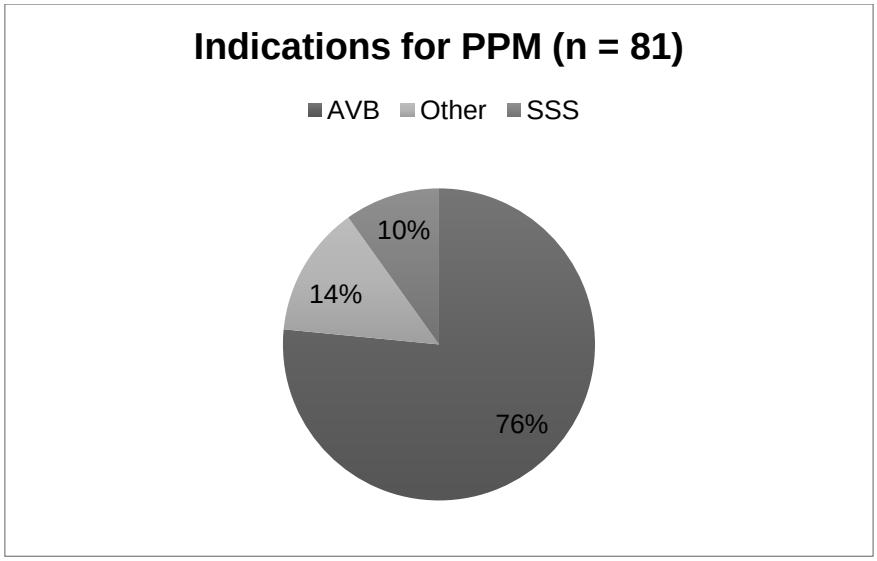

Figure 5. Ratio of each indication for PPM implantation following both SAVR and TAVR.

Clinical characteristics of PPM patients with AVB are described in table 9. During a mean follow up time of 384.1±332.0 days, 37.1% of patients recovered from their AVB after a mean time of 31.2±44.5 days from their date of implant. Average time from surgery to PPM placement was significantly shorter for the TAVR patients at a mean of 1.8±9.0 days while SAVR patient‘s waited for a mean of 9.1±8.7 days before getting a PPM (p = 0.012). Rate of AVB recovery, time until recovery and follow up time did not differ significantly between the SAVR and TAVR patients. Of those 62 patients, three were lost to follow-up.

Table 9. Clinical characteristics of PPM patient‘s with AVB compared between SAVR and TAVR cohorts.

Variable	All patients (n = 62)	SAVR patients (n = 11)	TAVR patients (n = 51)	P-value
Age	81.1±9.7	73.5±9.9	82.7±8.9	0.013
Female gender	28 (45.2%)	4 (36.4%)	24 (47.1%)	0.647
Time from surgery to PPM (days)	3.1±4.9	9.1±8.7	1.8±9.0	0.017
Recovered from AVB	23 (37.1%)	5 (45.5%)	18 (37.5%)	0.736
Time until recovery (days)	31.2±44.5	30.8±55.7	31.3±42.5	0.986
Follow up time (days)	384.1±332.0	514.7±388.4	354.2±314.6	0.223
DDD programming	54 (87.1%)	10 (90.9%)	44 (86.3%)	1.000
Lower rate limit (bpm)	61.9±5.6	60.9±5.4	62.2±5.6	0.499

AVB = atrioventricular block, bpm = beats per minute, PPM = permanent pacemaker, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.

4.6.2 Long term PPM dependency

Of the 62 patient‘s that required a pacemaker following AVR, 23 (37.1%) recovered from their AVB and 36 (58.1%) did not and three were lost to follow-up (4.8%). Table 10 compares recovered and non-recovered patients with regard to to general demographic and clinical variables. The patients who did not recover from their AVB had a significantly higher rate of PVD (OR: 4.15, 95% CI: 1.08 –

20.15). They also had higher rates of pre-operative Ca^{+2} channel blocker (CCB) therapy, diabetes, previous CABG, previous MI and pre-operative AVBI as well as a shorter time period between surgery and PPM implantation but all non-significantly.

Table 10. Predictors of long term PPM dependency in patients with AVB.

Variable	Recovered (n = 23)	No recovery (n = 36)	P value
General demographics			
Age	82.0±8.9	80.4±10.5	0.530
Female gender	12 (52.2%)	13 (36.1%)	0.284
Time from surgery to PPM (days)	3.9±3.9	2.7±5.6	0.263
CCB therapy	1 (4.3%)	9 (25.0%)	0.072
Diabetes	7 (30.4%)	14 (38.9%)	0.585
Hypertension	16 (69.6%)	27 (75.0%)	0.766
PVD	4 (17.4%)	17 (47.2%)	0.026
Previous CVA	2 (8.7%)	2 (5.6%)	0.639
Previous CABG	4 (17.4%)	9 (25.0%)	0.540
Previous MI	4 (17.4%)	9 (25.0%)	0.540
Arrhythmias			
AF/AFL	3 (13.0%)	6 (16.7%)	1.000
Conduction abnormalities	13 (56.5%)	25 (69.4%)	0.405
- **AVBI**	3 (13.0%)	13 (36.1%)	0.073
- **RBBB**	10 (43.4%)	14 (38.9%)	0.790
- **LBBB**	2 (8.7%)	2 (5.6%)	0.639
- **LAHB**	3 (13.0%)	4 (11.1%)	1.000
Echocardiographic parameters			
LVEF (mm)	60.0±9.8	59.6±12.0	0.900
LVEDD (mm)	46.0±8.9	44.8±6.8	0.597
LVESD (mm)	28.7±9.1	29.4±6.6	0.756
IVS thickness (mm)	12.5±2.8	12.7±2.6	0.813
AVC	19 (82.6%)	26 (89.7%)	0.686
MAC	6 (26.1%)	8 (25%)	1.000
Surgical aspects			
Prosthetic size	26.7±3.8	27.2±3.4	0.563
Redo/Valve in valve	1 (4.3%)	1 (2.8%)	1.000
CoreValve	14 (77.8%)	19 (63.3%)	0.351
Post dilatation	4 (22.2%)	5 (16.7%)	0.711

AF = atrial fibrillation, AFL = atrial flutter, AVBI = first degree atrioventricular block, AVC = aortic valve calcification, BAV = bicuspid aortic valve, BMI = body mass index, CABG = coronary artery bypass graft, CCB = Ca^{2+} channel blocker, CVA = cerebral vascular accident, IVS = interventricular septum, LAHB = left anterior hemiblock, LBBB = left bundle branch block, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, MAC = mitral annular calcification, MI = myocardial infarct, PPM = permanent pacemaker, PVD = peripheral vascular disease, RBBB = right bundle branch block, SAVR = surgical aortic valve replacement.

4.6.3 Risk factors for long-term PPM dependency

CCB therapy, PVD and pre-operative AVB were analysed in a multivariate logistic regression model for identification of individual risk factors for long-term PPM dependency (table 11). CCB therapy and PVD were found to be statistically significant independent risk factors for long term PPM dependency ($p = 0.018$ and $p = 0.011$ respectively).

Table 11. Multivariate logistic regression analysis for identification of individual risk factors for long term PPM dependency.

Variable	Odds Ratio	95% Confidence Interval	P value
CCB therapy	14.91	2.25 – 300.75	0.018
PVD	5.91	1.61 – 25.81	0.011
AVBI	3.78	0.90 – 20.26	0.086

AVBI = first degree atrioventricular block, CCB = Ca^{2+} channel blocker, PPM = permanent pacemaker, PVD = peripheral vascular disease.

5 Discussion

We compared rates, risk factors and long-term utilization of PPM between SAVR and TAVR procedures. The main findings of the study are summarized as follows: The rates of PPM in our study population were 4.6% and 14.4% following SAVR and TAVR respectively. RBBB was an individual risk factor for requiring a PPM following a TAVR procedure. No statistically significant individual risk factors were found for PPM placement following SAVR. Our analysis on long-term PPM utilization revealed that 37.1% of those who‘s indication for a PPM was AVB did not need the PPM after a mean of 31.2±44.5 days. Pre-operative CCB therapy and PVD were identified as individual risk factors for long-term PPM dependency.

5.1 Rates and risk factors for PPM following SAVR and TAVR

In our study the rate of PPM placement following SAVR was 4.6% (23 out of 499). This rate is reflected in the current literature with rates of PPM post-SAVR ranging from 3% to 11.8% and a mean of 7%.(46) Although our study did not identify any individual risk factors for PPM placement following SAVR, diabetes, smaller LVESD and larger IVS thickness were positively associated with PPM placement. Larger LVESD has been associated with risk of PPM following SAVR which contradicts our findings.(46) Other previously recognized risk factors for PPM placement following SAVR are preoperative AVBI, LAHB, RBBB or LBBB, as well as AR as an indication for surgery, previous MI and longer cardiopulmonary bypass time.(46)

The rate of PPM following TAVR was 14.4% (59 out of 404) in our study population. Further dividing of the TAVR cohort reveals that patients with CoreValve implants had a PPM rate of 18.2% versus 9.9% of the patients with Sapien implants. These rates are similar to those described in the current literature with post-TAVR rates ranging from 2% to 51% and a median of 28% for CoreValve versus 6% for the Sapien valve.(50) One independent risk factor for PPM placement following TAVR was identified in our study by a multivariate logistic regression analysis, RBBB. Known risk factors for PPM placement following TAVR are male gender, pre-operative first degree AVB, LAHB or RBBB and intraprocedural AVB.(50) In the PARTNER trial, smaller LVEDD was identified as an independent risk factor for PPM.(54) Gender-related differences in PPM rates are conflicting between individual studies and may be explaind by the tendency of males undergoing TAVR to have more comorbidities than females and receive a larger prosthesis on average.(55, 56) Mitral annular calcification has also been associated with higher rates of PPM following both SAVR and TAVR.(57, 58)

There are many possible explanations for the fact that we did not find any individual risk factors for PPM in the SAVR group, one might be the low ratio of AVB from surgical trauma as an indication for PPM. It is possible that some of those post-SAVR PPM implantations for SSS or severe bradycardia were not directly related to stress on the heart during surgery. Another explanation might be the sample size with only 23 SAVR patients requiring a PPM, thereby we may not have had adequate power to identify significant differences in the cohort.

A comparison of variables significantly associated with higher rates of PPM placement from univariate analysis shows considerable difference between the SAVR and TAVR cohorts. While

diabetes and increased IVS thickness were the only significant factors in the SAVR group ($p = 0.039$ and $p = 0.048$, respectively), preoperative AVBI and RBBB, larger prosthetic valve size and valve type (CoreValve) were all significant in the TAVR group ($p = 0.030$, $p < 0.001$, $p = 0.022$ and $p = 0.005$, respectively). This concludes that the SAVR and TAVR cohorts did not share any risk factors or positive associations with PPM placement in our study population.

AVC was inversely associated with PPM placement in the SAVR cohort ($p = 0.033$) and the same goes for MAC in the TAVR cohort although not statistically significant ($p = 0.053$). These results are surprising given the fact that, as mentioned above, all three of these factors have been associated with higher rates of PPM following AVR. We can look critically at the method used for quantifying AVC and MAC. Both AVC and MAC were coded as binary variables in the study database with moderate and severe being positive and mild and none being negative. These descriptions were taken from pre-operative echocardiograph reports and when there was no mention of calcification in either the aortic valve or the mitral annulus it was assumed that there was none. Since most patients that are indicated for an AVR at YNHH have a degenerative disease of the aortic valve it is surprising that only 78.4% (632 out of 903) of patients had AVC according to our criteria. The same goes for MAC as to the validity of the data.

The mean time from surgery to PPM implantation for any indication in our study was 9.5±8.7 days for SAVR and 3.84±9.0 days for TAVR. For AVB indication it was 9.1±8.7 days and 1.8±9.0 days for SAVR and TAVR respectively. This shows that TAVR patients that required a PPM for any other indication than AVB waited longer than those with AVB. There are currently no guidelines in practice at YNHH for how much time patients developing AVB after surgery should be given to potentially recover from it. Times from SAVR to PPM placement vary between studies and range from 6.1 – 13 days.(46) The mean time from TAVR to PPM implantation is mostly reported around 4 days(53, 54) The 2013 European Society of Cardiology (ESC) guidelines recommend clinical observation for up to 7 days to assess PPM need for high degree and complete AVB following SAVR and TAVR but a shorter period in cases of complete AVB with low rate of escape rhythm.(59) The 2008 American Heart Association/American College of Cardiology/Heart Rhythm Society (ACC/AHA/HRS) guidelines leave it up to the physician to assess the timing of PPM implant.(37) Expert consensus recommends continuous monitoring of post-TAVR patients and longer monitoring for those in high risk of PPM requirement.(60)

PPM implantation following TAVR has been associated with higher mortality and repeat hospitalization.(54) This was not mirrored by our results as thirty day and one year mortality was not significantly higher in the PPM groups after TAVR nor SAVR (tables 3 and 6).

5.2 Long-term utilization of PPM

Of the 62 patients that required a PPM because of an AVB, 23 (37.7%) recovered and subsequently did not need their PPM anymore within an average of 31.2±44.5 days. The median follow-up time was 384.1±332.0 and varied widely between patients since interrogation reports and cardiologist notes were in some instances unretrievable for certain time periods. Although the patients that recovered waited for an average of 1.3 days longer before getting a PPM placement the difference was non-significant. The only variable significantly associated with long-term PPM depencency was PVD ($p = 0.026$). No other demographic or clinical variables included in our study were found to be significantly different between the patients who recovered and those who did not although preoperative first or second degree AVB and CCB therapy came close ($p = 0.073$ and $p = 0.072$, respectively). A multivariate logistic regression analysis that included PVD, preoperative AVBI and CCB therapy found PVD and CCB therapy to be individual risk factors for long-term PPM dependency ($p = 0.011$ and $p = 0.018$, respectively).

The rate of recovery in this study is mirrored by some of the current literature although the definition of dependency and demographics of the cohorts between studies varies. Huynh et al. who described rates of PPM dependency in a mean follow-up of 32 months after a PPM placement for any indication post-SAVR, found 30.0% recovery in their cohort.(61) In that study, PPM dependency was defined as going without an underlying escape rhythm greater than 30 beats/min for 30 seconds. A study by Ribeiro et al. which included patients undergoing SAVR, both isolated and in combination with other cardiac surgeries, found recovery rates of 36% during a mean follow up of 1026.6 ± 732.0 days. Their definition of PPM dependency was the absence of sinus rhythm or atrial fibrillation with appropriate ventricular response at a pacing rate of 30 beats/min for 10 sec.(62) They also found that valve etiology, specifically endocarditis, prosthetic dysfunction or BAV increased risk of no recovery compared to rheumatic, degenerative or unknown etiology.

Onalan et al. found a recovery rate of 51% following AVB indicated PPM placement after a SAVR at long term follow which was a median of 32 months.(52) Their definition of PPM dependency was any pacing activity at a rate of 30 beats/min. Baraki et al., which included any indication for PPM post-SAVR, found a recovery rate of 9% within the follow up time of 5.3 ± 4.7 years, with PPM-dependency definition of continuous ventricular stimulation without any pacemaker inhibition by spontaneous cardiac activity.(51) The rate of recovery following general cardiac surgery ranges from 27% to 60%.(52, 63-65) These studies all have their individual but similar definitions of PPM dependency, different follow-up times and different sets of indications for PPM included in their study cohorts as well as varying demographics of their cohorts.

A proportion of conduction system disorders resulting from TAVR have been shown to recover.(29, 66, 67) A recent study which assessed long term AVB persistence in a cohort with PPM implants post-TAVR found recovery rates of 51% the day after PPM implant and 77.6% at two month follow up.(53) In their study, PPM independency was defined as a ventricular pacing (VP) percentage under 5% and complete dependency was VP over 95%. Number of balloon dilatations during the procedure, early implantation and pre-op RBBB were associated with higher risk of long term

dependency but only early implantation was found to be an independent risk factor by a multistep regression analysis.(53) Our study did not confirm those findings as balloon post-dilatations and RBBB rates were both higher in the non-dependent group but non-significantly. However our data shows that dependent patients had PPM implanted earlier than non-dependent, but non-significantly (2.7±5.6 vs. 3.9±3.9, p = 0.263).

Ramazzina et al. found that 17% of PPM patients following TAVR recovered at 12 months with PPM independence defined as < 1% VP and complete AV conduction.(68) Their findings supported early PPM implantation for AVB but suggested a conservative approach for new-onset LBBB. Fraccaro et al. found 6% recovery at 6.0 ± 4.2 months after PPM implantation following TAVR with PPM dependency defined as continued pacing at lowest rate possible with VVI programming.(41) Boerlage et al. defined their PPM dependency following TAVR similarly and their recovery rate was 22% at a mean follow up of 340 days.(58)

5.3 Clinical implications

Our results confirm that RBBB is a significant risk factor for developing AVB and requirement of a PPM following TAVR and as such should be considered when patients get evaluated before surgery. Our findings of almost 40% recovery from AVB following PPM in a median of 30 days as well as the 1.8 day average time between TAVR and PPM placement could suggest that patients should be given more time in the hospital under surveilance, especially following TAVR. No significant differences were found in rates of pacemaker implants between individual surgeons/cardiologists so we can safely assume that the procedures were performed in a similar and standard fashion.

5.4 Limitations

Although our initial cohorts were considerably large the PPM patients with AVB as primary indication were only 62 which influenced the study‘s statistical power. Baseline differences in patient demographics between the SAVR and TAVR groups may have confounded the rates of PPM implants. The TAVR patients were older, had more comorbidities, higher rates of arrhythmias and worse outcomes of the echocardiographic variables at time of surgery. PPM patients follow up was often inconsistent due to the variation in the frequency and location of the pacemaker interrogation reports. Some patients had interrogation reports processed at outside medical facilities that could not be accounted for. Follow-up times varied between patients which made it difficult to assess exact time of AVB resolution in some cases.

5.5 Conclusions

The rate of PPM implantation is higher after TAVR than SAVR. Within the TAVR group it is higher in patients receiving the CoreValve versus Sapien valve. RBBB is an independent risk factor for PPM placement following TAVR. A large portion of patients with AVB indication for PPM placement become independent of the PPM a short time after implantation. Pre-operative CCB therapy and PVD are independent risk factors for long-term PPM dependency.

6 References

1. 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-Reykjavik study. International journal of cardiology. 2014;176(3):916-22.
2. Durko AP, Osnabrugge RL, Van Mieghem NM, Milojevic M, Mylotte D, Nkomo VT, et al. Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections. European heart journal. 2018.
3. Drake RL, Vogl AW, Mitchell AWM. Gray's Anatomy For Students. 3rd ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2015. 1161 p.
4. Sawaya F, Liff D, Stewart J, Lerakis S, Babaliaros V. Aortic stenosis: a contemporary review. The American journal of the medical sciences. 2012;343(6):490-6.
5. Schwarz F, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel HC, et al. The effect of aortic valve replacement on survival. Circulation. 1982;66(5):1105-10.
6. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. European heart journal. 2003;24(13):1231-43.
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. Journal of the American College of Cardiology. 1997;29(3):630-4.
8. Otto CM. Calcific aortic stenosis--time to look more closely at the valve. The New England journal of medicine. 2008;359(13):1395-8.
9. Huntington K, Hunter AG, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. Journal of the American College of Cardiology. 1997;30(7):1809-12.
10. 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;95(4):892-8.
11. Schwartz LS, Goldfischer J, Sprague GJ, Schwartz SP. Syncope and sudden death in aortic stenosis. The American journal of cardiology. 1969;23(5):647-58.
12. Januzzi JL, Isselbacher EM, Fattori R, Cooper JV, Smith DE, Fang J, et al. Characterizing the young patient with aortic dissection: results from the International Registry of Aortic Dissection (IRAD). Journal of the American College of Cardiology. 2004;43(4):665-9.
13. Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, et al. Acquired von Willebrand syndrome in aortic stenosis. The New England journal of medicine. 2003;349(4):343-9.
14. Stoddard MF, Hammons RT, Longaker RA. Doppler transesophageal echocardiographic determination of aortic valve area in adults with aortic stenosis. American heart journal. 1996;132(2 Pt 1):337-42.
15. Otto CM, Nishimura RA. New ACC/AHA valve guidelines: aligning definitions of aortic stenosis severity with treatment recommendations. Heart (British Cardiac Society). 2014;100(12):902-4.
16. Moura LM, Ramos SF, Zamorano JL, Barros IM, Azevedo LF, Rocha-Goncalves F, et al. Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis. Journal of the American College of Cardiology. 2007;49(5):554-61.
17. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J. Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation. 2010;121(2):306-14.
18. Maurer G. Aortic regurgitation. Heart (British Cardiac Society). 2006;92(7):994-1000.
19. Akinseye OA, Pathak A, Ibebuogu UN. Aortic Valve Regurgitation: A Comprehensive Review. Current problems in cardiology. 2017.
20. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). The American journal of cardiology. 1999;83(6):897-902.
21. Lee JC, Branch KR, Hamilton-Craig C, Krieger EV. Evaluation of aortic regurgitation with cardiac magnetic resonance imaging: a systematic review. Heart (British Cardiac Society). 2018;104(2):103-10.
22. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, 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. Journal of the American College of Cardiology. 2014;63(22):e57-185.

23. 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;89(2):642-50.
24. Brown JM, O'Brien SM, Wu C, Sikora JA, 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;137(1):82-90.
25. Stahle E, Kvidal P, Nystrom SO, Bergstrom R. Long-term relative survival after primary heart valve replacement. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 1997;11(1):81-91.
26. 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? European heart journal. 2005;26(24):2714-20.
27. 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. Circulation Cardiovascular interventions. 2008;1(1):74-81.
28. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. The New England journal of medicine. 2011;364(23):2187-98.
29. 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. The New England journal of medicine. 2010;363(17):1597-607.
30. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. The New England journal of medicine. 2016;374(17):1609-20.
31. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. The New England journal of medicine. 2017;376(14):1321-31.
32. Siemieniuk RA, Agoritsas T, Manja V, Devji T, Chang Y, Bala MM, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. BMJ (Clinical research ed). 2016;354:i5130.
33. Rosato S, Santini F, Barbanti M, Biancari F, D'Errigo P, Onorati F, et al. Transcatheter Aortic Valve Implantation Compared With Surgical Aortic Valve Replacement in Low-Risk Patients. Circulation Cardiovascular interventions. 2016;9(5):e003326.
34. Chakos A, Wilson-Smith A, Arora S, Nguyen TC, Dhoble A, Tarantini G, et al. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. Annals of cardiothoracic surgery. 2017;6(5):432-43.
35. Rapsang AG, Bhattacharyya P. Pacemakers and implantable cardioverter defibrillators--general and anesthetic considerations. Brazilian journal of anesthesiology (Elsevier). 2014;64(3):205-14.
36. Bernstein AD, Daubert JC, Fletcher RD, Hayes DL, Luderitz B, Reynolds DW, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group. Pacing Clin Electrophysiol. 2002;25(2):260-4.
37. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Journal of the American College of Cardiology. 2008;51(21):e1-62.
38. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet (London, England). 2015;385(9986):2477-84.
39. Deeb GM, Reardon MJ, Chetcuti S, Patel HJ, Grossman PM, Yakubov SJ, et al. 3-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. Journal of the American College of Cardiology. 2016;67(22):2565-74.

40. Reardon MJ, Adams DH, Kleiman NS, Yakubov SJ, Coselli JS, Deeb GM, et al. 2-Year Outcomes in Patients Undergoing Surgical or Self-Expanding Transcatheter Aortic Valve Replacement. Journal of the American College of Cardiology. 2015;66(2):113-21.
41. Fraccaro C, Buja G, Tarantini G, Gasparetto V, Leoni L, Razzolini R, et al. Incidence, predictors, and outcome of conduction disorders after transcatheter self-expandable aortic valve implantation. The American journal of cardiology. 2011;107(5):747-54.
42. Jilaihawi H, Chakravarty T, Weiss RE, Fontana GP, Forrester J, Makkar RR. Meta-analysis of complications in aortic valve replacement: comparison of Medtronic-Corevalve, Edwards-Sapien and surgical aortic valve replacement in 8,536 patients. Catheter Cardiovasc Interv. 2012;80(1):128-38.
43. Cao C, Ang SC, Indraratna P, Manganas C, Bannon P, Black D, et al. Systematic review and meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. Annals of cardiothoracic surgery. 2013;2(1):10-23.
44. Kondur A, Briasoulis A, Palla M, Penumetcha A, Mallikethi-Reddy S, Badheka A, et al. Meta-Analysis of Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis. The American journal of cardiology. 2016;117(2):252-7.
45. Robich MP, Schiltz NK, Johnston DR, Mick S, Krishnaswamy A, Iglesias RA, et al. Risk Factors and Outcomes of Patients Requiring a Permanent Pacemaker After Aortic Valve Replacement in the United States. Journal of cardiac surgery. 2016;31(8):476-85.
46. Matthews IG, Fazal IA, Bates MG, Turley AJ. In patients undergoing aortic valve replacement, what factors predict the requirement for permanent pacemaker implantation? Interactive cardiovascular and thoracic surgery. 2011;12(3):475-9.
47. Limongelli G, Ducceschi V, D'Andrea A, Renzulli A, Sarubbi B, De Feo M, et al. Risk factors for pacemaker implantation following aortic valve replacement: a single centre experience. Heart (British Cardiac Society). 2003;89(8):901-4.
48. Elahi M, Usmaan K. The bioprosthesis type and size influence the postoperative incidence of permanent pacemaker implantation in patients undergoing aortic valve surgery. J Interv Card Electrophysiol. 2006;15(2):113-8.
49. Dawkins S, Hobson AR, Kalra PR, Tang AT, Monro JL, Dawkins KD. Permanent pacemaker implantation after isolated aortic valve replacement: incidence, indications, and predictors. The Annals of thoracic surgery. 2008;85(1):108-12.
50. Siontis GC, Juni P, Pilgrim T, Stortecky S, Bullesfeld L, Meier B, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. Journal of the American College of Cardiology. 2014;64(2):129-40.
51. Baraki H, Al Ahmad A, Jeng-Singh S, Saito S, Schmitto JD, Fleischer B, et al. Pacemaker dependency after isolated aortic valve replacement: do conductance disorders recover over time? Interactive cardiovascular and thoracic surgery. 2013;16(4):476-81.
52. Onalan O, Crystal A, Lashevsky I, Khalameizer V, Lau C, Goldman B, et al. Determinants of pacemaker dependency after coronary and/or mitral or aortic valve surgery with long-term follow-up. The American journal of cardiology. 2008;101(2):203-8.
53. Gaede L, Kim WK, Liebetrau C, Dorr O, Sperzel J, Blumenstein J, et al. Pacemaker implantation after TAVI: predictors of AV block persistence. Clin Res Cardiol. 2018;107(1):60-9.
54. Nazif TM, Dizon JM, Hahn RT, Xu K, Babaliaros V, Douglas PS, et al. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. JACC Cardiovascular interventions. 2015;8(1 Pt A):60-9.
55. Hayashida K, Morice MC, Chevalier B, Hovasse T, Romano M, Garot P, et al. Sex-related differences in clinical presentation and outcome of transcatheter aortic valve implantation for severe aortic stenosis. Journal of the American College of Cardiology. 2012;59(6):566-71.
56. Buja P, Napodano M, Tamburino C, Petronio AS, Ettori F, Santoro G, et al. Comparison of variables in men versus women undergoing transcatheter aortic valve implantation for severe aortic stenosis (from Italian Multicenter CoreValve registry). The American journal of cardiology. 2013;111(1):88-93.
57. Nair CK, Sketch MH, Ahmed I, Thomson W, Ryschon K, Woodruff MP, et al. Calcific valvular aortic stenosis with and without mitral anular calcium. The American journal of cardiology. 1987;60(10):865-70.
58. Boerlage-Van Dijk K, Kooiman KM, Yong ZY, Wiegerinck EM, Damman P, Bouma BJ, et al. Predictors and permanency of cardiac conduction disorders and necessity of pacing after transcatheter aortic valve implantation. Pacing Clin Electrophysiol. 2014;37(11):1520-9.
59. 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). European heart journal. 2013;34(29):2281-329.
60. Holmes DR, Jr., Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: developed in collaboration with the American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Mended Hearts, Society of Cardiovascular Anesthesiologists, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. The Annals of thoracic surgery. 2012;93(4):1340-95.
61. Huynh H, Dalloul G, Ghanbari H, Burke P, David M, Daccarett M, et al. Permanent pacemaker implantation following aortic valve replacement: current prevalence and clinical predictors. Pacing Clin Electrophysiol. 2009;32(12):1520-5.
62. Ribeiro V, Mota Garcia R, Frutuoso C, Melao F, Pereira M, Pinho P, et al. Permanent pacemaker implantation after aortic valve replacement: Long-term dependency or rhythm recovery? Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology. 2015;34(9):529-33.
63. 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;32(1):7-12.
64. Glikson M, Dearani JA, Hyberger LK, Schaff HV, Hammill SC, Hayes DL. Indications, effectiveness, and long-term dependency in permanent pacing after cardiac surgery. The American journal of cardiology. 1997;80(10):1309-13.
65. Raza SS, Li JM, John R, Chen LY, Tholakanahalli VN, Mbai M, et al. Long-term mortality and pacing outcomes of patients with permanent pacemaker implantation after cardiac surgery. Pacing Clin Electrophysiol. 2011;34(3):331-8.
66. 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. The American journal of cardiology. 2011;108(11):1600-5.
67. Gutierrez M, Rodes-Cabau J, Bagur R, Doyle D, DeLarochelliere R, Bergeron S, et al. Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. American heart journal. 2009;158(2):302-8.
68. Ramazzina C, Knecht S, Jeger R, Kaiser C, Schaer B, Osswald S, et al. Pacemaker implantation and need for ventricular pacing during follow-up after transcatheter aortic valve implantation. Pacing Clin Electrophysiol. 2014;37(12):1592-601.