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Conduction abnormalities after TAVI with SAPIEN 3 prosthesis –
Influence of ratio between size of prosthesis and aortic annulus anatomy derived from multislice CT

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Dissertation to receive the doctorate

Dr. med.

by

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Summary

The transcatheter aortic valve implantation (TAVI) is performed on a regular basis at countless sites around the globe. Investigators have been looking at a broad variety of aspects of the TAVI procedure, such as access site, comorbidities impacting outcome, and differences between prosthesis types. This thesis aims to explore TAVI with the SAPIEN 3 prosthesis, especially the influence of sizing of the valve and native aortic valve dimensions on new-onset conduction abnormalities (CA) and the need for permanent pacemaker implantation (PPI).

244 consecutive patients at the Deutsches Herzzentrum München were treated with the SAPIEN 3. After excluding 36 patients due to preexisting PPI, valve-in-valve procedure, and bicuspid native valves, 208 patients were analyzed for the primary end point new PPI. A subpopulation of 184 patients without preexisting complete bundle branch blocks (LBBB; RBBB) were analyzed for new-onset or worsened CA or PPI. Measurements of the native aortic valve were derived from a multislice CT in all cases.

PPI was necessary in 34 of 208 patients (16.3 %) and new-onset or worsened CA or PPI occurred in 57 of 184 patients (31.0 %). Device success was achieved in 203 patients (97.6 %). Survival at discharge was 100 %. Prosthesis oversizing was significantly associated with new-onset or worsened CA (*see Figure 11.2*). Implantation depth at the septal side (OR: 1.063 [1.017 to 1.110]; $p = 0.006$ per each % of frame below the aortic annulus) predicted new or worsened CA and PPI. Included in a multivariate analysis, complete RBBB at baseline (OR: 11.965 [3.406 to 42.026]; $p < 0.001$) proved to be an independent predictor for new PPI.

These findings suggest that TAVI with the SAPIEN 3 might contribute to excellent outcomes, especially when oversizing and low implantation of the prosthesis are avoided. Patients with preexisting RBBB should be viewed as at particularly high risk for new PPI.

Key words: SAPIEN 3, TAVI, permanent pacemaker implantation, conduction abnormalities.

Zusammenfassung

Die katheter-gestützte Implantation einer Aortenklappenprothese (TAVI) wird weltweit an zahlreichen Zentren durchgeführt. Versuchsleiter haben sich bereits mit zahlreichen Aspekten der Intervention, beispielsweise dem Zugangsweg, dem Einfluss von Komorbiditäten auf das Outcome und den Unterschieden der verfügbaren Prothesentypen, beschäftigt. Diese Arbeit möchte den Einsatz der SAPIEN 3 Prothese, insbesondere die Auswirkungen der Prothesengröße und der anatomischen Gegebenheiten auf neu auftretende Rhythmusstörungen (CA) und notwendiger Schrittmacherimplantation (PPI), untersuchen.

244 aufeinanderfolgende Patienten wurden am Deutschen Herzzentrum München mit der SAPIEN 3 versorgt. Nach dem Ausschluss von 36 Patienten (vorbestehender Schrittmacher, Kunstklappe, oder native bikuspide Klappe) wurden 208 für den primären Endpunkt PPI untersucht. Eine Untergruppe von 184 Patienten ohne vorbestehenden Schenkelblock (LBBB; RBBB) wurde auf neue oder aggravierte Rhythmusstörungen hin untersucht. Vermessungen der nativen Klappe wurden mittels Multislice-CT vorgenommen.

PPI erfolgte bei 34 von 208 Patienten (16.3 %) und neue bzw. verschlimmerte CA wurde bei 57 von 184 Patienten (31.0 %) beobachtet. Eine erfolgreiche Implantation gelang bei 203 Patienten (97.6 %); das Überleben bei Entlassung lag bei 100 %. Überdimensionierung der Prothese war signifikant mit neuer bzw. verschlimmerter CA assoziiert (*siehe Figure 11.2*). Tiefe der Implantation, gemessen an der Septumseite, sagte neue bzw. verschlimmerte CA vorher (OR: 1.063 [1.017 – 1.110]; p = 0.006 pro % der Rahmenhöhe unterhalb des Aortenklappenannulus) voraus. In einer multivariaten Analyse wurde RBBB als unabhängiger Prädiktor für PPI identifiziert (OR: 11.965 [3.406 – 42.026]; p < 0.001).

Durch die SAPIEN 3 Prothese können sehr gute Ergebnisse erzielt werden, insbesondere wenn Überdimensionierung und tiefe Implantation vermieden werden. Patienten mit vorbestehendem RBBB sollten als besonders gefährdet für PPI betrachtet werden.

Key words: SAPIEN 3, TAVI, permanent pacemaker implantation, conduction abnormalities.

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Note. CA = conduction abnormalities; CT = computed tomography; PPI = permanent pacemaker implantation.

Tables

Note. CT = computed tomography; ECG = electrocardiogram; NYHA = New York Heart Association; PPI = permanent pacemaker implantation; TAVI = transcatheter aortic valve implantation.

Abbreviations and Acronyms

AF	Atrial fibrillation
AS	Aortic stenosis
AR	Aortic regurgitation
AVA	Aortic valve area
AVB	Atrio-ventricular block
bpm	Beats per minute
CA	Conduction abnormality
CAD	Coronary artery disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DHM	Deutsches Herzzentrum München
ECG	Electrocardiogram
Fr	French
GA	General anesthesia
GARY	German aortic valve registry
IVCA	Intraventricular conduction abnormality
IQR	Interquartile range
LACS	Local anesthesia and conscious sedation
LAHB	Left anterior hemi block

LBBB	Left bundle branch block
LES	Logistic EuroSCORE
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
NYHA	New York Heart Association
PAD	Peripheral artery disease
PCI	previous coronary intervention
PHV	Percutaneously implanted heart valve
PPI	Permanent pacemaker implantation
PVL	Paravalvular leakage
RBBB	Right bundle branch block
SAVR	Surgical aortic valve replacement
TA	Transapical approach
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiography
TF	Transfemoral approach
TTE	Transthoracic echocardiography

1 Introduction

„PHV [percutaneously implanted heart valve] might become an important therapeutic alternative for the treatment of selected patients with nonsurgical aortic stenosis." Alain Cribier wrote in 2002 (p. 3006) after publishing the first human case description in *Circulation* of what is now known as TAVI [transcatheter aortic valve implantation] or TAVR [transcatheter aortic valve replacement]. Today, TAVI can be seen as an established, routine procedure that offers treatment for an expanding population of patients.

1.1 Aortic Stenosis – Prevalence and Pathogenesis

Facing an ever-aging population, aortic stenosis (AS) should be seen as an issue of increasing importance. Meta analyses showed its prevalence in persons over the age of 75 years to be 12.4 % (Osnabrugge et al., 2013), yet single studies exploring older age categories even reported it to be up to 22.8 % (Vaes et al., 2012).

Medical research led to an evolving concept of the pathophysiology of AS. Bicuspid valves (Tzemos et al., 2008) and rheumatic fever (Dare et al., 1993) have been long-known to pose a high risk for AS. Linking risk factors for atherosclerosis to AS (Stritzke et al., 2009; Thanassoulis et al., 2010) added to a more profound understanding of what was gradually seen as an active disease rather than solely deterioration due to mechanical stress. However, randomized trials trying to assess the impact of cholesterol lowering statins failed to show significant inhibiting effects on the progression of AS (Chan et al., 2010; Cowell et al., 2005; Rossebø et al., 2008). Despite those results, recent data revealed a significant decline in age-adjusted incidence of AS as well as a decrease in mortality related to AS. These results suggest that medical treatment over the last years did have a positive effect after all (Martinsson et al., 2015). The increased use of angiotensin-converting enzyme inhibitors might account to some extent for these findings, as randomized trials recently showed (Bull et al., 2015; Dalsgaard et al., 2014).

Amongst others, calcium homeostasis has been thoroughly looked into when exploring additional pathophysiological pathways and looking for parameters predicting the natural course of AS. Aortic valve calcification can be used to predict overall mortality (Clavel et al., 2014) and calcification itself plays a central role in the progression of the disease (Pawade, et al., 2015). Distinct mutations in genes coding for molecules preventing osteoblast-like gene expression and consecutive accumulation of extracellular calcium have been described, one of which being RANKL (Kaden et al., 2004), another one being NOTCH1 (Nigam & Srivastava, 2009). Disrupting the signaling cascade of RANKL with the antibody Denusomab has been shown to inhibit calcification of valvular interstitial cells in vitro (Lerman et al., 2016) and is being investigated in the SALTIRE II trial ("SALTIRE II | The University of Edinburgh", 2020).

Further attention has been attracted by hyperlipidemia as a target for medical treatment options of AS. Suspecting similar pathogenetic causes for AS and ischemic cardiovascular events, randomized-controlled trials exploring statin-use were conducted. Unfortunately, results failed to show positive effects on AS and AS-related adverse outcomes (Chan et al., 2010; Rossebø et al., 2008). However, analyzing Lipoprotein (a) showed a distinct correlation between prevalence and progression of AS and high levels of Lipoprotein (a) (Capoulade et al., 2015; Chan et al., 2010; Kamstrup et al., 2014; Thanassoulis et al., 2013). Promising results after treatment with antisense oligonucleotides have been published and were able to show significant lowering of Lipoprotein (a) levels (Tsimikas et al., 2020; Viney et al., 2016). Further investigations are needed to elucidate clinical benefits of reducing Lipoprotein (a) levels.

1.2 Interventional Approach

TAVI has proven its value and safety as an alternative to SAVR under various settings. Long-term outcomes and meta-analyses are contributing further to a sound evaluation of risks and benefits of TAVI. Additionally, registries help generating large study populations and contribute to validating results.

The 30-day mortality amongst patients undergoing TAVI has been analyzed to be 7.5 % in a meta-analysis (Giordana et al., 2014) and showed no significant difference to SAVR (Panchal et al., 2013). However, percentages vary between study populations from 3.3 % (Adams et al., 2014) to 9.7 % (Gilard et al., 2012). Long-term mortality after five years ranges

from 53.1 % (Ludman et al., 2015) to 71.8 % (Kapadia et al., 2015) but has been shown to be significantly better than 93.6 % mortality after five years amongst patients treated with standard therapy (Kapadia et al., 2015).

Nonetheless, TAVI indeed poses risks for procedure-related adverse events and the decision for TAVI should only be made on an individual case-to-case basis. The possibility of new onset or worsened conduction abnormalities [CA], major vascular events, bleeding events and malfunctioning of the prosthesis have to be factored in when assessing the patient's eligibility for TAVI.

1.3 Conduction Abnormalities

CA unfortunately have to be considered a rather frequent complication after TAVI. However, prevalence differs considerably throughout the publications and has been shown to be dependent on several factors.

1.3.1 Conduction abnormalities and indications for permanent pacemaker implantation seen after TAVI

The spatial proximity of the aortic valve and parts of the cardiac conduction system certainly facilitates the occurrence of some of the new onset CA after TAVI. Particularly the left bundle branch with its anterior and posterior fascicle is within millimeters of the aortic annulus and runs superficially along the ventricular septum (Piazza, de Jagaere et al., 2008). Analyzing the theory of direct mechanical stress on and damage to the anatomical structures of the cardiac conduction system, investigators looked at the time of onset of CA. It was demonstrated that most CA occur during the procedure for the first time (Godin et al., 2010; Nuis et al., 2011; Piazza, Onuma et al., 2008).

Although varying in severity, new onset or worsened CA might lead to an indication for permanent pacemaker implantation (PPI).

As outlined above, damage to the left bundle branch is easily done. Hence any pre-existing right bundle branch block (RBBB) facilitates origination of complete atrioventricular block (AVB) which makes up the majority of all indications for PPI reported (Siontis et al.,

2014). Bearing in mind that not all studies reported specific indications for PPI, statements on frequency of each indication are somewhat limited. If reported, indications seemed to vary notably amongst publications. In addition to second degree type II AVB (Type Mobitz) and sick sinus syndrome, new onset left bundle branch block (LBBB) in combination with unfavorable qualities such as low (> 35 %) left ventricular ejection fraction (LVEF; De Carlo et al., 2012) or new onset LBBB in general (Van Der Boon et al., 2013) was treated with PPI. For a more profound understanding of who will profit most likely from PPI, a standardized and detailed reporting on its indications and ultimately an agreement on unambiguous criteria is desirable in order to save patients and healthcare systems alike from unnecessary interventions.

1.3.2 Permanent pacemaker implantation associated with prosthesis type

Even though a variety of implantable heart valves by more than two companies are available or are being developed at the time this study population had been investigated, by far the most scientific evidence and experience existed for Medtronic's and Edwards Lifescience Corporation's products. In 2007, Edwards Lifesciences Corporation received CE marking in Europe for its SAPIEN Transcatheter Heart Valve, as did the CoreValve ReValving system, back then privately-held by the CoreValve Inc., (Medtronic Inc., 2009). In the US, Edwards Lifesciences Corporation received FDA approval in 2011 and Medtronic Inc. announced FDA approval of its device in January of 2014. CE Mark for the SAPIEN 3 by Edwards Lifesciences Corporation was issued in 2014 and the FDA's approval followed in 2015.

Ever since the first large cohorts were evaluated scientifically, great differences in the frequency of CA and PPI after TAVI has been reported.

Rates of new onset LBBB have consistently been demonstrated to be higher with the CoreValve across various studies. Analyzing pooled data, Erkapic et al. found in 2012 the odds ratio (OR) to be 5.93 when comparing the CoreValve to the SAPIEN model and Martinez-Selles et al. reported in 2014 the mean rate of new-onset LBBB to be 14.0 % with the SAPIEN prosthesis and 45.2 % with the CoreValve. These results are being supported by longterm follow-up data (Massoullié et al., 2016; Nazif et al., 2014).

PPI is reported by virtually all publications, thus creating a solid foundation for assessing its incidence. Early SAPIEN-results from the randomized Placement of Aortic Transcatheter Valves (PARTNER) trial, that would later on lead to the FDA's approval, showed

a rate of 22.9 % of PPI in Cohort B (Leon et al., 2010) and shortly after, a rate of 20.0 % of PPI in Cohort A (Smith et al., 2011). Results published around the same time regarding the Medtronic CoreValve, namely 16.3 % reported by Petronio et al. in 2010, suggested similar outcomes at first. However, one of the first meta-analyses investigating prosthesis types, alongside concurrent publications (Erkapic et al., 2012), suggested that there was a distinction regarding some outcomes (Jilaihawi, Chakravarty, et al., 2012). They reported the rate of new PPI was 5.9 % in patients treated with the Edwards SAPIEN prosthesis and 24.5 % in patients treated with the Medtronic CoreValve. The SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry showed a need for PPI in 7.0 % (Thomas et al., 2010). Further publications confirmed this trend and a more recent meta-analysis including 41 studies showed a median of 28 % (interquartile range (IQR) 24-35) new PPI after TAVI with the CoreValve and a median of 6 % (IQR 5-7) after TAVI performed with SAPIEN valves (Siontis et al., 2014). Additionally, consecutive results from the UK TAVI registry reinforced those findings (Ludman et al., 2015).

Results for the latest Edwards generation, the SAPIEN 3, vary remarkably between publications, as do the numbers of patients that were included in the studies. Rates of PPI have been shown to be as little as 3.8 %, affecting 2 out of 52 patients, (Wöhrle et al., 2015) and as high as 25.5 %, affecting 13 out of 51 patients, (Murray et al., 2015).

Looking at more investigators, however, puts these findings into perspective. Table 1 lists a selection of publications on patient cohorts treated with the SAPIEN 3 and suggests individual results should be judged in conjunction with further findings.

Table 1

New PPI after TAVI with SAPIEN 3

Study	*N*	new PPI in no.	new PPI in %
Kodali et al., 2016	1661	186	11.2 %
Wöhrle et al., 2016	235	41	17.4 %
Kim et al., 2016	163	32	19.6 %

De Torres-Alba et al., 2016	162	31	19.1 %
Schwerg et al., 2016	131	24	18.3 %
Bocksch et al., 2016	102	14	13.7 %
Gonska et al., 2016	100	14	14.0 %
Kazuno et al., 2016	39	8	20.0 %
Jochheim et al., 2015	100	22	22.0 %
Wöhrle et al., 2015	52	2	3.8 %
Murray et al., 2015	51	13	25.5 %
Tarantini et al., 2015	29	6	20.7 %
Webb et al., 2014	150	20	13.3 %
Binder et al., 2013	15	1	6.7 %
total	2 990	414	13.8 %

Note. The study by Alec Vahanian et al. (2016) was not included in the list above as the investigators excluded all patients with pre-existing conduction abnormalities including right bundle branch block.

1.3.3 Conduction abnormalities – prediction and predictive value

Other than prosthesis type, multiple potential risk factors have been analyzed in order to identify patients at higher risk for developing new onset CA. Depth of implantation has been shown to be associated with an increased risk significantly for new onset LBBB for both the CoreValve and the SAPIEN prosthesis (Aktug et al., 2012; Franzoni et al., 2013; van der Boon et al., 2015). Results concerning the prosthesis size are rather ambiguous as its predictive value has been demonstrated for the 26 mm CoreValve prosthesis (Boerlage-Van Dijk et al., 2014) as well as the 26 mm SAPIEN prosthesis (Houthuizen et al., 2012) but was later not identified with any of the SAPIEN sizes (Nazif et al., 2014).

Despite all distinction, new onset LBBB after the implantation of either prosthesis type resolves quite frequently, percentages ranging from 19.1 % (Boerlage-Van Dijk et al., 2014) to

55.6 % (Aktug et al., 2012) of the cases for the CoreValve and from 25.0 % (Franzoni et al., 2013) to 46.2 % (Aktug et al., 2012) for the SAPIEN device. If persistent, LBBB has been shown to be associated with significantly higher rates of PPI and significantly lower left ventricular ejection fraction during follow-up (Nazif et al., 2014). The predictive value of LBBB for all-cause mortality has been reported to be significant in a non-TAVI population referred for symptom limited nuclear exercise testing (Hesse et al., 2001). Houthuizen et al. (2012) and Schymik et al. (2015) reported it to be an independent predictor for all-cause mortality in a TAVI cohort as well. However, this could not be confirmed by other investigators (Ludman et al., 2015; Nazif et al., 2014; Urena et al., 2014) or when included in a large meta-analysis (Ando & Takagi, 2016). Further investigation is henceforth required.

Amongst those baseline characteristics suspected of increasing the likelihood of PPI, particularly pre-existing RBBB has been shown to be of high predictive value. Pre-existing LBBB, however, is not associated with the need for PPI, regardless of prosthesis type, (Erkapic et al., 2012; Siontis et al., 2014).

Despite the big differences between the CoreValve and the SAPIEN prostheses in terms of new onset CA and CoreValve's predictive value for PPI, mortality does not seem to be dependent on prosthesis type (Ludman et al., 2015; Moretti et al., 2015). This consequently raises the question whether or not PPI affects clinical outcomes in an adverse fashion at all. Comparing patients who had undergone PPI prior to TAVI, after TAVI or not at all with each other, Buellesfeld et al. (2012) found no significant difference in mortality at 30 days or 12 months. Consecutive findings supported those results and were unable to show that PPI was amongst independent predictors for 30-day as well as midterm mortality like acute kidney injury stage 3, increased pro-BNP levels, periprocedural acute myocardial infarction (AMI; Giordana et al., 2014) or aortic regurgitation (AR; Escárcega et al., 2015; Walther et al., 2015). Whether or not PPI affects longterm mortality has also been investigated. Study populations followed up for years and analyzed for correlations between PPI and mortality did not reveal a positive predictive value of any kind (Bagur et al., 2011; Escárcega et al., 2015; Ludman et al., 2015).

Nonetheless and additionally to the general risks of PPI such as infection, perforation and bleeding, PPI was shown to be associated with a higher rate of stroke in the German Aortic Valve Registry (GARY; Ledwoch et al., 2013), and increases length of stay and costs after TAVI as well as after SAVR (Bagur et al., 2011; Chevreul et al., 2013). It is therefore undoubtedly of universal interest to avoid PPI if medically reasonable and achievable.

2 Objectives

Being the third generation of Edwards' balloon-expandable aortic valve prostheses the SAPIEN 3 was designed to improve earlier weaknesses and is now being widely used in clinical routine. As outlined above, avoiding complications such as new onset CA and consecutively the need for PPI is crucial since TAVI is expected to be the treatment of choice for an expanding group of patients. Evaluating precisely who will benefit from TAVI in general and the Edwards SAPIEN 3 prosthesis specifically contributes to better outcomes and improves patient care.

Therefore, this thesis will address the following questions concerning new onset CA and the need for PPI:

- What frequencies of new onset CA can be expected after the implantation of the SAPIEN 3 prosthesis?
- How frequent is the need for PPI after the implantation of the SAPIEN 3 prosthesis?
- Is prosthesis sizing, in particular oversizing, of predictive value for new onset CA or the need for PPI?
- Is implantation depth of predictive value for new onset CA or the need for PPI?
- Are CA at baseline associated with a higher rate of PPI?
- Do the immediate in-hospital clinical outcomes of patients experiencing new onset CA or PPI deviate from patients not experiencing those complications?

3 Technical and Procedural Background

The devices used to generate the data analyzed later on are going to be described hereafter. This section aims to outline the strengths and weaknesses of each step along the process and compare it to potential alternatives.

3.1 Electrocardiogram (ECG)

For depicting the cardiac cycle of the heart's systole and diastole composed of coordinated contractions of the atria and the ventricles, the ECG has always played a crucial role in medicine. Its non-invasive, pain-free and easy-to-use characteristics have guaranteed the ECG an irreplaceable role in examining a patient's heart.

Besides allowing the physician to make statements on the heart's rhythm, it reveals information about the presence and location of diseased areas in the heart. Hence, by judging the patterns of the standard 12-lead ECG one can allocate disturbances of the conduction system quickly. Careful positioning of the electrodes and correct measurement of the waves recorded and printed is therefore vital for evaluation.

Surawicz, Childers, Deal, & Gettes (2009) published criteria for intraventricular conduction disturbances recommended by the Council on Clinical Cardiology of the American Heart Association, the American College of Cardiology, the Heart Rhythm Society, and the International Society for Computerized Electrocardiography.

Due to relevance concerning this thesis, only criteria for diagnosing complete LBBB and RBBB in adults older than 16 years will be summarized in Table 2 according to Surawicz, Childers, Deal, & Gettes (2009):

Table 2

Criteria for Diagnosing Complete LBBB and Complete RBBB

CA	criteria
LBBB	1) QRS greater than or equal to 120 ms
	2) Broad notched or slurred R wave in leads I, aVL, V5, and V6 and an occasional RS pattern in V5 and V6 attributed to displaced transition of QRS complex
	3) Absent q waves in leads I, V5, and V6
RBBB	1) QRS greater than or equal to 120 ms
	2) rsr′, rsR′, or rSR′ in leads V1 or V2. The R′ or r′ deflection is usually wider than the initial R wave. In a minority of patients, a wide and often notched R wave pattern may be seen in lead V1 and/or V2.
	3) S wave of greater duration than R wave or greater than 40 ms in leads I and V6

Note. Adapted from "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" by Surawicz et al., 2009, Circulation, Volume 119, Issue 10, pp. e236-e237, Copyright 2009 American Heart Association, Inc, American College of Cardiology Foundation, and the Heart Rhythm Society. All criteria have to be met for diagnosing complete LBBB and complete RBBB. CA = Conduction Abnormality; LBBB = left bundle branch block; RBBB = right bundle branch block.

3.2 Multislice Computed Tomography (CT)

For the prosthesis size has to be determined ahead of time, accurate and reliable measurements of the aortic annulus need to be provided in advance. Due to the in general elderly patient population TAVI is designed for, comorbidities such as peripheral artery disease (PAD)

might affect the choice of access site. In case of conversion into emergency open heart surgery, proper knowledge of the patient's anatomy is appreciated by all physicians involved.

Alternatives for multislice CT are transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). CT was found to be more accurate than the two-dimensional TEE in determining the actual size of the aortic annulus (Lehmkuhl et al., 2013). Also, a high interobserver and intraobserver agreement is adding value to CT, now being considered the gold standard (Schmidkonz et al., 2014; Schuhbaeck et al., 2014). Besides precision in measurements, encouraging results have also been able to show that paravalvular leakage (PVL) after TAVI may be predicted and reduced when using CT for pre-procedural evaluation (Jilaihawi, Kashif, et al., 2012).

Availability of multislice CT is of no concern when looking at TAVI sites. Its limitations rather lie within radiation exposure and –potentially quite restricting during every day routine– the use of contrast. If the patient is suffering from renal impairment and therefore multislice CT cannot be considered, three-dimensional TEE can deliver equally satisfying results and may be chosen instead (Husser et al., 2013).

3.3 TAVI

Delivering the valve to its predestined position as well as the deployment of the prosthetic heart valve is performed individually and depends on model and access site chosen.

3.3.1 TAVI procedure

The implantation of a prosthetic heart valve demands many decisions to be made, beginning with the location of the procedure (section 3.3.1.1), type of anesthesia (section 3.3.1.2), access site (section 3.3.1.3), delivery (section 3.3.1.4) and choices associated with prosthesis type (section 3.3.2).

3.3.1.1 Location

TAVI has been designed to serve as an alternative to standard medical treatment for AS and has been shown to be of equal quality compared to SAVR (Smith et al., 2011). This background is reflected by the debate about where to perform the procedure: in the catheterization laboratory under local anesthesia and conscious sedation (LACS) or in a hybrid operating room under general anesthesia (GA).

The ACCF/ AATS/ SCAI/ STS Expert Consensus Document (Holmes et al., 2012) suggested the appropriate room for TAVI contain imaging systems, devices providing sufficient anesthesia, catheterization material, and enough space to hold highly trained staff performing the procedure. Both can be found in either catheterization laboratories or hybrid operating rooms, performing comparably (Babaliaros et al., 2014).

3.3.1.2 Anesthesia

Posing an advantage over SAVR, GA is not always required for the TAVI procedure; LACS without ventilator dependency is possible and commonly used. Multiple studies have shown comparable results in term of 30-day mortality (Fröhlich et al., 2014), one-year mortality (Bergmann et al., 2011), as well as neurocognitive outcomes (Mayr et al., 2015). However, findings concerning length of stay and length of procedure show significantly shorter durations for LACS (Attizzani et al., 2015; Goren et al., 2015). Despite conversion from LACS to GA is necessary infrequently (Fröhlich et al., 2014), and conversion into emergency open heart surgery has been reported to be as low as 1.3 % in the GARY (Walther et al., 2015), GA might affect outcomes positively in those emergency cases (Tam et al., 2015).

3.3.1.3 Access site

In the first human case performed by Cribier et al. in 2002, the femoral vein was accessed and the native valve was reached by septal penetration. Additionally to causing a defect to the septum, venous walls are less resilient to mechanical manipulation; hence arterial vessels have become the most commonly accessed vessels for the TAVI procedure (Walther et al., 2015). In case conventional access sites appear to be non-suitable with some patients due to severe calcification or tremendously tortuous arteries, multiple possibilities have been

evaluated. Results regarding mortality associated with the transapical approach (TA), at the time of recruitment being the most commonly used alternative, have been reported to be both worse than as well as equal to the femoral approach. Higher 30-day mortality rates have been shown, though the TA had been performed in higher risk patients (Thomas et al., 2010). Other investigators were unable to demonstrate that TA was an independent predictor for all-cause mortality (Walther et al., 2015) and TA was not associated with higher 30-day mortality rates or poorer longterm outcomes if groups showed comparable baseline characteristics (Schymik, Wurth et al., 2014).

Even though used less frequently, the subclavian approach and the radial approach have both been shown to result in comparable outcomes. Outcomes for those access sites proved to be similar (Ciuca et al., 2015; Petronio et al., 2012). Though generally being of a smaller diameter, the radial artery has been reported to be a safe access route for percutaneous coronary intervention (PCI; Allende et al., 2014, 2015; Joyalet al., 2012).

In patients showing very unfavorable anatomy or comorbidities not allowing any of the above mentioned to appear safe, several case reports on rarely considered access sites have been published. Experience grows and feasibility has been demonstrated for the direct aortic access (Bapat et al., 2012; Latsio et al., 2010). Additionally, successful valve implantation has been reported for the axillary access (Cioni et al., 2011), the transcarotid approach, under GA (Modine et al., 2014) and as well as under local anesthesia (Rajagopal et al., 2014), the brachiocephalic access route (Philipsen et al., 2015), and the transcaval access (Ott et al., 2015).

3.3.1.4 Delivery

Whilst guide wires, pigtail catheters, and pacer wires used during TAVI are of rather small diameters ranging around 4–6 French (Fr), aortic valve prostheses need to be delivered by larger devices. Most arterial access approaches are designed to match an 18 Fr sheath while transapical routes are generally performed with larger sizes.

The latest generation of Edwards balloon-expandable valves, the SAPIEN 3, requires a 14 Fr introducer sheath for the small and medium sized valves and a 16 Fr for the larger valve when the TF is chosen. Thus, vessels of 5.0 mm and 5.5 mm diameters can be accessed. For the TA 18 Fr and 21 Fr sheaths, respectively, are available. (Edwards Lifesciences Corporation, 2016a)

Medtronic Inc. (2016) as well has reduced the size of its delivery system from an 18 Fr for the CoreValve to 14 Fr for its EvolutR. The LotusValve by Boston Scientific comes with an 18 Fr introducer sheath for the 23 mm prosthesis and with 20 Fr sheath for the larger sizes (Meredith et al., 2014). Symetis' Acurate is compatible with an 18 Fr sheath for all three sizes advancing through the TF (SYMETIS, 2016) and uses a sheathless delivery system for the TA comparing to a 28 Fr diameter (Kempfert et al., 2012). Specifically designed for the TA, the JenaValve uses a 32 Fr sheath (Treede et al., 2012).

In general a pacing electrode is advanced to the right ventricle through a central venous access site, even though left ventricular pacing has been described (Guérios et al., 2013). Ahead of deploying the prosthesis, the native valve is pre-dilated under rapid ventricular pacing to facilitate positioning of the prosthesis. This step of TAVI can contribute to the risk for several complications seen in study populations such as stroke and aortic annulus rupture, and causes transient circulatory impairment due to functional cardiac arrest during rapid pacing (Selle et al., 2014). Hence investigators looked into feasibility of TAVI without pre-dilation and were able to prove its safety and demonstrate good outcomes (Conradi et al., 2015; Grube et al., 2011; Möllmann et al., 2014; Witzke et al., 2009).

3.3.2 Prosthesis types

Devices vary in shape and size, depending on what features specifically have been valued the most.

The SAPIEN XT (see Figure 1.1) is composed of a cobalt chromium alloy frame and three leaflets made from bovine pericardial tissue. When compared to its predecessor, the SAPIEN 3 (see Figure 1.2), now four instead of formerly two rows of cells create greater radial strength and a polyethylene terephthalate outer skirt has been added to the lower edge of the prosthesis to reduce PVL. (Edwards Lifesciences Corporation, 2016)

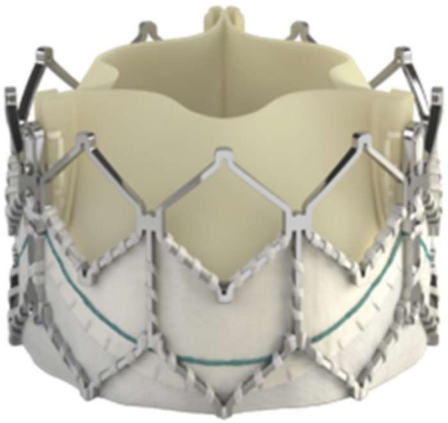


Figure 1.1. The Edwards SAPIEN XT™ Valve. Reprinted from "Edwards SAPIEN XT Valve / Edwards Ascendra + System" by Europa Digital & Publishing, 2014, n.d., Retrieved November 13 2016, from http://www.pcrdevices.com/Valves/Products-FINDER/Edwards-SAPIEN-XT-Valve-Edwards-Ascendra-System, Copyright 2016 by Edwards Lifesciences Corporation. Reprinted with permission.
Note. The predecessor of the SAPIEN 3 is made of a frame of two rows of cobalt-chromium cells and bovine pericardial tissue. (Edwards Lifesciences Corporation, 2016b)

This study looked at the clinical performance of the SAPIEN 3 prosthesis. Its specific features – as described above – are depicted in Figure 1.2.

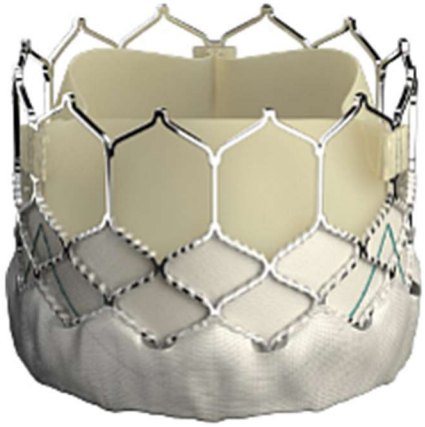


Figure 1.2. The Edwards SAPIEN 3™ Valve. Reprinted from "Transcatheter aortic valve implantation - update and evidence" by Van Linden et al., 2015, Minimally Invasive Therapy and Allied Technologies, Volume 24, Issue 5, p. 256. Copyright 2016 by Edwards Lifesciences Corporation. Reprinted with permission.
Note. Its cobalt-chromium frame is now made out of four rows of cells and it is additionally equipped with an outer skirt out of polyethylene terephthalate to reduce paravalvular leakage. (Edwards Lifesciences Corporation, 2016a)

It comes in a 23 mm, a 26 mm, and a 29 mm size and is designed for annuli of 18-22 mm, 21-25 mm, and 24-28 mm, respectively.

Delivery systems have evolved and the S3 uses the eSheath Introducer Set for the TF and the larger Certitude Sheath for TA. Despite belonging to the balloon-expandable valves, rapid pacing during implantation is – contrary to its predecessors – not necessary.

The latest model by Edwards Lifesciences is the SAPIEN 3 ultra, an updated version of the SAPIEN 3. It has an increased outer-skirt height, which is made out of textured PET material. It comes in three sizes, 20mm, 23mm, and 26mm, now offering a smaller option. For appearance see Figure 1.3.

Figure 1.3. The Edwards SAPIEN 3 ultra™ Valve. Reprinted from "Newsroom - Image gallery" by Edwards Lifesciences, Retrieved March 5th, 2020, from https://edwardsprod.blob.core.windows.net/media/Default/about%20us/media%20gallery/sapien3-ultra-large.png by Edwards Lifesciences Corporation. Reprinted with permission.

Compared to Medtronic's self-expanding devices, especially prosthesis frame height distinguishes both designs (see Figure 2). The 26 mm S3 valve is 20 mm tall when fully deployed compared to Medtronic's second generation valve EvolutR measuring 45 mm, which is thus saving 10 % of height over the CoreValve.

Figure 2. The CoreValve by Medtronic Inc. Reprinted from "Media Kits" by Medtronic, n.d., Retrieved March 2nd 2020, from http://media.corporate-ir.net/media_files/IROL/25/251324/Images/CoreValve-TAVR-System.jpg. Copyright 2015 by Medtronic. Reprinted with permission.

Note. The nitinol frame allows a self-expanding valve design. The frame height is distinctly taller than the previously described balloon-expandable Edwards valves. (Medtronic Inc., 2015)

Self-expandable valves including the CoreValve and EvolutR, the JenaValve, the Accurate TA and Acurate neo/TF, as well as the Lotus valve all are composed of a nitinol frame. This metal has been designed to be rather flexible when cold and to become rigid at body temperature. Hence, a nitinol frame allows manufacturers to develop repositionable valves such as JenaValve, the Lotus, the EvolutR, and the new self-expandable Edwards CENTERA.

4 Methods

Written consent for collecting data and analyzation of collected data had been obtained by all patients upon arrival. Data were analyzed retrospectively and pseudonyms were used to protect patients' privacy. No further diagnostic or therapeutic procedures were performed, hence, no specific ethics vote had to be issued.

4.1 Study Population

In order to depict a representative study population, 244 consecutive patients were treated with the SAPIEN 3 heart valve at the Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum München (DHM). Indication for TAVI was issued or – in case of referred patients – reviewed by experienced cardiologists at the DHM. The patients' written informed consent was obtained in every case

Ensuring optimal spatial conditions for procedure techniques and physicians, TAVI was performed in a hybrid operation suite. It had been left to the discretion of the physician in charge to select GA or LACS on a case-to-case basis, while the TF had been chosen in all cases to provide solid data for future analysis of vascular complications.

Of the initial cohort of 244 patients, 36 patients were excluded to judge new PPI solely related to new aortic valves implanted with TAVI. Any pre-existing pacemaker (n = 23), degenerated biologic prostheses (n = 8), and a bicuspid native valve (n = 5) were defined as exclusion criteria leaving 208 patients for analysis. Next, all patients with complete bundle branch blocks at baseline (n = 24) were excluded. Those 184 patients were investigated for new onset or worsened CA or PPI. The detailed analysis plan is depicted in Figure 3.

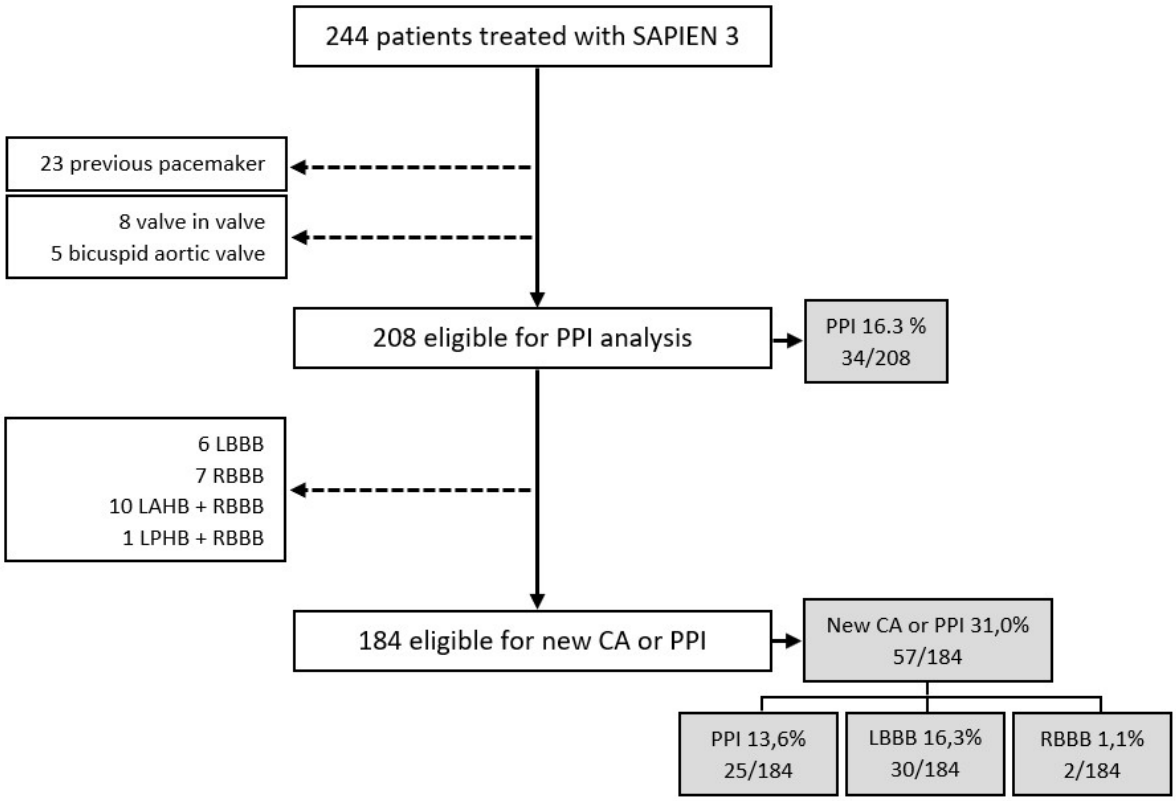


Figure 3. Study Flow. Reprinted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 246. Copyright 2016 by Elsevier. Reprinted with permission.

Note. Dotted arrows pointing to the left indicate at what time patients were excluded. Exclusion criteria and number of patients affected are listed inside those same boxes. Grey boxes show study populations of which X % met criteria for primary endpoints. CA = conduction abnormalities, LAHB = left anterior hemi block, LBBB = left bundle branch block, LPHB = left posterior hemi block, PPI = permanent pacemaker implantation, RBBB = right bundle branch block.

4.2 Measurement of Aortic Stenosis

Measurements for detailed assessment of AS were obtained by either TTE or TEE. Examinations were performed during the same or prior visits when indications for TAVI had been evaluated. Several parameters and equations were used for classification of the severity of aortic stenosis (see Figure 4).

$$\textbf{Aortic jet velocity } [m/s] = \textbf{highest velocity measured with CWD}$$

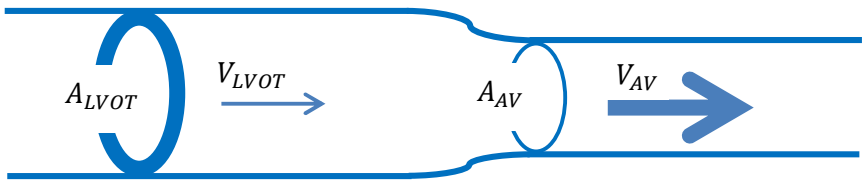
$$\textbf{Mean gradient } [mmHg] = \frac{\sum 4v^2}{N}$$

$$AVA\ [cm^2] = \frac{CSA_{LVOT} \times VTI_{LVOT}}{VTI_{AV}}$$

Figure 4. Parameters for Classification of Aortic Stenosis and Their Equations. Adapted from "Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice" by Baumgartner et al., 2009, European Journal of Echocardiography, Volume 10, Issue 1, p. 4.

Note. AV = aortic valve; AVA = aortic valve area; CWD = continuous wave Doppler; CSA = cross sectional area; LVOT = left ventricular outflow tract; N = number of instantaneous measurements; v = velocity; VTI = velocity time integral.

The aortic valve area was calculated based on the continuity equation as shown in Figure 5 below.



$$A_{AV} \times V_{AV} = A_{LVOT} \times V_{LVOT}$$

Figure 5. Continuity Equation.

Note. Fluids running through any hollow object experience an increase in velocity if the diameter decreases. Therefore blood from the left ventricle ejected via the LVOT through the AV accelerates. The smaller the diameter of the AV is, the greater the acceleration is. A = area; AV = aortic valve; LVOT = left ventricular outflow tract; V = velocity.

Severity of AS was classified according to recommendations by the European Society of Cardiology and the American Heart Association/ American College of Cardiology Guidelines (Baumgartner et al., 2009). Patients were considered suffering from severe AS once they met at least one out of the three criteria "Jet velocity", "Mean gradient", or "Aortic Valve Area" as listed in Table 3.

Table 3

Grading of Severity of AS

Parameter	Mild	Moderate	Severe
Jet velocity [$^{m}/_{s}$]	2.6–2.9	3.0–4.0	> 4.0
Mean gradient [*mmHg*]	< 20^{a} {< 30^{b}}	$20-40^{a}$ {$30-50^{b}$}	> 40^{a} {> 50^{b}}
AVA [cm^2]	> 1.5	1.0–1.5	< 1.0

Note. Adapted from "Echocardiographic assessment of valve stenosis: EAE / ASE recommendations for clinical practice" by Baumgartner et al., 2009, European Journal of Echocardiography, Volume 10, Issue 1, p. 11, Copyright 2008 H. Baumgartner. AVA = aortic valve area.

^{a} = AHA/ACC Guidelines; ^{b} = ESC Guidelines.

4.3 Measurements Derived from Multislice CT

Choice of prosthesis size was based on measurements of the native valve derived from a multislice CT in multiple plane reconstruction according to the expert consensus document of the Society of Cardiovascular Computed Tomography (Achenbach et al., 2012). Appraisal of images was technically supported by FDA approved and CE labeled software (OsiriX MD 3.9.4, Pixmeo, Switzerland).

The effective diameter d_{eff} of the aortic annulus was calculated according to Husser, Pellegrini, et al. (2016) using the minimum and maximum diameter measured on the generated images

$$d_{eff} = \frac{diameter_{min} + diameter_{max}}{2} \quad (1)$$

Sizing was judged by comparing prosthesis perimeter and area to the perimeter and area of the virtual aortic annulus.

As the aortic annulus is commonly of a somewhat oval shape, its eccentricity was calculated as the eccentricity index *e* with *e = 0* theoretically indicating a perfectly round annulus

$$e = 1 - \frac{diameter_{min}}{diameter_{max}} \quad (2)$$

(Husser, Pellegrini, et al., 2016)

Valvular calcification was visually graded at the height of the aortic cusps, annulus, and left ventricular outflow tract (LVOT) as “none”, “mild”, “moderate”, and “severe”.

Depth of implantation was determined according to Husser, Pellegrini, et al. (2016) by measuring the position of the implanted prosthesis in relation to the aortic annulus. Equation 3 was used to generate values in %. For examples, see Figure 6.

$$depth_{implantation} = \frac{frame\ height\ below\ aortic\ annulus}{entire\ prosthesis\ frame\ height} \times 100\ \% \quad (3)$$

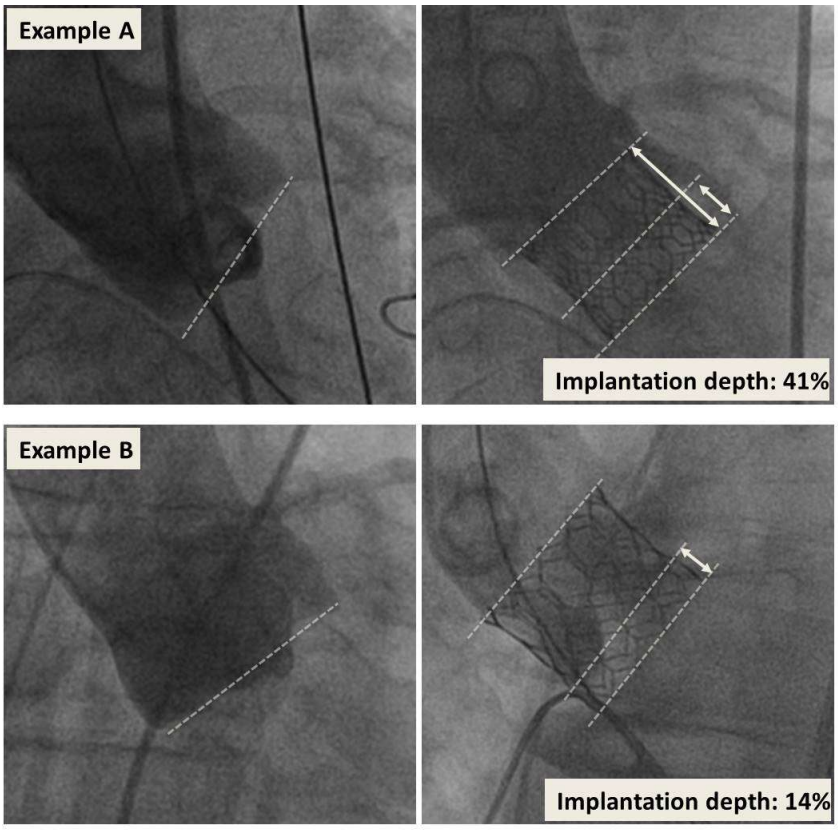


Figure 6. Implantation Depth of the SAPIEN 3. Reprinted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 248. Copyright 2016 by Elsevier. Reprinted with permission.

Note. The left image of example A and B each show the native aortic annulus without prosthesis. The dotted white line represents its exact height by intersecting the sinus of Valsalva. Example A shows a deep implanted valve. 41 % of the prosthesis frame was below the aortic annulus. Example B shows a high implanted valve presenting with 14 % of the frame height being below the aortic annulus. Both examples show the valve from an orthogonal view.

4.4 Prosthesis Sizing

Guided by manufacturer's recommendations (see Table 4), choosing the appropriate size of the prosthesis was ultimately left to the discretion of the physicians in charge. Deviations from or accordance with suggestions by Edwards Lifesciences were labelled "undersized", "within range" and "oversized".

Table 4

SAPIEN 3 Nominal Prosthesis Dimensions and Sizing Recommendations by the Manufacturer

Prosthesis dimensions	**23 mm**	**26 mm**	**29 mm**
Frame height (mm)	18.00	20.00	22.50
Outer diameter (mm)	22.75	25.71	28.75
Outer perimeter (mm)	71.47	80.74	90.32
Outer area (cm^2)	4.06	5.19	6.49
Sizing recommendations			
Area (range, cm^2)	3.38-4.30	4.30-5.46	5.40-6.80
Area-derived diameter (range, mm)	20.7-23.4	23.4-26.4	26.2-29.4

Note. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 247. Copyright 2016 by Elsevier. Reprinted with permission.

Extent of oversizing was reported in percentage and calculated according to Equation 4 for area, perimeter and effective diameter corresponding as introduced by Husser, Pellegrini, et al. (2016)

$$oversizing = \frac{nominal\ prosthesis\ dimension - patient\ anatomy}{patient\ anatomy} \times 100\ \% \qquad (4)$$

Figure 7 shows an example of the calculated degree of oversizing of a 26 mm SAPIEN 3 prosthesis.

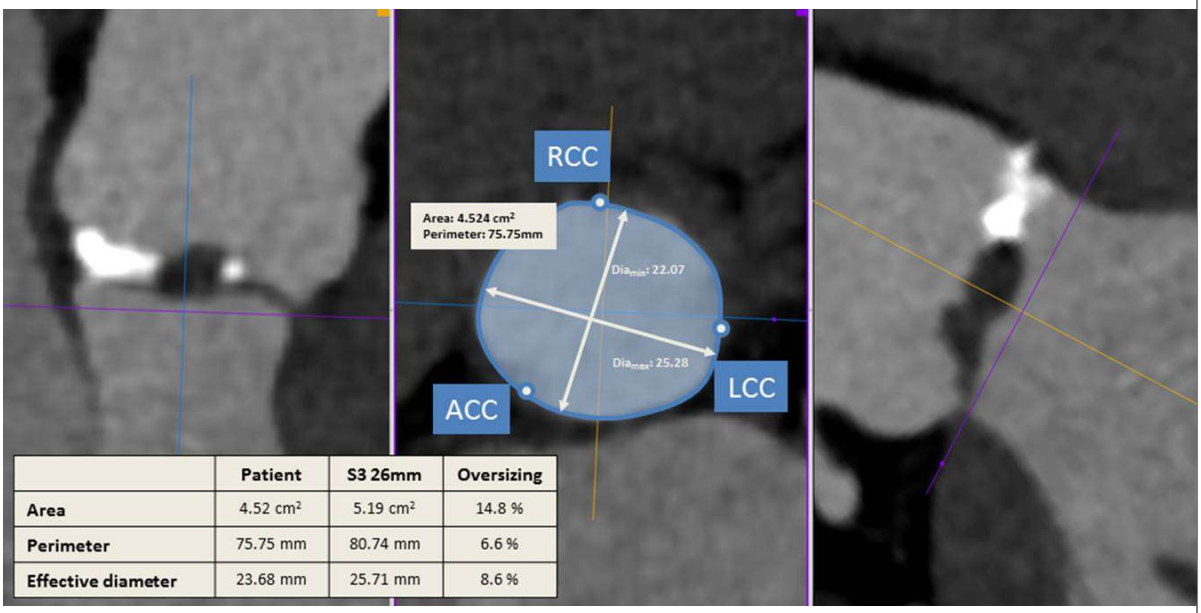


Figure 7. Multislice CT Analysis and Calculation of Oversizing for a 26 mm TAVI. From "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 247. Copyright 2016 by Elsevier. Reprinted with permission.

Note. Degree of prosthesis oversizing was calculated according to Equation 4. Hence, 14.8 % oversizing was computed for this patient-prosthesis match. ACC = non coronary cusp; LCC = left coronary cusp; RCC = right coronary cusp.

4.5 Baseline Characteristics

LVEF Functional capacity of the heart was calculated based on data obtained by echocardiography, either performing TTE or TEE. Left ventricle dimensions were measured in apical four- and two-chamber views and volumes of end-diastole and end-systole were computed using Simpson's method of disks (Oh et al., 2006). Ultimately, LVEF was recorded as percentage values of end-diastolic volume.

PAD PAD was considered to be present if symptomatic patients had been diagnosed, i.e. consistent with Fontaine's classification. Diagnosis in absence of symptoms was issued based on images showing corresponding morphology (occluded walls, calcified arterial walls, with or without collaterals) or previous interventions.

PCI Any previous stent implantation was recorded as PCI. Information was collected from previous discharge letters, referral letters, and oral case history taken on admittance.

COPD Chronic obstructive pulmonary disease [COPD] was defined as long-term application of bronchodilators or steroids for pulmonary disease.

NYHA classification The first set of criteria for diagnosing and staging of heart disease was published by the New York Heart Association (NYHA) in 1928. Assuming that cardiac disease is present, patients were assigned to one out of four stages based on symptoms and resulting limitation according to Table 5.

Table 5

NYHA Classification

Symptoms and limitations	**NYHA Class**
Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	I
Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	II
Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	III
Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	IV

Note. Adapted from "Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels" by Dolgin & New York Heart Association. Criteria Committee, 1994, 9th edition, editor M. Dolgin, page 253-256, Little, Brown, Boston.

Logistic EuroSCORE Risk scores allow the approximate comparison between individuals based on one computed parameter. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was introduced in 1999 to meet the need of pre-operative assessment of patients about to undergo cardiac surgery (Roques et al., 1999). Having been designed initially to calculate a percentage value indicating the expected risk of death, it has been replaced by the EuroSCORE II for this purpose. As the logistic EuroSCORE (LES) tends to overestimate mortality, it is now used as a tool to compare baseline characteristics which is broadly available and hence of great importance for international clinical research.

Patient and procedure related risk factors are entered in the logistic regression equation and predicted mortality is then calculated using Equation 5. For details see Supplemental Table 1.

$$logistic\ EuroSCORE = \frac{e^{(\beta_o + \sum \beta_i X_i)}}{1 + e^{(\beta_o + \sum \beta_i X_i)}} \quad (5)$$

Note. From "The logistic EuroSCORE" by Roques, Michel, Goldstone, & Nashef, 2003, European Heart Journal, Volume 24, Issue 9, p. 881. Copyright 2003 by The European Society of Cardiology.

The LES can easily be calculated online on free websites and can be integrated into electronic patient data management systems. Figure 8 shows an example of a user-friendly online mask.

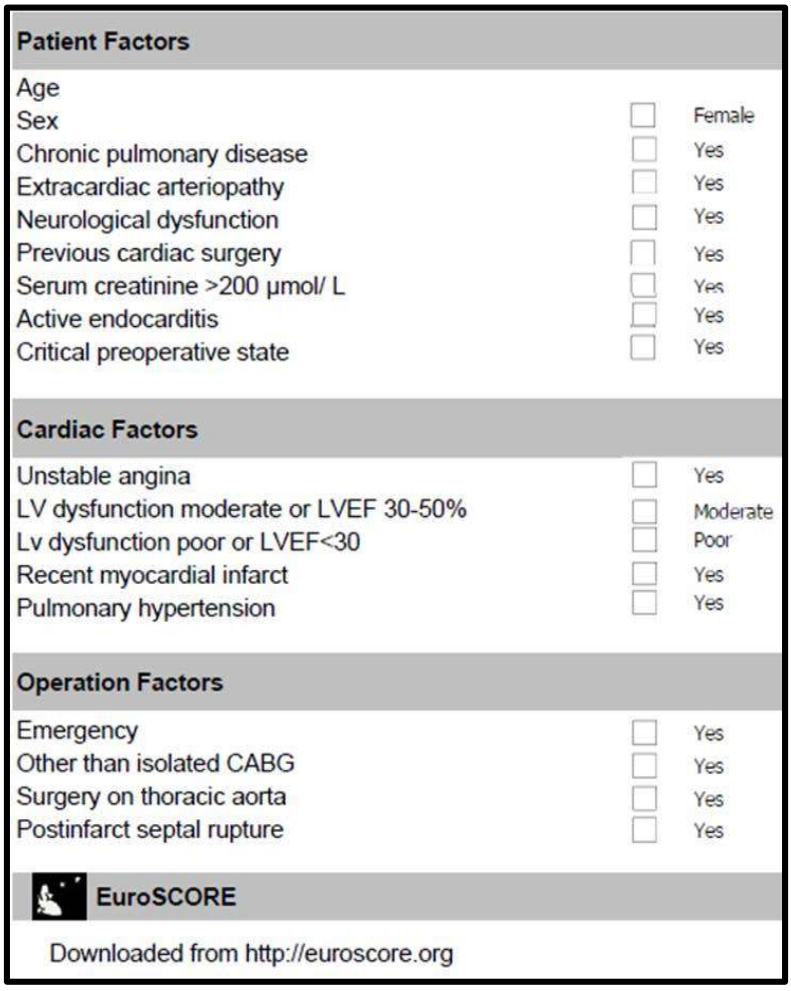


Figure 8. Example of a Logistic EuroSCORE Calculator. Adapted from EuroSCORE Website by Goldstone, n.d., http://euroscore.org/calculators.htm, retrieved December 14, 2016.

Note. The LES was computed by entering the patient's risk factors into Equation 5. Each risk factor is represented as a variable X_i and is assigned a coefficientβ_i. The constant β_o of the logistic regression model is - 4.789594. (Roques et al., 2003). CABG = coronary artery bypass graft; LV = left ventricle; LVEF = left ventricular ejection fraction.

4.6 ECG and Conduction Abnormalities

Data on patients' electrophysiology was generated by a standard 12-lead ECG recorded on admission and after TAVI prior to discharge. Two physicians evaluating the ECGs assessed rhythm, heart rate in beats per minute, PQ and QRS intervals in ms, atrioventricular conduction disturbances, and intraventricular conduction disturbances. Consensus was reached for all cases that were of question initially. Rhythm as well as intraventricular conduction was labelled

"pacemaker" if patients presented with a pre-existing pacemaker for its stimulation might influence and change ECG patterns.

Physicians evaluating ECGs were blinded to clinical data as recommended by the AHA/ACCF/HRS (Surawicz et al., 2009).

4.7 Definition of Study End Points

PPI prior to discharge was defined as primary study end point for the study population without pre-existing pacemaker ($N = 208$). New-onset or worsened CA or PPI were defined as primary study end point for patients neither having a pacemaker nor bundle branch blocks at baseline ($n = 184$).

Indication for PPI was based on the judgement of the physicians in charge and was reported for every case (see Figure 10). If baseline ECG showed neither complete LBBB nor RBBB, detecting any of those in discharge ECG was reported as new-onset or worsened CA according to the criteria described above (Surawicz et al., 2009).

Secondary study end points were in-hospital outcome, device success, and procedural complications and were defined according to the Valve Academic Research Consortium–2 (VARC2) criteria (Kappetein et al., 2012).

In-hospital outcome Amongst others, procedural mortality, myocardial infarction and stroke, bleeding and vascular complications, and acute kidney injury were investigated.

Procedural complications Conversion to open surgery, unplanned use of cardiopulmonary bypass, coronary obstruction, vascular access site complications, or cardiac tamponade were among the criteria that were referred to as "procedural complications".

Device success Proper valve function is the basis for good results and an improvement of symptoms. It has therefore been reported and can be compared to results published by other investigators. In order to be considered a successful implantation the following criteria had to be met:

1) Absence of periprocedural mortality AND
2) Correct positioning AND
3) Intended performance of the valve.

(Husser, Pellegrini, et al., 2016)

Not achieving at least one of the criteria above was considered valve dysfunction.

4.8 Statistical Analysis

Continuous variables are presented as mean ± standard deviation for variables following normal distribution or as median (IQR = 25^{th}–75^{th} percentile) for variables not following normal distribution.

If the variables of the samples were expected to follow a normal distribution and samples were independent from one another, variables were compared using the unpaired Student *t*-test. If, however, variables were not following normal distribution the Mann-Whitney-U test was applied to test the null-hypothesis**.**

Discrete or categorical variables are presented as absolute numbers and percentages. The Chi-squared test was used for the comparison of independent variables that were expected to follow a normal distribution. Fisher's exact test was used when the Chi-squared test was not appropriate, i.e. variables counted less than five and/ or did not follow a normal distribution.

All results were tested for statistical significance based on a two-sided alpha level of .05.

Variables showing a *p*-value <.1 in univariate analysis or being known to influence the primary end points were included in multivariable logistic regression models in order to identify independent predictors for new-onset or worsened CA and PPI. Neither oversizing by area nor implantation depth were found to meet those criteria in terms of *p*-value but were still included in multivariate analysis. Results were presented as OR with 95 % confidence intervals (CI).

All data were processed and statistical analyses were performed using IBM SPSS version 22 (SPSS Inc, Chicago, IL, USA).

(Husser, Pellegrini, et al., 2016)

5 Results

5.1 Baseline Characteristics

This study analyzed 208 patients treated with the SAPIEN 3 valve at the German Heart Center Munich. Baseline characteristics are displayed in Table 6.

Mean age in this study population was 81 ± 6 years with no significant difference between patients who were going to receive PPI and those who were not. Yet, analyzing patients with new-onset or worsened CA and new PPI and those without, age appeared to differ significantly, (82 ± 6 vs. 80 ± 6; $p = .01$). Gender was evenly distributed, 45.1 % of all patients were female. The LES was 16 ± 12 % for all 208 patients and 19 ± 15 % in patients undergoing PPI compared to 15 ± 12 % in patients without new PPI. These findings were not of statistical significance.

Coronary artery disease (CAD) was present in 65.9 % of all patients, 38.9 % had had a coronary intervention before, and 5.8 % had undergone surgery for coronary bypass. Symptoms recorded according to the NYHA classification were grade III or IV more often in patients with new PPI (79.4 % vs. 62.4 %; $p = .053$) while other comorbidities such as Diabetes or low ejection fraction were rather evenly distributed.

Table 6

Baseline Characteristics

Variable	All patients	New Permanent Pacemaker			PPI and new or worsened CA		
	(*N*=208)	Yes (*n*=34)	No (*n*=174)	*p*	Yes (*n*=57)	No (*n*=127)	*p*
Age (years)	81 ± 6	82 ± 6	81 ± 6	0.194	82 ± 6	80 ± 6	0.012

Female	94 (45)	11 (32)	83 (48)	0.100	28 (49)	59 (47)	0.738
Logistic EuroSCORE, %	16 ± 12	19 ± 15	15 ± 12	0.106	17 ± 13	14 ± 10	0.065
NYHA functional class III/IV	135 (65)	27 (79)	108 (62)	0.053	41 (72)	76 (60)	0.115
COPD	27 (13)	8 (24)	19 (11)	0.045	8 (14)	14 (11)	0.560
PAD	28 (14)	4 (12)	24 (14)	0.999	8 (14)	16 (13)	0.789
Extracardiac arteriopathy	58 (28)	9 (27)	49 (28)	0.841	16 (28)	33 (26)	0.767
GFR, ml/min	54 ± 37	49 ± 29	55 ± 39	0.409	49 ± 27	58 ± 43	0.162
Coronary artery disease	137 (66)	23 (68)	114 (66)	0.811	41 (72)	83 (65)	0.379
Myocardial infarction	19 (9)	3 (9)	16 (9)	0.999	5 (9)	13 (10)	0.757
PCI	81 (39)	15 (44)	66 (38)	0.499	22 (39)	52 (41)	0.764
CABG	12 (6)	3 (9)	9 (5)	0.419	4 (7)	6 (5)	0.503
Diabetes mellitus	59 (28)	11 (32)	48 (28)	0.573	14 (25)	35 (28)	0.671
Stroke	20 (10)	1 (3)	19 (11)	0.209	4 (7)	14 (11)	0.398
LVEF <35%	21 (10)	4 (12)	17 (10)	0.756	7 (12)	10 (8)	0.340

Note. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 249. Copyright 2016 by Elsevier. Reprinted with permission. CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; GFR = glomerular filtration rate; LES = Logistic EuroSCORE; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PAD = peripheral artery disease; PCI = previous coronary intervention; NYHA = New York Heart Association.

TAVI was performed under conscious sedation in 81 patients (38.9 %). The 23 mm size was chosen for the majority of procedures (43.8 %), followed by the 26 mm size (36.5 %), and the 29 mm size (18.3 %).

Device success was achieved in 203 (97.6 %) patients. One patient required a second valve (0.5 %), and PVL ≥ 2 was observed in a total of four patients (2.0 %; one receiving new PPI, three not receiving new PPI). Device success did not differ between groups (see Table 7).

Patients stayed a median of 6 ± 4 days in hospital with no significant difference between groups being observed. Survival at discharge was 100 %.

Table 7

Procedural Characteristics and Outcome

Variable	All patients	New Permanent Pacemaker		*p*	PPI and new or worsened CA		*p*
	(*N*=208)	Yes (*n*=34)	No (*n*=174)		Yes (*n*=57)	No (*n*=127)	
23 mm (n, %)	91 (44)	12 (35)	79 (45)		24 (42)	60 (47)	
26 mm (n, %)	79 (38)	12 (35)	67 (39)		21 (37)	48 (38)	
29 mm (n, %)	38 (18)	10 (29)	28 (16)		12 (21)	19 (15)	
LACS (n, %)	81 (39)	17 (50)	64 (37)	0.148	29 (51)	44 (35)	0.037
Procedural time (min)	61 ± 24	61 ± 21	61 ± 24	0.929	61 ± 27	61 ± 23	0.967
Fluoroscopy time (min)	16 ± 16	13 ± 5	16 ± 17	0.353	13 ± 4	16 ± 15	0.186
Contrast (ml)	116 ± 67	92 ± 27	120 ± 71	0.027	109 ± 63	123 ± 71	0.205
Post-dilation (n, %)	72 (35)	11 (32)	61 (35)	0.762	19 (33)	48 (38)	0.561
Multiple valves (n, %)	1 (1)	0 (0)	1 (1)	0.999	0 (0)	1 (1)	0.999
PVL ≥ 2 (n, %)	4 (2)	1 (3)	3 (2)	0.513	1 (2)	3 (2)	0.999
Device Success (n, %)	203 (98)	33 (97)	170 (98)	0.999	56 (98)	123 (97)	0.999
Length of stay (days)	6 ± 4	7 ± 3	6 ± 4	0.118	7 ± 3	6 ± 4	0.313
Intra hospital death (n, %)	0 (0)	0 (0)	0 (0)	—	0 (0)	0 (0)	—

30-day mortality	1 (0.5)	1 (3)	0 (0)	0.163	0 (0)	0 (0)	—

Note. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 250. Copyright 2016 by Elsevier. Reprinted with permission. LACS = local anesthesia and conscious sedation; PVL = paravalvular leakage.

5.2 Influences of Anatomy on new CA or PPI after TAVI

The anatomy of the aortic annulus was comparable among all groups based on the diameter and the eccentricity index *e*. The extent of oversizing recorded in % did not differ remarkably between patients with and without new PPI. Table 8 provides results for extent of oversizing. Data is available for 206 patients for two patients did not undergo multislice CT prior to TAVI due to renal failure.

Native aortic valve dimensions and oversizing did not differ remarkably between groups. Yet, the maximal diameter (p = .046) was larger in patients receiving new PPI.

Table 8

Multislice CT Measurements of the Aortic Annulus

Variable	All patients	New Permanent Pacemaker		*p*	PPI and new or worsened CA		*p*
	(*N*=206)	Yes (*n*=34)	No (*n*=172)		Yes (*n*=57)	No (*n*=126)	
Minimal diameter (mm)	21.03 ± 2.35	21.61 ± 2.33	20.91 ± 2.34	0.116	20.98 ± 2.52	20.99 ± 2.25	0.983
Maximal diameter (mm)	26.94 ± 2.70	27.78 ± 2.90	26.77 ± 2.64	0.046	26.89 ± 2.69	26.84 ± 2.68	0.906
Eccentricity Index	0.22 ± 0.06	0.22 ± 0.07	0.22 ± 0.06	0.799	0.22 ± 0.06	0.22 ± 0.06	0.727
Perimeter (mm)	77.06 ± 7.43	79.10 ± 7.51	76.66 ± 7.37	0.080	76.97 ± 7.68	76.85 ± 7.34	0.920

% Oversizing	2 [−1 to 5]	1 [0 to 3]	2 [−2 to 5]	0.495	2 [0 to 6]	2 [−2 to 5]	0.209
Area (cm^2)	4.62 ± 0.91	4.87 ± 0.91	4.57 ± 0.91	0.083	4.61 ± 0.95	4.60 ± 0.90	0.932
% Oversizing	7 [0 to 14]	6 [2 to 11]	8 [−1 to 15]	0.566	6 [2 to 15]	7 [−1 to 19]	0.177

Note. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 250. Copyright 2016 by Elsevier. Reprinted with permission.

Section 6.3 will further investigate the significance of aortic valve calcification (AVC) since it has been reported to influence outcomes after TAVI. This study, however, did not show an impact of AVC on the primary end points. Calcification did not differ between groups, neither at the height of the cusps, nor the annulus nor the LVOT, as shown in Table 9.

Table 9

Multislice CT Measurements of Degree of Calcification

moderate/severe Calcification at	**All patients**	**New Permanent Pacemaker**		***p***	**PPI and new or worsened CA**		***p***
	(*N*=206)	Yes (*n*=34)	No (*n*=172)		Yes (*n*=57)	No (*n*=126)	
Cusps (n, %)	148 (72)	24 (71)	124 (72)	0.859	30 (68)	93 (74)	0.452
Annulus (n, %)	21 (10)	3 (9)	18 (11)	0.999	9 (16)	12 (10)	0.218
LVOT (n, %)	12 (6)	2 (6)	10 (6)	0.999	5 (9)	7 (6)	0.521

Note. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p 250. Copyright 2016 by Elsevier. Reprinted with permission. LVOT = left ventricular outflow tract.

5.3 Baseline ECG and new CA or PPI after TAVI

Several categories in patients' baseline ECGs revealed differences between patients who were going to receive new PPI and those who were not. Figures 9.1 and 9.2 show frequencies of conduction abnormalities before TAVI and at discharge.

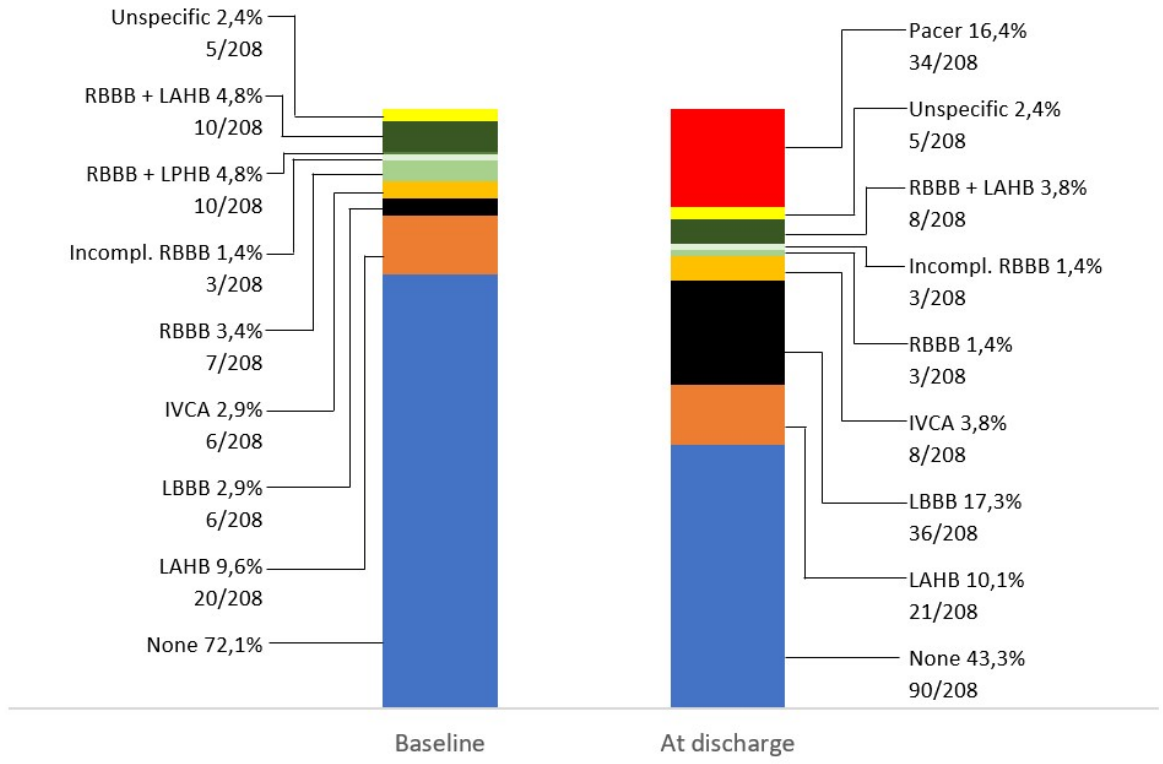


Figure 9.1 CA and PPI at Baseline and at Discharge (*N* = 208). Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 252. Copyright 2016 by Elsevier. Reprinted with permission.

Note. IVCA = intraventricular conduction abnormality; LAHB = left anterior hemi block; LBBB = left bundle branch block; RBBB = right bundle branch block.

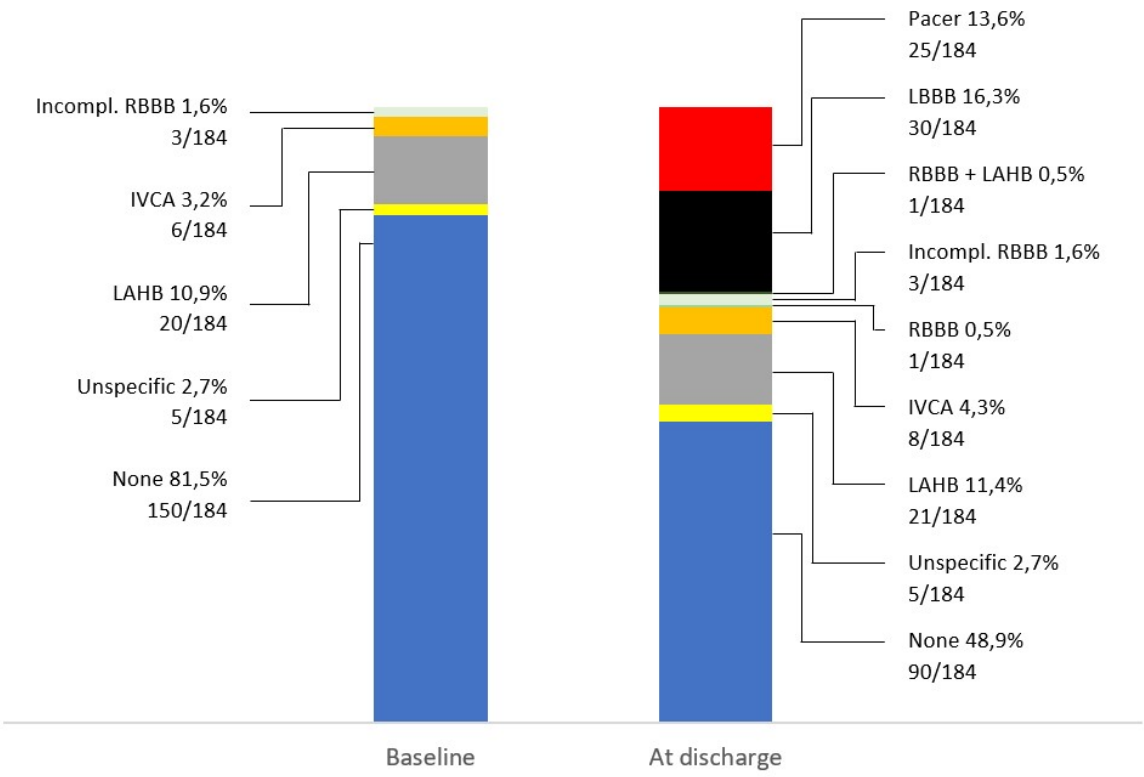


Figure 9.2. CA and PPI at Baseline and at Discharge (*n* = 184). Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 252.

Note. IVCA = intraventricular conduction abnormality; LAHB = left anterior hemi block; LBBB = left bundle branch block; RBBB = right bundle branch block

New-onset or worsened CA was seen more often in patients presenting with peculiar ECGs on admission. Mean QRS duration was longer (100 ± 24 ms vs. 93 ± 11 ms; $p = .006$) and unspecific intraventricular conduction abnormalities (IVCA) more frequent (8.8 % vs. 1.7 %; $p = .012$).

Table 10 shows the baseline ECG findings. Pre-existing unspecific IVCA tended to be present more often in patients later undergoing new PPI (8.8 % vs. 1.7 %; $p = .057$). PQ-intervals (197 ± 44 vs. 179 ± 35; $p = .035$) were and QRS duration (115 ± 31 ms vs. 98 ± 19 ms; $p = < .001$) was longer in patients receiving PPI. Atrial fibrillation (AF; 44.1 % vs. 24.1 %; $p = .017$), bradycardia with a heart rate of < 60 beats per minute (bpm; 38.2 % vs. 21.2 %; $p = .034$),

and complete RBBB (26.5 % vs. 5.1 %; $p = < .001$) all were more commonly found in baseline ECGs of patients later receiving new PPI.

Table 10

Baseline ECG results

Variable	All patients	New Permanent Pacemaker			PPI and new or worsened CA		
	(*N*=208)	Yes (*n*=34)	No (*n*=174)	*p*	Yes (*n*=57)	No (*n*=127)	*p*
AF (n, %)	57 (27)	15 (44)	42 (24)	0.017	15 (26)	31 (24)	0.782
Heart rate (bpm)	72 ± 14	68 ± 15	73 ± 14	0.073	69 ± 13	73 ± 14	0.107
Bradycardia (<60 bpm)	50 (24)	13 (38)	37 (21)	0.034	19 (33)	27 (21)	0.080
PQ-interval (ms)	181 ± 37	197 ± 44	179 ± 35	0.035	182 ± 43	181 ± 34	0.955
AVB I° (n, %)	34 (16)	8 (24)	26 (15)	0.216	12 (21)	19 (15)	0.307
QRS duration (ms)	100 ± 22	115 ± 31	98 ± 19	<0.001	100 ± 24	93 ± 11	0.006
LAHB (n, %)	20 (10)	3 (9)	17 (10)	0.999	5 (9)	15 (12)	0.540
Incomplete RBBB (n, %)	3 (1)	0 (0)	3 (2)	0.999	1 (2)	2 (2)	0.999
Nonspecific IVCA (n, %)	6 (3)	3 (9)	3 (2)	0.057	5 (9)	1 (1)	0.011
RBBB (n, %)	18 (9)	9 (27)	9 (5)	0.001	—	—	—
LBBB (n, %)	6 (3)	0 (0)	6 (3)	0.592	—	—	—

Note. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 247. Copyright 2016 by Elsevier. Reprinted with permission. AF = atrial fibrillation; AVB = atrioventricular block; bpm = beats per minute; IVCA = intraventricular conduction abnormality; LAHB = left anterior hemi block; LBBB = left bundle branch block; RBBB = right bundle branch block.

When included in a multivariate analysis, complete RBBB at baseline (OR: 11.965 [95% CI: 3.406 to 42.026]; p < 0.001), AF (OR: 3.996 [95% CI: 1.567 to 10.192]; p = 0.004),

and heart rate on admission (OR: 0.941 [95% CI: 0.907 to 0.977]; p = 0.001, per bpm increase) were found to be independent predictors for new PPI after TAVI . QRS duration (OR: 1.033 [95% CI: 1.011 to 1.056]; p = 0.003 per ms) was an independent predictor for new onset or worsened CA or PPI.

5.4 Diagnoses Contributing to PPI

The decision on whether a pacemaker needed to be implanted was ultimately left to the discretion of the physician in charge. Diagnoses that led to the decision were reported for every case. Figure 10 gives an overview over diagnoses leading to the decision for PPI, for a detailed list see Supplemental Table 2. In some cases, more than one diagnosis added up to the individual indication for PPI.

For example, LBBB alone was not considered an indication for PPI but could contribute to the decision together with symptomatic bradycardia or intermittent AVB II. Likewise, an isolated AVB I did not lead to new PPI but was documented alongside other diagnoses, such as symptomatic bradycardia, intermittent AVB II, or pause > 2.5 seconds, if present.

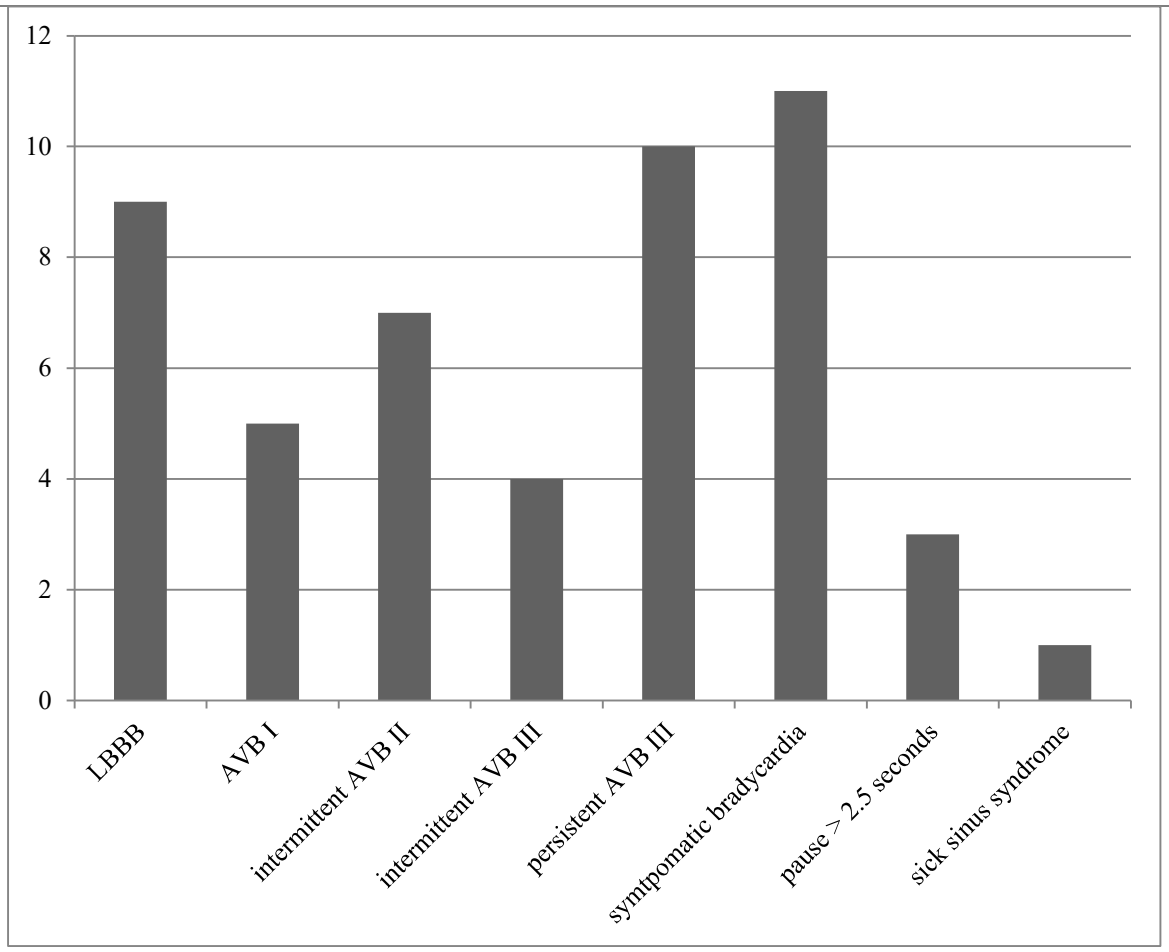


Figure 10. Diagnoses Contributing to the decision for PPI. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, Appendix Supplemental table 1. Copyright 2016 by Elsevier. Reprinted with permission.
Note. AVB = atrioventricular block; LBBB = left bundle branch block.

5.5 Influence of Prosthesis Sizing on new CA or PPI

For mechanical stress is suspected to cause direct damage to the conduction system, prosthesis sizing has been evaluated. Figures 11.1 and 11.2 depict sizing of the three different SAPIEN 3 valves relative to the aortic annulus. However, anatomical references can only be made regarding 206 patients as for two patients were not fit for multislice CT due to renal impairment.

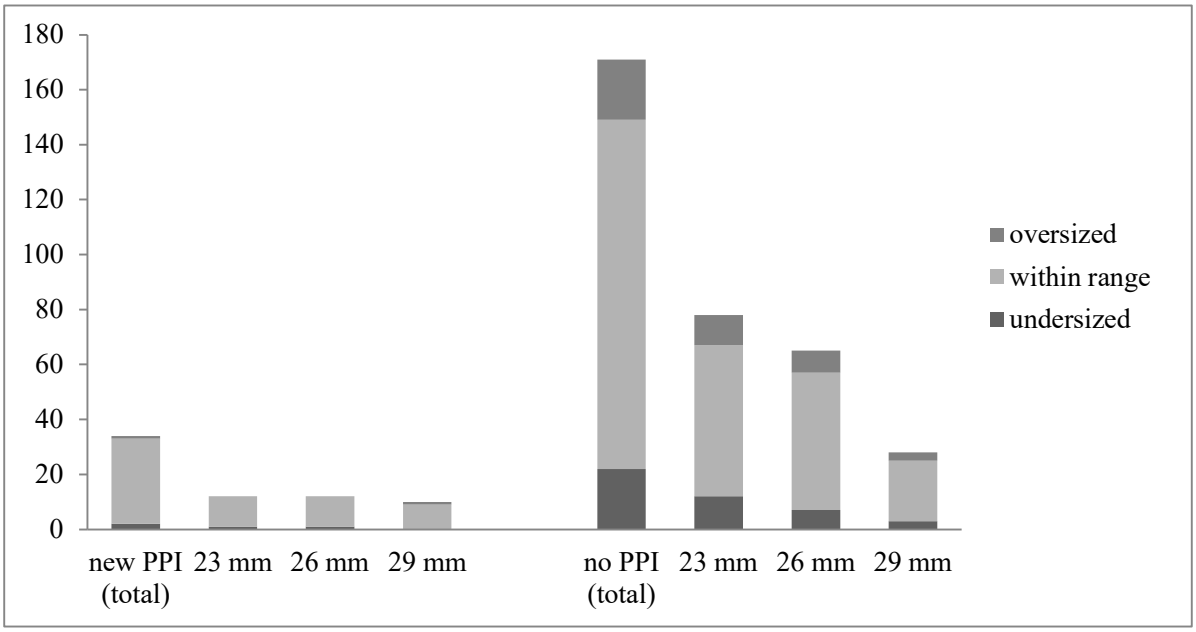


Figure 11.1. Prosthesis Sizing and New PPI. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 251. Copyright 2016 by Elsevier. Reprinted with permission.

Note. Results are shown for all prosthesis sizes combined and the three different sizes, 23mm/ 26mm/ 29mm, respectively. PPI = permanent pacemaker implantation.

While no statistically significant correlation between prosthesis oversizing and new PPI could be demonstrated (OR 0.22, 95 % CI [0.03-1.74]; p = .151), prosthesis oversizing was more common amongst patients with new-onset or worsened CA (19% [11 of 57] vs. 6% [8 of 126]; p = .007) in this study population.

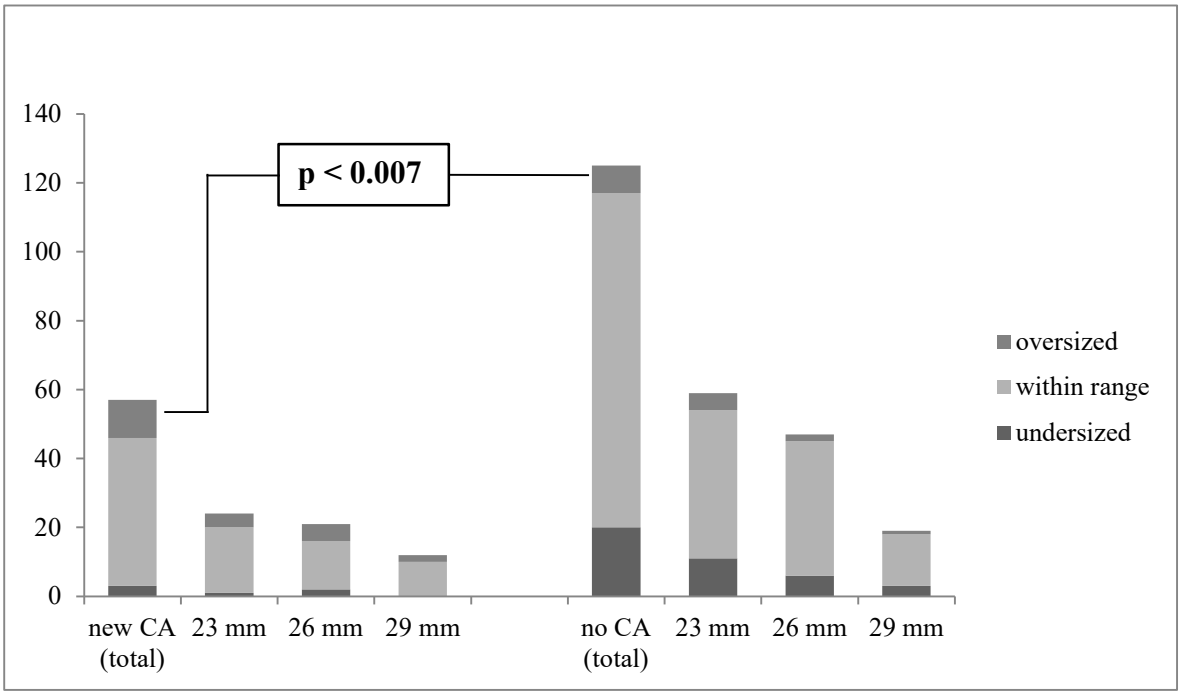


Figure 11.2. Prosthesis Sizing and New PPI and New-Onset or Worsened CA. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p. 251. Copyright 2016 by Elsevier. Reprinted with permission.

Note. Results are shown for all prosthesis sizes combined and the three different sizes, 23mm/ 26mm/ 29mm, respectively. CA = conduction abnormalities.

Included in a multivariate analysis, out-of-range oversizing was additionally found to be an independent predictor for new or worsened CA (OR: 3.489 [1.236 - 9.848]; p = 0.018).

5.6 Influence of Implantation Depth on new CA or PPI

Correct positioning of the valve is vital for device success and minimizing complications such as migration, severe insufficiency, or PPI. Depth of implantation was shown to be strongly associated with new or worsened CA and PPI. Implantation depth measured at the septal side seemed to be of particularly strong correlation (29 ± 8 vs. 25 ± 7; p = .003).

Valves in patients with new PPI also tended to be implanted deeper at the non-septal side than in patients without new PPI, yet statistical significance could not be demonstrated (28 ± 9 vs. 25 ± 7; p = .077).

Both parameters were found to be of predictive value: implantation depth at the non-septal side (OR 1.07, 95 % CI [1.01-1.12]; p = .025, per % of frame below annulus) predicting new PPI and implantation depth at the septal side (OR 1.06, 95 % CI [1.02-1.11]; p = .006 per % of frame height below the aortic annulus) predicting new or worsened CA and PPI. Table 11 summarizes the values of depth of implantation according to subgroups.

Table 11

Depth of Implantation

Depth of implantation (in %) at	**All patients**	**New Permanent Pacemaker**			**PPI and new or worsened CA**		
	(*N*=208)	Yes (*n*=34)	No (*n*=174)	*p*	Yes (*n*=57)	No (*n*=127)	*p*
septal side (NCC)	26 ± 8	27 ± 9	26 ± 8	0.265	29 ± 8	25 ± 7	0.003
non-septal side (LCC)	26 ± 7	28 ± 9	25 ± 7	0.081	27 ± 8	25 ± 7	0.035
mean	26 ± 7	28 ± 9	25 ± 7	0.145	28 ± 8	25 ± 7	0.010

Note. Adapted from "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, p 250. Copyright 2016 by Elsevier. Reprinted with permission. LCC = left coronary cusp; NCC = non coronary cusp.

6 Discussion

AS is of great socioeconomic concern and its natural progression of disease is associated with high mortality rates. The following chapter discusses the findings of this thesis and aims to examine its results for accordance or inconsistency with relevant literature as well as current developments.

6.1 Study Population

While mortality in asymptomatic patients is rather low (Freeman & Otto, 2005), once AS causes symptoms, patients face very poor prognoses. Progression from aortic sclerosis to AS has been reported to be 8.8 % over five years (Novaro et al., 2007), 15.9 % over a median follow-up of 7 ± 3 years for mild and 7 ± 4 years for moderate/ severe aortic stenosis (Cosmi et al., 2002) and up to 32.8 % over a mean follow-up of 44 ± 30 months (Faggiano et al., 2003). Survival rates for severe AS are devastating with outcomes as poor as 49.3 % (Leon et al., 2010) to 60.8 % (Kang et al., 2015) at one year and 6.4 % (Kapadia et al., 2015) to 20 ± 10 % (Kearney et al., 2013) at five years.

Thus, invasive therapy is strongly recommended for symptomatic patients since SAVR and TAVI both have been demonstrated to be superior over current non-invasive treatment options. In order to produce reliable results, comparability of baseline characteristics must be ensured. The LES is commonly reported and may be used to compare baseline characteristics between study populations. It was derived from baseline characteristics collected from 19 030 consecutive patients undergoing cardiac surgery at over one hundred sites across eight European countries in late 1995 (Roques et al., 1999).

Ultimately, patient related, cardiac related, and procedure related factors that had been proven to be related to mortality in a multivariate analysis were included. The LES can now be conveniently computed online or integrated in electronic patient data management systems where relevant characteristics are entered automatically as weighed variables into the formula shown as Equation 5.

This study population showed a LES of 16 ± 12 % and hence is comparable to the general patient population undergoing TAVI in Germany at the time (Walther et al., 2015). They reported a LES of 18.3 % (IQR 11.0-30.5) amongst 15 964 patients enrolled in the GARY during the years 2011 to 2013. A meta-analysis involving 5 024 patients who underwent TAVI reported a mean LES of 25.3 ± 17.7 % (Jilaihawi, Chakravarty, et al., 2012) and results from the FRANCE2 registry regarding 3 195 patients enrolled during 2010 and 2011 showed a mean LES of 21.5 ± 13.8 % (Van Belle et al., 2014). Investigators from the UK TAVI registry analyzing data from 3 980 patients enrolled between 2007 and 2012 reported a mean LES of 21.9 ± 13.7 % (Ludman et al., 2015). Other S3 studies reported the LES to be 17.7 ± 11.8 % (Wöhrle et al., 2015), 21 ± 12 % (Murray et al., 2015), and 21.6 ± 12.3 % (Webb et al., 2014).

This study population tends to be at risk at a lesser degree compared to international study populations while being within range of national cohorts. Reporting on a single center experience at a high-volume site with many referred patients might have lead to issuing indications comfortably for TAVI at an earlier point in time. Furthermore, neither emergency procedure nor conversion to open cardiac surgery was necessary with any patient thus reducing the perioperative risk.

The overall trend shows that TAVI can also be a viable alternative to SAVR for intermediate (Singh et al., 2018) and low-risk patients (Hofer et al., 2019; Witberg et al., 2019). Overall survival after two years was similar in a large study comparing TAVI using the SAPIEN XT and SAVR in intermediate risk patients (Leon et al., 2016). And very recently, a meta-analysis of three randomized controlled trials including a total of 2633 patients found that all-cause one-year mortality after TAVI tended to be lower than after SAVR and risk of cardiovascular death was indeed significantly lower after TAVI (Polimeni et al., 2020). Durability and valve functioning suggest that TAVI is suitable for long-term therapeutic goals (Blackman et al., 2019; Chakos et al., 2017; Duncan et al., 2015; Vollenbroich et al., 2019).

6.2 ECG at Baseline

The impact of new-onset CA on mortality after TAVI is rather ambiguous and a negative effect has not been proven by large-scale trials and study populations. On the other hand, results on CA detected in unselected populations seem to be sufficient. A consistent correlation with age has been established as multiple studies showed CA to be more frequent in elderly patients

(Furberg et al., 1992; Haataja et al., 2013; Imanishi et al., 2006) compared to younger individuals (Pelliccia et al., 2007).

Prevalence of LBBB, RBBB, and unspecific IVCA ranged from < 1 %, mean age 44 ± 8.5 years, (Aro et al., 2011) to 2.2 % for RBBB and 4.1 % for IVCA, mean age 60 ± 13 years, (Badheka et al., 2013) amongst unselected populations.

Investigating the impact on mortality, LBBB and RBBB have both been demonstrated to cause an effect. It has been shown that LBBB and incomplete RBBB raised the risk for all-cause mortality as well as for cardiovascular mortality (Haataja et al., 2015). Complete RBBB seemed to not impact mortality in their study but, as well as LBBB, has been shown to affect cardiovascular mortality (Zhang et al., 2012) and all-cause mortality in other studies (Badheka et al., 2013; Freedman, Alderman, Sheffield, Saporito, & Fisher, 1987; Hesse et al., 2001). Increased width of the QRS-complex without meeting the criteria for LBBB or RBBB has also been shown to affect mortality adversely (Aro et al., 2011; Haataja et al., 2015).

This study population with an average age of 81 ± 6 years, COPD present in 13.0 %, NYHA class III / IV present in 65.2 %, CAD being present in 66.2 %, and AS being present in 100 % of patients composes an in general sicker population than those looked at in the publications above. LBBB was present in 2.9 %, RBBB in 10.6 %, and IVCA was detected in 1.4 % of all patients. These rates being somewhat higher than those expected in an unselected population may be explained by the association between CA and CAD (Fahy et al., 1996), COPD (Goudis et al., 2015), and heart failure (Baldasseroni et al., 2002).

Since impact on mortality has mostly been evaluated on a long-term follow-up basis, strong correlations were not expected in this study. Larger cohorts and longer follow-up periods need to further investigate this issue.

Nonetheless, this study did show new onset or worsened CA after TAVI to be present more often in patients with abnormal ECGs at baseline. Complete RBBB, AF, and heart rate on admission were found to be independent predictors of new PPI after TAVI.

6.3 Calcification

Its predictive value for adverse outcomes amongst baseline characteristics is still unclear. The correlation between AVC and PVL has been reported to be significant by several publications (Fonseca et al., 2016; John et al., 2010; Seiffert, Fujita, et al., 2015; Tang et al., 2018). Staubach et al. (2013) and Gerstmeyer et al., 2017 , however, found that AVC does not affect post-procedural PVL. Looking closely at each of those publications, it was found that all investigators chose to grade AVC differently using individual thresholds which may have led to those discrepancies: Staubach et al. (2013) divided their study population into three groups labelled "mild", "moderate" and "severe" AVC, without specifying who rated it on what basis. Gerstmeyer et al. (2017) described a semi-quantitative approach and had four blinded investigators rate the severity of AVC on a three-point-scale from "0 = no calcium" to "2 = large amounts of calcium". John et al. (2010) used the Agatston score and semi-quantitatively rated AVC as "mild", "moderate", "severe", and "massive" while Seiffert, Fujita et al. (2015) referenced two papers that both worked with Hounsfield units and calculated the amount or volume of calcium in mm^3(Ewe et al., 2011; Khalique et al., 2014). Besides different methods of measuring and reporting of AVC, different valves were used, hence conflicting results regarding the association between AVC and PVL might also be partially attributed to prosthesis features and morphology.

Reports on AVC predicting mortality are just as divergent. The predictive value of AVC concerning mortality has been, by some investigators, shown to be significant (Koos et al., 2013; Leber et al., 2013) while others did not see their 30-day mortality to be related to AVC (Haensig et al., 2012).

This study focused on new-onset CA and PPI as outcome parameters. The severity of AVC was graded visually as "0 – none", "1 – mild", "2 – moderate", and "3 – severe". Overall, AVC was rated moderate/ severe most frequently at the cusps (71.8 %), followed by the aortic annulus (10.2 %), and the LVOT (5.8 %). This study did not show a significant correlation between AVC and new-onset CA or PPI for any location. These findings are consistent with results from the GARY (Staubach et al., 2013) and other investigators (Fraccaro et al., 2011; Khawaja et al., 2011; Ledwoch et al., 2013; Munoz-Garcia et al., 2010; Urena et al., 2012; Watanabe et al., 2015). However, another study investigating 81 patients treated with the CoreValve prosthesis found a significant correlation between calcification of the device landing zone, consisting of valvular cusps, aortic annulus, and LVOT altogether, and PPI (Latsios et

al., 2010). They reported a slightly increased risk with the OR being 1.06 [1.02-1.11] but when assessing the calcification of the non-coronary cusp only, no significant impact on PPI was found. Mauri et al., 2016, looked at the SAPIEN 3 prosthesis and reported that calcification of the LVOT was of predictive value for PPI while another S3 study reported contrary results and did not show any influence on new PPI (Gonska, Von Keil, et al., 2016). Pollari et al., 2019, showed a statistically significant correlation between AVC and new PPI and AVB. Depending on the precise location of calcification differences in persistence of new AVB were reported. However, results were reported for patients receiving the SAPIEN 3 and the CoreValve combined. Thus, specific implications for specific prosthesis types cannot be derived from this particular set of data.

The results referenced above appear to be rather inconsistent. However, findings from this study and the majority of publications suggest that AVC does not affect or play a major role in new onset CA or PPI after TAVI with the SAPIEN valves.

Nonetheless, in order to clarify the significance of AVC international standards for rating and reporting severity of AVC is necessary. While most valves available rely on some degree of calcification to attach and hold on to, one might expect that too much calcium prevents the valve from unfolding properly and consequently resulting in PVL. Also, pushing calcified structures away from the lumen might increase the risk of injuring the conduction system, further described under section 6.6.

Therefore, valve selection has to be adapted to anatomical conditions and impact of AVC on new PPI needs to be investigated depending on prosthesis type, implantation mode, and standardized grading of AVC.

6.4 Anesthesia

As previously described under section 5.3.1.2, LACS and GA may be seen as equally safe options for anesthesia during TAVI. 30-day mortality does not differ significantly while length of stay is shorter with LACS (Motloch et al., 2012; Oguri et al., 2014). Even next-day discharge after TAVI under LACS has been reported to be a safe option and showed comparable results to other forms of anesthesia (Costa et al., 2020). Nonetheless, data on anesthesia's impact on new-onset CA and PPI are scarce.

This study showed that new onset CA and PPI was more common under LACS than under GA (50.9 % vs. 34.9 %; p = .041) while investigating new PPI alone revealed no significant differences (50.0 % vs. 37.0 %; p = .155). Previous findings on new PPI have been rather divergent. One study reported new PPI to be more frequent after local anesthesia in their study population of 2 807 patients (p = < .01; Dall'Ara et al., 2014) but Oguri et al. (2014), publishing results on 2 326 patients from the FRANCE 2 registry, did not find any significant difference (p = .37). Other studies involving far less patients, between 74 and 176, showed no significant differences either (Gauthier et al., 2015; Motloch et al., 2012; Yamamoto et al. 2013).

Dall' Ara et al. (2014), reported that the Medtronic CoreValve was used more often in the LACS group (50.0 %), than in the GA group (46.0 %) (p = .04), hence those findings need to be looked at carefully. Additionally, neither paper reported ECG baseline characteristics other than AF, or depth of implantation, or oversizing. Those information would be crucial for evaluating the true predictive value of anesthesia type concerning new PPI.

6.5 Sizing

The spatial proximity between the cardiac conduction system and the aortic valve suggests that force applied to the annulus, as is happening when implanting any prosthesis, might interfere with the conduction system. Whilst a mild degree of oversizing is needed for optimal function (Leber et al., 2013) applying more force might result in more damage.

Investigating this question, this study showed no significant variation of oversizing by area between patients with and without new onset CA or PPI. Yet, oversizing was indeed significantly related to new onset CA (see Figure 11.2). Overall, 11 (19.3 %) out of 57 new cases of CA were treated with a prosthesis considered oversized while only 8 (6.3 %) out of 126 patients without new CA received an oversized valve (p = .007). Additionally, out-of-range oversizing was found to be an independent predictor for new or worsened CA (OR: 3.489 [1.236 - 9.848]; p = 0.018).

This correlation has been reported showing a correlation between new left anterior hemi block (LAHB) (Gutiérrez et al., 2009) and LBBB (Zaid et al., 2020) and valve oversizing. New CA detected after TAVI have been shown, in many cases, to resolve (Houthuizen et al., 2012; Miura et al., 2019; Poels et al., 2014; Urena et al., 2012). This suggests a rather transient injury

without causing persisting damage to the conduction system and would allow a hesitant approach to PPI. Oversizing has further been linked to an increased need for PPI (OR 2.78 [1.09-7.08]; p = .032; Schroeter et al., 2012). Also, the correlation between balloon-size and new-onset AVB as well as the correlation between the difference between balloon-size and aortic annulus and new-onset AVB was shown to be statistically significant (Bleiziffer et al., 2010). They demonstrated that intraoperative new-onset AVB was an independent predictor of new PPI (OR 4.82 [2.0-11.9]; p = .001) and high-grade AVB was the most commonly reported indication for PPI.

Additionally, rupture of the aortic annulus, undoubtedly of rather dramatic and potentially life-threatening nature (Eggebrecht et al., 2013; Pasic et al., 2012), might be caused by oversized valves applying too much force to the aortic annulus, as previous suggest (Blanke et al., 2012; Schymik, Heimeshoff, et al., 2014).

Thus, oversizing should be considered a potential risk factor for complications and avoiding severely oversized valves might consequently help reduce adverse outcomes after TAVI. Existing data suggest that it will always be a fine line between trading off reduction in PVL and risking new onset CA (Debry et al., 2016).

6.6 Depth of Implantation

Ensuring a coordinated contraction, the membranous septum of the heart isolates the atria electrically from the ventricles. In order to reach the ventricles, the electrical signal travels with the bundle of His through the membranous septum to the apex of the muscular septum where it splits up into the right and left bundle branch. The bundle of His is therefore in close spatial proximity to the aortic valve, since the valve is also part of the heart's fibrous skeleton.

Hence, depth of implantation, measured as percentage of frame height below the aortic annulus, is of great interest when addressing post-implantation CA and or PPI.

This study showed evidence that depth of implantation is associated with new onset or worsened CA and PPI. Patients requiring PPI or experiencing new or worsened CA did have their prostheses implanted deeper into the LVOT, at the septal side (p = .003) as well as at the non-septal side (p = .035). Mean depth of implantation, measured in % of frame height below

aortic annulus, was 26 ± 7 for all patients. Valves in patients with new PPI and new or worsened CA had been implanted at 28 ± 8, and in patients without PPI or new CA it had been 25 ± 7.

These findings appear to be backed by the spatial proximity of aortic valve and conduction system as described above. Furthermore, they are also alongside other publications investigating the development of new-onset CA.

A SAPIEN 3 study also reporting their results in percentages of frame height below and above aortic valve annulus published similar results. They found that a ratio of 73/27 % aortic/ventricular extension of frame height led to a rate of 6.5 % of new PPI, whereas depth of implantation on the ventricular side of more than 27 % caused new PPI in 32.9 % of patients (De Torres-Alba et al., 2016). A previous study, looking at SAPIEN 3 and SAPIEN XT valves, reported similar results and found higher valve implantation significantly reduced the rate of PPI (Tarantini et al., 2015). They suggested that the central marker of the crimped heart valve was to be positioned at 3mm above the baseline of the coronary cusps, leaving 6mm to 8mm of the heart valve below the base of the coronary cusps. These results were confirmed by other investigators, also looking exclusively at the SAPIEN 3 (Schwerg et al., 2016). Choosing 2mm to be the length between central marker and aortic cusps to be their cut off point, they compared low implantation valves (< 2mm) with high implantation valves (≥ 2mm). They found the difference in need for new PPI to be significant: valves that were implanted lower required new PPI in 32.3 % of the cases compared to 4.7 % in the high implanted group ($p < .001$). Similar results were reported by Unzué et al., 2019, reporting less new LBBB when the depth of implantation was less than 34%.

While a clear trend can be derived from a multitude of studies available, standardized reporting of valve positioning, e.g. in percentage of frame height below aortic annulus as described in this study, could lead to better comparison and eventually international standards for valve placement.

6.7 Paravalvular Leakage

Further improvement of outcomes needs both, working on procedural techniques and developing excellent devices. The SAPIEN 3 is available in sizes 23mm, 26mm, and 29mm diameter, hence covering aortic annuli with diameters ranging between 18mm to 28mm according to the manufacturer's recommendations. Its outer skirt of polyethylene terephthalate

was designed to reduce PVL for it has been shown multiple times to be a common adverse event as well as to worsen outcomes.

The vast majority of AR after TAVI is paravalvular, after implanting self-expanding prostheses and balloon-expanding valves alike. Any paravalvular AR has been reported to occur in 56.1 % of patients treated with the CoreValve (Gotzmann et al., 2012). Looking at both prosthesis types, the UK TAVI registry showed any paravalvular AR in 61.0 % (Moat et al., 2011), and the FRANCE2 registry revealed any AR in 65.2 % of patients (Van Belle et al., 2014). When compared for PVL ≥2, balloon-expandable valves appeared to be better than their self-expandable counterparts: 9.6 % vs. 17.3 % (Moat et al., 2011) and 13.0 % vs. 21.5 % (Van Belle et al., 2014).

A large meta-analysis strongly suggested the SAPIEN 3 is superior over its predecessor concerning PVL ≥2 (Ando et al., 2016). Differences in stent-frame morphology after implantation have been investigated and might explain clinical results (Kazuno et al., 2016). Also, the outer skirt of polyethylene terephthalate might aide reduction of PVL and should therefore be considered when designing future generations of aortic valve prostheses.

This study involving 208 patients treated with the SAPIEN 3 prosthesis showed device success in $n = 203$ patients translating into a success rate of 97.8 %. Only four patients (1.9 %) were found to have PVL grade ≥2 and one required a second valve (0.5 %). These findings support previous excellent results published by other investigators evaluating the S3. Webb et al., (2014b) reported only 3.5 % of the 150 patients enrolled at the study sites showed at least moderate PVL and Wöhrle et al. (2015), as well as Murray et al. (2015) reported no case of moderate PVL amongst their study population of 52 and 51, respectively.

Schymik, Heimeshoff, et al. (2015), published similar outcomes for PVL ≥2 after TAVI with different prosthesis types. They compared a population of less-than-high-risk patients, defined as LES ≤15.0 %, treated mainly with SAPIEN or SAPIEN XT valves but also with the CoreValve and the Symetis ACURATE, either choosing the TF or TA, to a group undergoing SAVR. Moderate aortic insufficiency ≥2 after TAVI was seen in 3.6 % of patients compared to 0.3 % after SAVR.

Those excellent results pose an exception to the rule as a closer look at other studies reveals. Compared to PVL ≥2 after SAVR, ranging between 0.9 % and 2.0 %, PVL ≥2 after TAVI ranges between 9.8 % with CoreValve or the SAPIEN XT (Tamburino et al., 2015), 12.2 % working with the SAPIEN heart-valve system (Smith et al., 2011), and 15.3 % after

TAVI with the CoreValve (Thyregod et al., 2015). PVL greater than or equal to mild 5 years after TAVI with the SAPIEN XT in intermediate risk patients has been reported to be 33.3% compared to 6.3% after SAVR (Makkar et al., 2020).

Adverse effects of PVL on 30-day mortality as well as 1-year have been reported to be significant (Gotzmann et al., 2012; Tamburino et al., 2011; Vasa-Nicotera et al., 2012). A large meta-analysis involving 1708 patients, including the above mentioned, confirmed the trend demonstrated by previous single publications (Athappan et al., 2016). With long-term data being available on a larger scale, it has been shown that severity of PVL correlates with increased mortality across several study populations (Makkar et al., 2020).

Hence, reduction of PVL needs to be considered when further developing procedural techniques and valve features. Future rates of valvular insufficiency after TAVI can be improved by working with the S3, as findings from this study population align with recent publications. Moderate or severe PVL at 30 days post TAVI was reported to be as low as 1.5 % (Thiele et al., 2020) or 2.7% (Schymik et al., 2019a) and 2% at one year post TAVI (Pellegrini et al., 2019). These results further back early results that suggested the S3 outperforms its predecessor regarding PVL (Kazuno et al., 2016).

6.8 Permanent Pacemaker Implantation and Conduction Abnormalities

As described previously, damage to the conduction system up to the need for PPI unfortunately appears rather frequently after TAVI. However, significant differences between prosthesis types and access routes can be seen.

PPI rates after TAVI with JenaValve have been reported to be from 9.1 % (Treede et al., 2012) to 14.8 % (Seiffert, Conradi, et al., 2015) after TA. Choosing TF with the LotusValve, 24.1 % (Wöhrle et al., 2016b) to 27.0 % (Wöhrle et al., 2015) of the patients treated needed new PPI. The Acurate neo led to 8.3 % new PPI (Möllmann et al., 2018).

The self-expandable CoreValve, one of the most commonly used valves, has been linked to higher rates of new CA and PPI compared to the balloon-expandable SAPIEN valves (Moretti et al., 2015; Peruzzi et al., 2014). Numbers for new onset LBBB after TAVI with the CoreValve prosthesis vary between 27.4 % (Testa et al., 2013) and 61.5 % (Nuis et al., 2011) in individual studies and, as described earlier, have been shown to be 45.2 % in a literature

review by Martinez-Selles et al. (2014). The same review reported the rate for new PPI to be 26.7 %, and Siontis et al. (2014) reported in their meta-analysis new PPI rate of a mean of 28 % (IQR 24-35).

Meanwhile, patients treated with the SAPIEN or SAPIEN XT were less likely to experience new CA or to receive new PPI. New-onset LBBB has been reported to occur in 12.0 % (Houthuizen et al., 2012) to 30.2 % (Urena et al., 2012), summarized and demonstrated by a meta-analysis to be 24.9 % (Ando & Takagi, 2016). Rates for new PPI were lower and have been reported to range around 6 % by meta-analyses (Bax et al., 2014; Erkapic et al., 2012; Siontis et al., 2014) as well as in national registries, such as ITER in Italy (Salizzoni et al., 2016).

The reoccurring differences regarding damage to the conduction system between the Medtronic and the Edwards valves may be explained by looking at the individual frame heights. The CoreValve measures 45-55 mm depending on size while the SAPIEN XT measures 13.5 mm to 19.1 mm. Thus, the CoreValve reaches deeper into the LVOT and hence is more prone to interfere with the bundle of His or the left bundle branch as described earlier. This mechanism might also contribute to the increase in new PPI found by several publications on the next generation Edwards valve, the SAPIEN 3 as its frame height ranges between 15.5 mm and 22.5 mm (Gaede et al., 2018; Thiele et al., 2020).

This study found new-onset LBBB in 16.4 % as well as new PPI in 13.6 % of patients treated with the SAPIEN 3. More data on new onset LBBB is limited, however, suggested to lie between 20.8 % (Webb et al., 2014), 26.7 % (Schwerg et al., 2016) and 31.0 % (Jochheim et al., 2015) and are hence within range of the results seen with its predecessor.

Summarizing findings by multiple investigators available at the time of publication of these results, the rate for new PPI appears to be around 13.8 %, see Table 1, compared to around 6 % after TAVI with the SAPIEN THV and SAPIEN XT (Bax et al., 2014; Erkapic et al., 2012; Siontis et al., 2014). Results on new PPI published in the meta-analysis by Ando et al. (2016) seemed to favor the SAPIEN XT over the SAPIEN 3, yet, without reaching statistical significance (OR 0.98, 95 % CI [0.98-1.80]). Directly comparing the XT and the S3 for new PPI at the German Heart Center Munich (Husser, Kessler, et al., 2016) did not find a significant difference between the two. Findings regarding this study population are very much comparable to results shown within other publications at the time, for comparison see Table 1.

As outlined earlier, depth of implantation and oversizing are strongly associated with new PPI. Yet, other factors are most likely contributing to new PPI as well. De Torres-Alba et al. (2016) showed a reduction in new PPI from 29.5 % PPI the first 50 % of patients to 12.3 % PPI in the second 50 %. This indicates a learning curve might have somewhat affected differing rates of new PPI, as its positive effect on reducing adverse outcomes has been shown by other investigators (Arai et al., 2016). Whilst this was not observed in the study population being presented in this dissertation, its impact on study endpoints remains unclear due to a lack of consistent reporting of learning curves.

Differing incidences of PPI after TAVI with the SAPIEN 3 were reported by other investigators: 24.0% (Ben-Shoshan et al., 2017), 22.9 % (Gaede et al., 2018), 13.6 % (Schymik et al., 2019b), 13.3 % (Giordano et al., 2019), 19.2 % (Thiele et al., 2020). As the ultimate decision for or against PPI is usually left to the discretion of the physician in charge, personal experiences and standards may affect results. Detailed information on indications for PPI are scarce, therefore standardized documentation is needed for understanding processes and outcomes.

Finally, pre-existing RBBB has been demonstrated numerous times to be an independent predictor of new PPI (Erkapic et al., 2012; Gaede et al., 2018; Kooistra et al., 2020; Siontis et al., 2014). These patients may profit from diligent pre-procedural work-up, including precise sizing with multislice CT and valve selection, and procedural emphasis on avoiding deep implantation.

7 Limitations

Reporting a single-center experience, transferring results and conclusions to the general population of TAVI patients may be somewhat limited. Yet, this study shows results from a high-volume TAVI center and delivers a real-world study cohort. Its patients' baseline characteristics are comparable to previous, larger TAVI cohorts and may therefore be included meta-analyses.

Depth of implantation, calcification as well as indications leading to PPI are not documented in a standardized manner across international publications, hence comparison to other study cohorts and results may be limited.

8 Conclusion

The results of this study revealed excellent in-hospital outcomes and device success for the SAPIEN 3 at the DHM. A strong correlation between depth of implantation and new-onset or worsened CA has been demonstrated, thus stressing the importance of correct positioning for valve prostheses. Meanwhile, prosthesis sizing showed no statistically significant impact on new-onset or worsened CA or PPI when adherent to the manufacturer's recommendations. New PPI was strongly predicted by baseline ECG and, even though rather high compared to studies involving one of its predecessors, in terms of incidence alongside previous publications on the SAPIEN 3 prosthesis.

9 Conflicts of Interest

The author has no conflicts of interest to declare.

10 Literature

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Appendix

Supplemental Table 1

β Coefficients for the Logistic Regression Model of EuroSCORE in the 1995 Pilot Study

Patient related factors		**β**
Age	Continuous	0.0666354
Sex	female	0.3304052
Chronic pulmonary disease	longterm use of bronchodilators or steroids for lung disease	0.4931341
Extracardiac arteriopathy	any one or more of the following: claudication, carotid occlusion or > 50 % stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	0.6558917
Neurological dysfunction disease	severely affecting ambulation or day-to-day functioning	0.841626
Previous cardiac surgery	requiring opening of the pericardium	1.002625
Serum creatinine	> 200 micromole / L preoperatively	0.6521653
Active endocarditis	patient still under antibiotic treatment for endocarditis at the time of surgery	1.101265
Critical preoperative state	any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria < 10 ml / hour)	0.9058132
Cardiac related factors		
Unstable angina	rest angina requiring iv nitrates until arrival in the anesthetic room	0.5677075
LV dysfunction	moderate or LVEF 30 – 50 % poor or LVEF < 30	0.4191643 1.094443

Cardiac related factors		
Recent myocardial infarct	(< 90 days)	0.5460218
Pulmonary hypertension	Systolic PA pressure > 60 mmHg	0.7676924
Operation related factors		
Emergency	carried out on referral before the beginning of the next working day	0.7127953
Other than isolated CABG	major cardiac procedure other than or in addition to CABG	0.5420364
Surgery on thoracic aorta	for disorder of ascending, arch or descending aorta	1.159787
Post-infarct septal rupture		1.462009

Note. Adapted from "How to calculate the logistic EuroSCORE" by Nashef, Roques, & Goldstone, n.d., retrieved December 14 2016, from http://euroscore.org/logisticEuroSCORE.htm. CABG = coronary artery bypass graft; LV = left ventricle; LVEF = left ventricular ejection fraction; PA = pulmonary artery.

Supplemental Table 2

Case by Case Presentation of Patients Requiring PPI after TAVI with S3

Case No.	Indication	Pacemaker	Days after TAVI
1	Intermittent AVB II	DDD	5
2	Persistent AVB III	DDD	2
3	Symptomatic Bradycardia	DDD	4
4	Persistent AVB III	DDD	Directly after TAVI
5	Intermittent AVB II	DDD	7
6	Symptomatic Bradycardia and AVB I	DDD	7
7	Persistent AVB III	DDD	0
8	Intermittent AVB III	DDD	5
9	Intermittent AVB II Mobitz	DDD	1
10	Persistent AVB III	VVI	Directly after TAVI
11	Symptomatic bradycardia and Pause > 2.5 seconds on holter	VVI	6
12	Intermittent AVB II	DDD	6
13	Persistent AVB III	VVI	4
14	Persistent AVB III	VVI	5
15	Persistent AVB III	VVI	Directly after TAVI
16	Intermittent AVB II Wenckebach and new LBBB	DDD	6
17	Symptomatic bradycardia and Pause > 2.5 seconds on holter	DDD	4
18	Intermittent AVB III	DDD	6

Case No.	Indication	Pacemaker	Days after TAVI
19	Symptomatic Bradycardia and new LBBB	DDD	7
20	Symptomatic bradycardia and intermittent LBBB	VVI	4
21	Symptomatic bradycardia	VVI	1
22	Intermittent AVB III	DDD	5
23	Persistent AVB III	VVI	1
24	AVB I and new LBBB	DDD	6
25	Symptomatic bradycardia, AVB I and new LBBB	DDD	1
26	Persistent AVB III	VVI	Directly after TAVI
27	Symptomatic bradycardia	VVI	1
28	Intermittent AVB III	DDD	3
29	Symptomatic bradycardia and new LBBB	VVI	1
30	Sick Sinus Syndrome	DDD	Directly after TAVI
31	Persistent AVB III	VVI	Directly after TAVI
32	Symptomatic bradycardia, AVB I, intermittent AVB II Wenckebach and new LBBB	DDD	6
33	Pause > 2.5 seconds on holter, AVB I and new LBBB	DDD	5
34	Intermittend AVB II and new LBBB	DDD	1

Note. From "Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve" by Husser, Pellegrini, et al., 2016, JACC: Cardiovascular Interventions, Volume 9, Issue 3, Appendix Supplemental table 1. Copyright 2016 by Elsevier. Reprinted with permission. AVB = atrio-ventricular block; LBBB = complete left bundle branch block.