Klinik für Herz-, Thorax- und Gefäßchirurgie
Deutsches Herzzentrum Berlin

DISSERTATION

Computed tomography aortic valve calcium scoring and its association with adverse events following transcatheter aortic valve implantation (TAVI)

Computertomographie-basierte Bestimmung von Aortenklappenkalk und seine Assoziation mit Komplikationen nach interventioneller Aortenklappenimplantation (TAVI)

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1 Abbreviations

A

ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
AKI	acute kidney injury
AS	aortic valve stenosis
AU	Agatston units
AV	aortic valve
AVA	aortic valve area
AVC	aortic valve calcification
AVR	aortic valve replacement
α-Gal	galactose- α -1,3 galactose β -1,4- N-acetylglucosamine

B

BAV	bicuspid aortic valve
BMI	body mass index
BNP	brain natriuretic peptide
BSA	body surface area

C

CE	Conformité Européenne
CF	calibration factor
CMR	cardiovascular magnetic resonance imaging
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CTA	computed tomography angiography

D

DHZB	German Heart Center Berlin
DLZ	device landing zone

E

EACTS	European Association for Cardio-Thoracic Surgery
EF	ejection fraction
EOA	effective orifice area
ESC	European Society of Cardiology
EuroSCORE	European System for Cardiac Operative Risk Evaluation

F

FDA	Food and Drug Administration
Fr	French

G

GA	general anesthesia
GARY	German Aortic Valve Registry
GLS	global longitudinal strain

H

HU	Hounsfield Units
HU_{Aorta}	mean luminal attenuation of the ascending aorta

I

ICC	interclass and intraclass correlation coefficients
ICU	intensive care unit
Indexed AVA	aortic valve area indexed by body surface area

L

LA	luminal attenuation
LCA	left coronary artery

LCC	left coronary cusp
LGE	late gadolinium enhancement
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
M	
MDCT	multidetector row computer tomography
MPG	mean pressure gradient
MRI	magnetic resonance imagining
MSCT	multi-slice computed tomography
N	
NCC	non-coronary cusp
NECT	non-contrast-enhanced computed tomography
NYHA	New York Heart Association
P	
PAD	peripheral artery disease
PARTNER	Placement of Aortic Transcatheter Valves
PCSK9	proprotein convertase subtilisin/kexin type 9
PPI	permanent pacemaker implantation
PVL	paravalvular leak
R	
RCA	right coronary artery
RCC	right coronary cusp
RCT	randomized controlled trial
S	
SAVR	surgical aortic valve replacement
SCOPE	Safety and Efficacy Comparison Of Two TAVI Systems in a Prospective Randomized Evaluation
SOLVE-TAVI	compariSon of secOnd-generation seLf-expandable vs. balloon-expandable Valves and gEneral vs. local anaesthesia in Transcatheter Aortic Valve Implantation
STE	speckle-tracking echocardiography
STS/ACC TVT	Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
T	
TAVI	transcatheter aortic valve implantation
TAV-in-TAV	transcatheter aortic valve in transcatheter aortic valve implantation
TEE	transesophageal echocardiography
TF	transfemoral
THV	transcatheter heart valve
TIA	transient ischemic attack
TTE	transthoracic echocardiography
V	
VARC	Valve Academic Research Consortium
VCD	vascular closure device
V_{max}	peak aortic jet velocity

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3 Abstract

3.1 English abstract

Background: Severe aortic valve calcification (AVC) has generally been recognized as a key factor in the occurrence of adverse events after transcatheter aortic valve implantation (TAVI). To date, however, a consensus on a standardized calcium detection threshold for aortic valve calcium quantification in contrast-enhanced computed tomography angiography (CTA) is still lacking. The present thesis aimed at comparing two different approaches for quantifying AVC in CTA scans based on their predictive power for adverse events and survival after a TAVI procedure.

Methods: The extensive dataset of this study included 198 characteristics for each of the 965 prospectively included patients who had undergone TAVI between November 2012 and December 2019 at the German Heart Center Berlin (DHZB). AVC quantification in CTA scans was performed at a fixed Hounsfield Unit (HU) threshold of 850 HU (HU 850 approach) and at a patient-specific threshold, where the HU threshold was set by multiplying the mean luminal attenuation of the ascending aorta by 2 (+100 % HU_{Aorta} approach). The primary endpoint of this study consisted of a combination of post-TAVI outcomes (paravalvular leak ≥ mild, implant-related conduction disturbances, 30-day mortality, post-procedural stroke, annulus rupture, and device migration). The Akaike information criterion was used to select variables for the multivariable regression model. Multivariable analysis was carried out to determine the predictive power of the investigated approaches.

Results: Multivariable analyses showed that a fixed threshold of 850 HU (calcium volume cut-off 146 mm^3) was unable to predict the composite clinical endpoint post-TAVI (OR=1.13, 95 % CI 0.87 to 1.48, p=0.35). In contrast, the +100 % HU_{Aorta} approach (calcium volume cut-off 1421 mm^3) enabled independent prediction of the composite clinical endpoint post-TAVI (OR=2, 95 % CI 1.52 to 2.64, $p=9.2x10^{-7}$). No significant difference in the Kaplan-Meier survival analysis was observed for either of the approaches.

Conclusions: The patient-specific calcium detection threshold +100 % HU_{Aorta} is more predictive of post-TAVI adverse events included in the combined clinical endpoint than the fixed HU 850 approach. For the +100 % HU_{Aorta} approach, a calcium volume cut-off of 1421 mm^3 of the aortic valve had the highest predictive value.

3.2 German abstract

Hintergrund: Ein wichtiger Auslöser von Komplikationen nach einer Transkatheter-Aortenklappen-Implantation (TAVI) sind ausgeprägte Kalkablagerung an der Aortenklappe. Dennoch erfolgte bisher keine Einigung auf ein standardisiertes Messverfahren zur Quantifizierung der Kalklast der Aortenklappe in einer kontrastverstärkten dynamischen computertomographischen Angiographie (CTA). Die vorliegende Dissertation untersucht, inwieweit die Wahl des Analyseverfahrens zur Quantifizierung von Kalkablagerungen in der Aortenklappe die Prognose von Komplikationen und der Überlebensdauer nach einer TAVI beeinflusst.

Methodik: Der Untersuchung liegt ein umfangreicher Datensatz von 965 Patienten mit 198 Merkmalen pro Patienten zugrunde, welche sich zwischen 2012 und 2019 am Deutschen Herzzentrum Berlin einer TAVI unterzogen haben. Die Quantifizierung der Kalkablagerung an der Aortenklappe mittels CTA wurde einerseits mit einem starren Grenzwert von 850 Hounsfield Einheiten (HU) (HU 850 Verfahren) und andererseits anhand eines individuellen Grenzwertes bemessen. Letzterer ergibt sich aus der HU-Dämpfung in dem Lumen der Aorta ascendens multipliziert mit 2 (+100 % HU_{Aorta} Verfahren). Der primäre klinische Endpunkt dieser Dissertation besteht aus einem aus sechs Variablen zusammengesetzten klinischen Endpunkt, welcher ungewünschte Ereignisse nach einer TAVI abbildet (paravalvuläre Leckage ≥mild, Herzrhythmusstörungen nach einer TAVI, Tod innerhalb von 30 Tagen, post-TAVI Schlaganfall, Ruptur des Annulus und Prothesendislokation). Mögliche Störfaktoren, die auf das Eintreten der Komplikationen nach TAVI Einfluss haben, wurden durch den Einsatz des Akaike Informationskriterium ermittelt. Um die Vorhersagekraft von Komplikationen nach einer TAVI durch beide Verfahren zu ermitteln, wurde eine multivariate Regressionsanalyse durchgeführt.

Ergebnisse: Die multivariaten logistischen Regressionen zeigen, dass die Messung der Kalkablagerungen anhand der HU 850 Messung (Kalklast Grenzwert von 146 mm^3) die Komplikationen und die Überlebensdauer nicht vorhersagen konnten (OR=1.13, 95 % CI 0.87 bis 1.48, p=0.35). Die nach dem +100 % HU_{Aorta} Verfahren (Kalklast Grenzwert von 1421 mm^3) individualisierte Kalkmessung erwies sich hingegen als sehr aussagekräftig, da hiermit Komplikationen nach einer TAVI signifikant vorhergesagt werden konnten (OR=2, 95 % CI 1.52 bis 2.64, p=$9.2x10^{-7}$). In Hinblick auf die postoperative Kaplan-Meier Überlebenszeitanalyse kann auch mit dem +100 % HU_{Aorta} Verfahren keine Vorhersage getroffen werden.

Fazit: Aus der Dissertation ergibt sich die Empfehlung, die Messung von Kalkablagerungen nach dem +100 % HU_{Aorta} Verfahren vorzunehmen, da Komplikationen wesentlich besser und zuverlässiger als nach der gängigen HU 850 Messmethode vorhergesagt werden können. Für das +100 % HU_{Aorta} Verfahren lag der optimale Kalklast Grenzwert bei 1421 mm^3.

4 Introduction

4.1 Aortic valve stenosis

4.1.1 Definition

Aortic valve stenosis (AS) refers to narrowing of the aortic orifice and increased resistance in the left ventricular outflow tract (LVOT), characterized by gradual thickening, fibrosis, decreased responsiveness, and calcific degeneration of the aortic valve leaflets. This increase in resistance leads to left ventricular (LV) pressure overload, which in the long term precipitates LV remodeling, excessive concentric LV hypertrophy, and myocardial stiffness (7). The later stages of disease progression are marked by atrial and ventricular dilatation, which cause symptoms to manifest and result in a sharp drop in survival (8).

4.1.2 Epidemiology and etiology

The age of the world's population as well as the mean life expectancy are steadily increasing and with it the occurrence of age-related cardiovascular diseases, in particular AS. AS is the most widespread acquired valvular heart disease in the western hemisphere. Its prevalence in adults aged 50-59 years is just 0.2 %, in over 75-year-olds it increases to 2.8 %, before reaching a staggering 9.8 % of age-matched adults in those aged 80-89 years (9).

Three distinct etiological pathways give rise to the formation of AS. Figure 1 illustrates the morphology of a healthy aortic valve (AV) (Figure 1, left) and that of the most common AS etiologies. These include calcific AS (Figure 1, middle left) and congenital AS, caused by a bicuspid AV (BAV) morphology (Figure 1, middle right) and a uniscupid AV morphology (not pictured in Figure 1), as well as rheumatic AS (Figure 1, right).

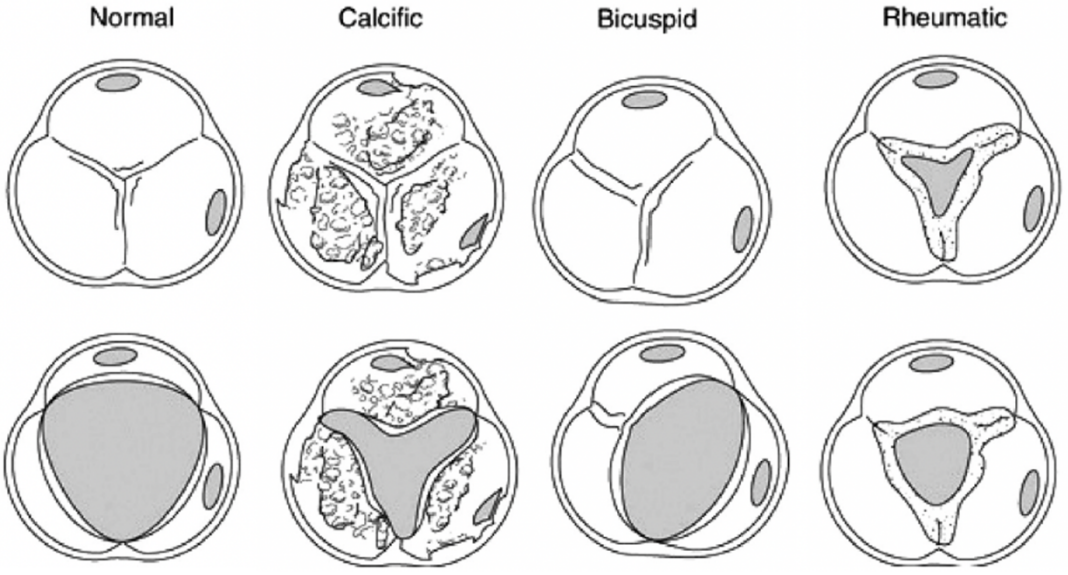


Figure 1. Etiology of aortic valve stenosis. Comparison of aortic valves displaying a normal morphology, calcific aortic valve stenosis, bicuspid aortic valve stenosis and rheumatic aortic valve stenosis (3). Adapted from Baumgartner H et al., Recommendations on the Echocardiographic Assessment of Aortic Valve Stenosis: A Focused Update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography, J Am Soc Echocardiogr. 2017;30(4):372-92. by permission of Oxford University Press.

Calcific aortic valve stenosis

Calcific AS of a tricuspid AV, the most common presentation of AS, is usually found in patients in their 60s and 70s (2-7 % of the population >65 years) (10, 11). AV sclerosis, which is considered a precursor to calcific AS, has an even higher prevalence. It affects about 25 % of the population above 65 years and 48 % of the population above 85 years (12). In about 15 % of patients, sclerosis progresses to stenosis within a period of 2-5 years. Once mild stenosis develops, further progression to severe AS occurs in almost every patient (9). The speed at which mild AS advances to severe AS differs widely between individuals. The mean annual increase in peak jet velocity is 0.1-0.3 m/s and in the mean gradient is 3-10 mmHg, whereas the aortic valve area (AVA) decreases by 0.1 cm^2 annually (13).

Calcific AS differs from other etiologies due to its arteriosclerotic pathogenesis (see 4.1.3) and its deferred age of onset. Furthermore, it differs in terms of its morphological appearance, as it presents without commissural fusion (Figure 1, middle left) (11).

Congenital (bicuspid and unicuspid) aortic valve stenosis

Congenital AS is the second most frequent etiology and predominantly affects younger patients in their 40s and 50s (mostly <65 years) (10, 11). It includes bicuspid (Figure 1, middle right) as well as unicuspid (not shown in Figure 1) AVs, though the latter is very rare. A BAV in adults, where two valves are fused together, can also be the result of calcification (3). BAV, the most common congenital heart disease, is found in 1-2 % of the US population (8, 9) and in around 6 % of patients eligible for transcatheter aortic valve implantation (TAVI) (14). Almost all BAV patients require aortic valve replacement (AVR) at some point in their life (9).

Rheumatic aortic valve stenosis

The incidence of rheumatic AS has plummeted in the developed world; however, in the developing world it remains prevalent in patients aged between 10 and 30 years (10, 11). It is caused by a throat infection with *Streptococcus pyogenes*, which can lead to long-term damage to the heart. Intramuscular administration of penicillin G is an effective treatment of *Streptococcus pyogenes* and explains the dwindling incidence of rheumatic AS in the developed world (15). In rheumatic AS, the cusps thicken and calcify mostly along the edges with the commissures fusing to create a triangular systolic orifice (Figure 1, right) (3, 13).

Figure 2 shows the historical transformation of AS from a mainly rheumatic and congenital etiology in the 1960s to a predominantly calcific etiology today. Figure 2 A was published in 1968 by Ross and Braunwald. It shows that patients with latent AS under the age of 60 years lived a fairly asymptomatic life with a comparable survival to the rest of the population. Towards the end of the latent phase, around the age of 60, severe symptoms became manifest, and survival fell dramatically. The transition towards the calcific etiology, which is currently the predominant form of AS and usually presents in older age groups, can be observed by the 15-year elongation of the latent period in Figure 2 B compared to Figure 2 A. It should be noted that the onset of severe symptoms still leads to a rapid decrease in survival unless AVR is performed promptly (6).

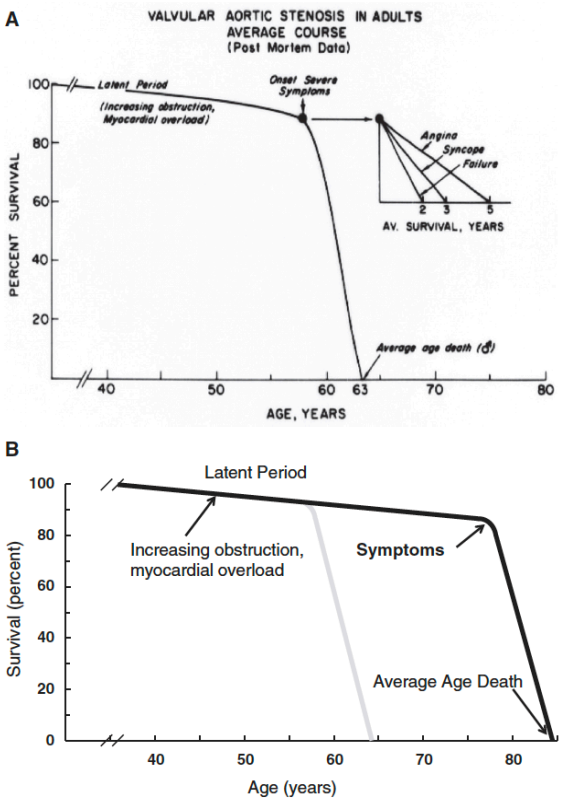


*Figure 2. **A**, Average survival in a cohort of AS patients, where AS was caused mainly by a rheumatic and congenital etiology around the 1950s. It illustrates the serious consequences of symptom presentation on average life expectancy. **B**, An adaption of diagram 2A showing the change of AS pathogenesis towards a calcific etiology today, which results in deferred symptom onset (6). Reprinted with kind permissions from Carabello BA, Introduction to aortic stenosis, Circ Res. 2013;113(2):179-85, https://www.ahajournals.org/doi/10.1161/circresaha.113.300156.*

4.1.3 Pathophysiological processes in aortic valve stenosis formation

Different modes of AS formation are known, each emerging from a complex interaction between genetic, immunological, and mechanical factors. Since the pathophysiology of calcific AS is pivotal to this study's research question, only this form will be described in detail. The hemodynamic changes that arise once AS has formed are mostly independent of its etiology. They are described below by illustrating the final common path of hemodynamic changes and structural myocardial transformations.

4.1.3.1 Pathophysiology of calcific aortic valve stenosis

Two distinct stages of calcific AS pathophysiology can be differentiated. The stage at which the disease originates is called the initiation phase, whereas the propagation phase describes the acceleration of disease progression. Both stages mostly occur consecutively; however, to some extent they also occur simultaneously.

The initiation phase starts with exposure of the AV to recurring mechanical and shear stress, which can lead to endothelial damage (16). From this point onward, the processes of this stage reflect an active inflammatory process similar to coronary arteriosclerosis (17). Following endothelial damage, immune cells infiltrate the AV leaflets, lipids accumulate, and leaflet fibrosis develops (16). This leads to thickening of the AV leaflets and ultimately triggers the

process of calcification. Both factors lead to progressive LVOT obstruction (16, 18). The similarity of this process to the development of coronary arteriosclerosis explains the important role of shared risk factors, which include male sex, advanced age, smoking, diabetes mellitus, metabolic syndrome, as well as increased blood levels of low-density lipoprotein cholesterol and lipoprotein(a) (3). Additional risk factors for aortic valve calcification (AVC) include thoracic radiation damage, e.g., due to radiation therapy in breast cancer treatment, which can cause changes in the aortic annulus and lead to severe calcification of the valves. Radiation damage can also lead to AS at a younger age (19).

The key process in the propagation phase is the transformation from valvular interstitial cells to osteoblast-like cells. This transformation is controlled by inflammatory cells which secrete certain cytokines (i.e., transforming growth factor beta 1 and others). The osteoblast-like cells cause an acceleration of disease progression by promoting further calcium deposition. During this progression the secretion of procalcific mediators becomes increasingly independent of immune cells, creating a positive feedback loop as more calcium deposits lead to further calcification. This is followed by a persistent accretion of AVC and fibrosis which, after some time, transitions from sclerosis to stenosis (16, 20). In histological samples, this process was shown to induce the development of cartilaginous and bone tissue in the valve. Furthermore, calcium deposits restrict leaflet motion resulting in worsening of LVOT obstruction and an increase in transvalvular pressure gradients (8). The extent of valve calcification has also been shown to predict the risk of heart failure, need for AVR, and death (3).

4.1.3.2 Hemodynamic changes during AS progression irrespective of AS etiology

Irrespective of AS etiology, progressive stenosis and consequent hemodynamic changes are similar. Decreased AV responsiveness caused by calcific degeneration, or a different etiology, leads to narrowing of the AV orifice. The resulting obstruction causes a decrease in blood flow from the left ventricle. To maintain the left ventricular ejection fraction (LVEF), the left ventricle compensates the obstruction by becoming progressively enlarged, resulting in concentric hypertrophy and chamber stiffness (21). LV hypertrophy is present in 60 % of patients undergoing TAVI (22). As the AV orifice area diminishes, hypertrophy progresses, which in turn reduces systemic and coronary blood flow while causing diastolic relaxation abnormalities (21). This results in LV diastolic dysfunction and increased filling pressure, which in turn was shown to be associated with higher mortality after AVR (22). Nevertheless, it should be mentioned that the extent of concentric hypertrophy is only partly attributable to the degree of obstruction of the AV; many other factors have also been shown to play a significant role (8).

Excessive afterload of the left ventricle leads to left atrial dilatation, which precipitates mitral regurgitation and atrial fibrillation (AF) (22). In later stages of the disease, ventricular dilatation develops. This process is promoted by an interplay of factors including myocardial ischemia, fibrosis, and apoptotic cell death. The process of ventricular dilatation parallels the onset of clinical symptoms, which is seen as a precursor to a sharp drop in survival (Figure 2) (8). The dwindling cardiac output also entails a decreased transvalvular gradient, while the pressure in the pulmonary artery and left atrium increases, which ultimately causes secondary pulmonary hypertension. Pulmonary hypertension is observed in 45-75 % of patients with severe AS and is

an independent predictor of mortality after AVR. Pulmonary hypertension eventually results in right ventricular remodeling, dilatation and ultimately to right ventricular dysfunction, which can be detected in 25 % of patients with severe AS and correlates with an increased risk of adverse events after AVR (11, 22).

4.1.4 Clinical background

The onset of symptoms marks a crucial juncture in the progression towards severe AS, as it leads to a plunge in survival (Figure 2). To identify individuals at risk of rapid disease progression, symptoms have to be spotted swiftly, for which knowledge of their underlying pathologies is critical (6).

Angina pectoris

This occurs when oxygen demand surpasses oxygen supply in the myocardium. In AS both oxygen demand and supply are affected by an interplay of anatomical and pathophysiological constraints. This leads to a high rate of 35 % of AS patients with angina pectoris as their main symptom (6).

Syncope

An interruption of cerebral blood flow caused by temporary hypotension is referred to as syncope. In patients with AS, a syncopal episode typically occurs during physical exercise. The interruption of blood flow often triggers a brief period of unconsciousness (6).

Dyspnea

Interestingly, the underlying mechanisms of this symptom are still unknown even though it is very common and presents early. Like the previous symptoms, an interplay of factors is thought to be the underlying cause. It is hypothesized to originate from systolic dysfunction, diastolic dysfunction, or both (6). Shortness of breath can be difficult to assess correctly, as some patients might maintain a much higher or lower level of daily physical activity than the average population (11).

Fatigue

Here, a combination of dyspnea and other factors come into play. Fatigue is a very early symptom, which is highly prevalent in the AS patient cohort. It is also more difficult to diagnose, as it causes patients to subconsciously reduce their daily activities, prompting a denial of symptoms at routine examinations (11).

Acute decompensation of heart failure

Acute decompensated heart failure commonly refers to a potentially life-threatening aggravation of pre-existing cardiomyopathy. In the case of AS, acute decompensations often occur supplementary to a continuous decline in health. These acute events are mostly due to concomitant preconditions to AS, like AF, which impairs filling of the hypertrophic left ventricle by stifling the atrial systole, or aortic regurgitation, which cannot be compensated by a small hypertrophic left ventricle. It presents with symptoms of obstruction and fluid overload (i.e.,

exertional dyspnea and peripheral edema). Acute decompensated heart failure has a high one-year mortality risk of up to 30 % after the index hospitalization (11, 23).

Even if patients are not aware of any current symptoms, great care must be taken to ensure proper diagnosis and patient management. In summary, early identification of AS patients based on clinical observations can be challenging, as symptoms are rather unspecific and could be consequences of other pre-existing comorbidities (11).

4.1.5 Classification

The classification of AS is constantly evolving and today increasingly distinguishes between hemodynamically distinct subtypes (24). The definition of high-gradient AS relies on four variables which are primarily assessed non-invasively using echocardiographic parameters: AVA, AVA indexed by body surface area (indexed AVA), mean pressure gradient (MPG), and peak aortic jet velocity (V_{max}) *(3)*.

High-gradient AS classification according to Baumgartner et al. (3):

- *Mild*: V_{max} 2.6 – 2.9 m/s, MPG <20 mmHg, AVA >1.5 cm^2, indexed AVA >0.85 cm^2/m^2
- *Moderate:* V_{max} 3-4 m/s, MPG 20-40 mmHg, AVA 1.0 cm^2 - 1.5 cm^2, indexed AVA 0.6-0.85 cm^2/m^2
- *Severe:* V_{max} ≥4 m/s, MPG ≥40 mmHg, AVA <1.0 cm^2, indexed AVA <0.6 cm^2/m^2

Nearly 25 % of individuals with severe AS develop a low-flow state (stroke volume index <35 mL/m^2). Of these, up to 10 % are low-flow low-gradient AS, which develops when the LV systolic function is also impaired. Paradoxical low-flow low-gradient severe AS is present in up to 15 % of patients and occurs when stroke volume is diminished while LVEF is normal (24). The current definition of severe AS extends to the low-flow low-gradient and paradoxical low-flow low-gradient hemodynamic subtypes; however, their diagnosis requires two additional echocardiographic variables: LVEF and stroke volume index (1).

- *Low-flow low-gradient severe AS with low LVEF*
  LVEF <50 %, stroke volume index <35 mL/m^2 and AVA ≤1 cm^2 in low-dose dobutamine stress testing, with V_{max} <4 m/s and MPG <40 mmHg (1).

- *(Paradoxical) Low-flow low-gradient severe AS with preserved LVEF*
  LVEF >50 %, stroke volume index <35 mL/m^2 and AVA ≤1 cm^2 in low-dose dobutamine stress testing, with V_{max} <4 m/s and MPG <40 mmHg (1, 25).

The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines also propose a classification system to grade AS severity. Beside slight deviations from the above definitions, it also includes anatomical properties of the AV, hemodynamic effects, and symptoms to allow a more detailed differentiation into seven distinct stages of AS severity. These subtypes range from patients at risk of developing AS to symptomatic severe low-gradient AS with preserved LVEF (26).

Recent studies proposed a new approach to stage AS severity using additional echocardiographic markers that represent the extent of extravalvular changes seen during disease progression (section 4.1.3). This novel classification was defined by Fukui et al. and proposes five distinct stages of cardiac damage (22):

- *Stage 0:* No cardiac damage identified

- *Stage 1:* Damaged left Ventricle
  - *Echocardiographic criteria*: High LV mass index, early mitral inflow to early diastolic mitral annulus velocity >14 or LVEF <50 %

- *Stage 2:* Damaged left atrium or mitral valve
  - *Echocardiographic criteria:* Indexed left atrial volume >34 mL/m^2, ≥moderate mitral regurgitation or evidence of AF

- *Stage 3:* Damaged pulmonary vasculature or tricuspid valve
  - *Echocardiographic criteria*: Systolic pulmonary hypertension ≥60 mmHg or ≥moderate tricuspid regurgitation

- *Stage 4:* Damaged right ventricle
  - *Echocardiographic criterion*: ≥moderate right ventricular dysfunction

This classification was shown to improve 1- and 2-year mortality predictions post-TAVI. Progression from one stage to the next leads to a 45 % increase in the 1-year mortality risk. This novel methodology provides for detecting patients in need of a thorough follow-up and allows a continuous evaluation of relevant extravalvular changes (22). However, it requires further prospective validation in mild, moderate and severe AS patients, as well as further examination of its predictive ability when combined with the current classification of AS severity (27).

4.1.6 Diagnostics

In most cases, AS is diagnosed coincidentally at regular physical checkups or an echocardiographic assessment due to another ailment. Additionally to the symptoms mentioned before, other early warning signs of severe AS may be present during patient examinations. These include ‘pulsus parvus et tardus’, which can be felt above the carotid artery, where ‘parvus’ refers to a small amplitude and ‘tardus’ to a slowly rising carotid pulse. This symptom is commonly absent in elderly patients suffering from arterial stiffness, thus decreasing its diagnostic usefulness (11). Physicians should also listen out for a heart murmur, click or other irregular sounds (17). The characteristic murmur of severe AS, which is typically transmitted to the carotids, can be described as crescendo-decrescendo and mid-systolic. Its intensity is specific to the degree of stenosis. Unfortunately, if cardiac output is low the intensity can be softened and thus its sensitivity in a significant patient segment is diminished (11).

Echocardiography

The diagnostic method of choice for diagnosing AS non-invasively and without radiation exposure is transthoracic echocardiography (TTE). The new European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines highlight that any echocardiographic classification of AS severity should be conducted under adequate blood pressure control (1). To assess AS severity, additional utilization of the echocardiographic Doppler mode is required. When interpreted correctly, both modes combined can provide most measurements needed for diagnosis and further therapeutic planning (11). They can help identify and measure LV function, effective orifice area (EOA), pressure gradients (including MPG), coexistent aortic regurgitation, AV morphology and sclerosis, as well as other aortic or valvular irregularities. The Doppler mode is also frequently used to monitor long-term patient outcomes (17). One of the most relevant predictive indicators is V_{max}, which is closely associated with adverse events, whose incidence rates steadily increase between mild (V_{max} <3 m/s) and very severe (V_{max} >5 m/s) stenosis. Very severe stenosis detected by TTE also significantly correlates with all-cause mortality in patients, irrespective of whether a therapeutic intervention is performed. 79 % of patients with rapidly progressing AS (i.e. V_{max} increase of >0.3 m/s/year plus ≥ moderate AVC) experience symptoms or mortality after 24 months (27). The Doppler mode can further be used to determine the Doppler velocity index (quotient of LVOT time velocity integral and V_{max}), which can aid decision making in the case of ambiguous TTE measurements. Severe AS is highly likely when the Doppler velocity index is <0.25 (1).

Accurate TTE measurements can be difficult to obtain in some patients and pressure can only be measured indirectly (17). If results are unambiguous (i.e. MPG >40 mmHg), no other measurements are required to diagnose severe AS. In case of suboptimal image quality, transesophageal echocardiography (TEE) can be used, as it enables an enhanced evaluation of AV morphology (8). In patients presenting with low LVEF and low gradient, TTE can be performed with additional low-dose dobutamine administration to rule out pseudo AS (28). In case of inconclusive dobutamine stress echocardiography results, the ESC/EACTS guidelines recommend using multidetector row CT (MDCT) calcium scoring to assess AS severity in patients with low-flow low-gradient AS or paradoxical low-flow low-gradient AS (1, 25, 29).

Speckle-tracking echocardiography (STE) is an innovative enhancement of conventional Doppler echocardiography. It allows the assessment of LV global longitudinal strain (GLS), which enables the detection of subclinical myocardial dysfunction not measurable by standard echocardiographic assessments. LV STE-GLS was shown to correlate with symptom emergence, myocardial fibrosis, need for AVR, and an increased mortality risk (22, 27). A recent meta-analysis showed that patients presenting with LV STE-GLS of ≥-14.7 % were more than 2.5 times more likely to experience premature mortality (30). In 10-20 % of patients, STE cannot be performed due to an insufficient echocardiographic assessment. In these cases, LV GLS determination using cardiovascular magnetic resonance imaging (CMR) or computed tomography angiography (CTA) was recently performed, but must be further validated in future studies (22, 27).

Coronary angiography and left heart catheterization
The current ESC/EACTS guidelines recommend performing coronary angiography before any AVR to evaluate the presence of relevant coronary artery disease. Contrariwise, retrograde LV catheterization is recommended only if patients exhibit typical clinical features of severe AS and all non-invasive diagnostic methods remain inconclusive (1). Retrograde LV catheterization provides the benefit of allowing direct pressure measurement, calculation of the EOA, and providing further –in most cases decisive– information (17). Nowadays, these angiographic approaches are not primarily used to assess AS presence or severity, but for instance rather to spot relevant coronary artery pathologies pre-AVR and to enable percutaneous coronary intervention when necessary (21).

Computed tomography
Computed tomography (CT) is currently not recommended by ESC/EACTS clinical guidelines as a primary tool to diagnose AS and should only be performed in cases of severe low-flow low-gradient AS combined with LV dysfunction without contractile reserve. This is where CT is superior to echocardiography, as it is unaffected by hemodynamic alterations (1, 16). Furthermore, CT offers the most precise annulus measurement and best quantification of AVC of all imaging modalities. Today, multi-slice CT (MSCT) –also called MDCT– scans are typically used due to their greater comparative cost-effectiveness and higher spatial as well as temporal resolution. Generally, MSCT scans can either be performed in a CTA mode, with administration of iodinated contrast medium, or using a non-contrast-enhanced (NECT) technique. Unlike the two previous modalities, an MSCT scan alone cannot provide hemodynamic data, making it impossible to calculate the EOA using only MSCT data (1, 17).

Determining AS severity by means of MSCT using other indicators is nonetheless feasible. Several publications showed that AVC significantly correlates with AS severity. Severe AS is very likely in patients presenting with a high concentration and degree of AVC in NECT scans (>3,000 Agatston units (AU) in men and >1,600 AU in women). Contrariwise, severe AS is unlikely in patients presenting with a non-severe concentration and degree of AVC in NECT scans (<1,600 AU in men and <800 AU in women). Furthermore, studies showed that severe AVC, determined with the sex-specific AU thresholds mentioned above, correlates with a three times faster progression of MPG. Therefore, NECT AVC measurements can help stratify patients according to their risk of disease progression, aiding the determination of individual follow-up intervals (16).

The drawback of NECT scans is that they are unable to detect non-calcific leaflet fibrosis. This is relevant as AS is the result of an interplay of gradual thickening, fibrosis, and calcification of AV leaflets. Furthermore, non-calcific leaflet fibrosis per se can lead to similar levels of hemodynamic obstruction, particularly in young females and patients with a BAV (16). It was thus recognized that NECT scans might underestimate AS severity in these patients, which led to further research into how the assessment of this pathological process can be enhanced. Cartlidge et al. demonstrated that both AVC and non-calcific leaflet fibrosis can be evaluated using CTA scans. CTA-derived fibrocalcific volume indexed to the annulus area was shown to evaluate AS severity accurately and in accordance with echocardiographic AS assessments. Furthermore,

they were able to show that CTA-derived indexed fibrocalcific volume correlates more strongly with TTE-derived V_{max} measurements than with those provided by NECT scans. However, these findings are based on a small patient collective and therefore require further validation (31).

As more and more publications are focusing on the role of calcification, its importance in AS formation and AS progression is becoming clearer. Many studies have suggested that severe AVC may be a significant indicator of cardiovascular morbidity and further adverse events. Its unique ability to examine AVC non-invasively and the extensive benefits mentioned above (17), makes MSCT an essential tool in the future. Drawbacks of the MSCT imaging modality are detailed in section 4.2.2.

Magnetic resonance imaging

Finally, another non-invasive modality which –until recently– has rarely been used in this setting is magnetic resonance imagining (MRI), specifically CMR. It is the only imaging technique that can acquire hemodynamic and anatomical data simultaneously, while also providing detailed three-dimensional information without requiring ionizing radiation. It was shown that CMR-derived aortic root dimensions correlate well with TTE data. However, in some aspects it is inferior to MSCT, e.g. lower spatial resolution, failure to adequately detect calcium, longer scan times, higher expenditure, and scarcer availability. In the past, these drawbacks have impeded its potential to become a standard diagnostic tool for AS assessment (17). Lately, more studies have focused on the ability of CMR to enhance the assessment of AS severity, as well as its role in pre-procedural risk stratification and optimization of AVR timing.

Currently, CMR is seen as the non-invasive gold standard for analyzing the extent of myocardial fibrosis. It was shown that CMR-derived myocardial fibrosis assessment can accurately evaluate LV cardiac damage and provide valuable information for AS risk stratification. Specifically, late gadolinium enhancement (LGE) on CMR shows irreversible replacement fibrosis, which is associated with a poor long-term prognosis even after AVR. Furthermore, CMR's native T1 mapping enables the detection and quantification of potentially reversible diffuse fibrosis and indexed extracellular volume. Both were found to be increased in AS patients and to independently correlate with adverse events. These new findings make CMR more appealing when it comes to AS diagnostics and risk stratification; however, more studies are needed to validate its usefulness in routine clinical use (22).

4.1.7 Therapy

Since AS is viewed more as an actively rather than a passively developing disease, analogous therapeutic approaches to those of arteriosclerosis have been tested and reported in the past. However, randomized controlled trials (RCTs) have shown that statin therapy, which is frequently used in arteriosclerosis, does not influence AS progression. Until now, no other pharmaceutical was found to influence AS formation (11). However, this does not mean that certain pharmaceuticals cannot improve the prognosis of AS. According to current guidelines, anti-hypertensive medication in patients with uncontrolled hypertension was shown to be beneficial. This is due to a reduction in afterload on the left ventricle which, without medication, would cause symptoms to present at a lower degree of EOA narrowing (24). Besides,

Angiotensin-converting enzyme inhibitors can have positive myocardial effects prior to symptom onset while also being beneficial after AVR (1). Another frequent concomitant disease to AS is coronary artery disease, which underlying cause, hypercholesteremia, should be carefully treated with statins (26).

Since there is currently no other viable therapeutic option available to delay or correct the process of AS formation, interventional AVR is the treatment of choice. Two main forms of intervention currently exist. Surgical aortic valve replacement (SAVR) is recommended by the current ESC/EACTS and ACC/AHA guidelines for treating severe AS in low surgical risk patients under the age of 75 years. The other intervention is the TAVI procedure, where the valve is replaced using a transcatheter technique. According to current ESC/EACTS guidelines TAVI is mostly restricted to patients over 75 years as well as to high- and intermediate surgical risk patients. In recent research, the patient groups deemed suitable for TAVI were extended to low-risk patients; however, only 2-year data have been published. These studies found TAVI with self- and balloon-expandable transcatheter heart valves (THV) to be non-inferior or slightly superior to SAVR in low surgical risk individuals (1, 26, 32-37).

During traditional SAVR the native AV is removed and replaced by a prosthetic valve. It requires a midline sternotomy as well as the use of cardiopulmonary bypass during the operation. Post-surgery, patients are strictly admitted to the intensive care unit (ICU) for 24 to 48 hours, followed by another 10 to 14 days on a normal care unit (21). SAVR allows a substantial improvement in symptoms and quality of life. It often entails a longer recovery time compared with TAVI; however, post-SAVR older patients display a comparable mortality to that of a group of age-matched individuals. In younger patients, SAVR accomplishes better outcomes compared to conservative therapy. In contrast, post-SAVR long-term survival of younger patients was found to be lower than that of age-matched controls (11). In recent years, minimally invasive approaches have become an option for SAVR, including mini-sternotomy, right anterior sternotomy, and other minimally invasive techniques. These approaches, although more technically demanding, shorten ICU and hospital stays while also decreasing postoperative pain. Recent studies have shown a similar level of mortality compared to traditional SAVR; however, additional RCTs are needed before minimally invasive SAVR is routinely performed (38).

The TAVI procedure offers a different approach to AVR, as the THV is placed within the native AV and no sternotomy or thoracotomy is required. It presents a less invasive technique, mostly using a percutaneous transfemoral (TF) access, to treat severe AS. The hemodynamic outcomes are often slightly inferior to those following SAVR, but the lower invasiveness results in a quicker convalescence and more rapid symptom relief post-TAVI (8, 11). ICU admittance post-TAVI is not mandatory; instead, patients are monitored for four hours after which they return to a normal care unit. Usually, patients are discharged within 48 hours post-TAVI (21). Even though TAVI has become a standard procedure for AVR in older patients, long-term data (≥5-8 years) comparing TAVI and SAVR are still lacking or are only available for selected cohorts (39). The TAVI technique is discussed in detail in section 4.2.

4.1.7.1 Therapeutic approaches to symptomatic severe aortic valve stenosis

An intervention should be offered to every symptomatic patient with confirmed severe AS as early as possible. This is the best option, since no other medical treatment significantly improves survival rates compared with the natural history of this disease. Nevertheless, aberration of sinus rhythm and concomitant hypertension should be treated and controlled consistently. As hypotension should be avoided, drugs should always be administered with caution. Furthermore, patients scheduled to undergo a procedure should be medically treated when presenting signs of heart failure. This treatment can include diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Similarly, those deemed unsuitable for an intervention due to heart failure should be treated and the procedural feasibility of AVR should be subsequently reevaluated (1, 11).

Current ESC/EACTS guidelines recommend criteria for performing TAVI or SAVR in patients with symptomatic AS. The ESC/EACTS guideline recommendations, including their definition of the different strengths of recommendation and levels of evidence, can be found in the original publication by Vahanian et al. (1).

ESC/EACTS guidelines recommend AVR in symptomatic patients with (1):

- severe high-gradient AS (MPG ≥40 mmHg or V_{max} ≥4 m/s and AVA ≤1.0 cm^2 or indexed AVA ≤0.6 cm^2/m^2) (class of recommendation I, level of evidence B)
- severe low-flow low-gradient AS with reduced LVEF and additional evidence of contractile reserve excluding pseudo-severe AS (class of recommendation I, level of evidence B)

ESC/EACTS guidelines state that AVR should be considered in symptomatic patients with (1):

- low-flow low-gradient AS with preserved LVEF after a thorough validation of severe AS being present (class of recommendation IIa, level of evidence C)
- severe low-flow low-gradient AS combined with LV dysfunction without contractile reserve, especially after severe AS is indicated by CT calcium scoring (class of recommendation IIa, level of evidence C)

Figure 3 provides an overview of how severe AS should be managed according to current guidelines. Criteria to determine the correct interventional mode in symptomatic patients with severe AS are explained in detail in section 4.2.4.

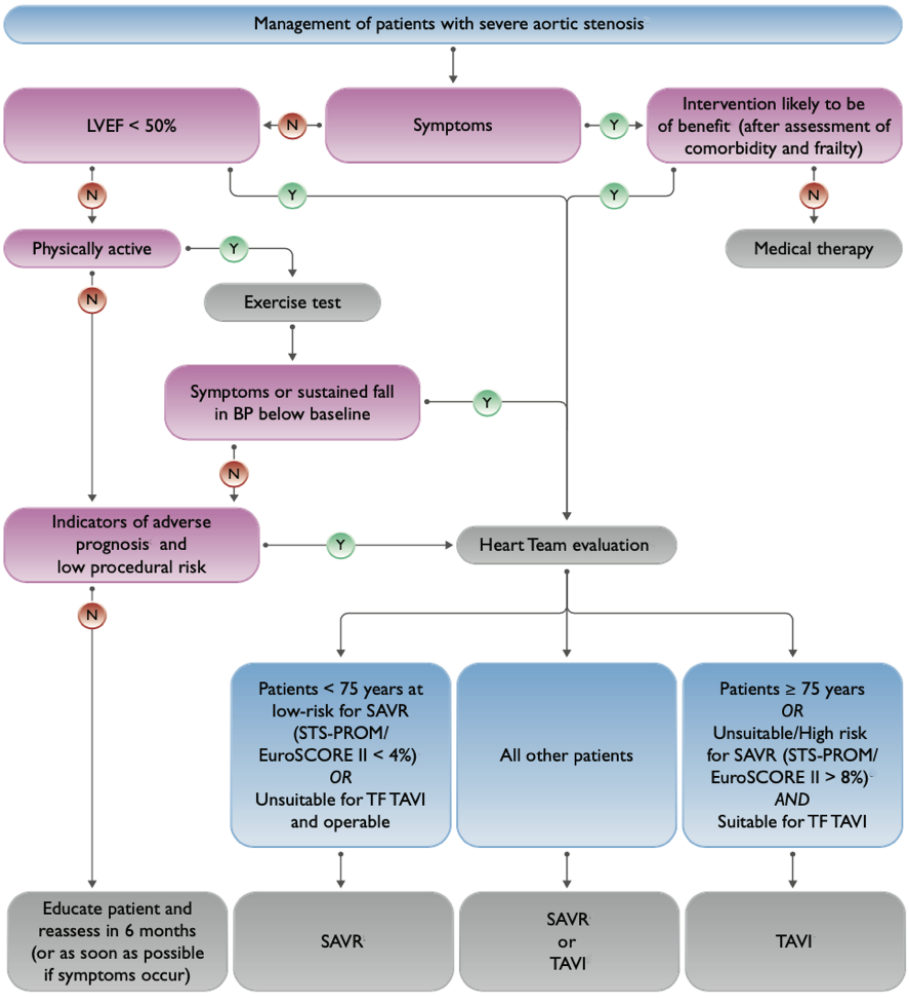


Figure 3. Flow chart showing severe AS management and procedural options (1). ***BP*** *= blood pressure;* ***EuroSCORE*** *= European System for Cardiac Operative Risk Evaluation;* ***LVEF*** *= left ventricular ejection fraction;* ***SAVR*** *= surgical aortic valve replacement;* ***STS-PROM*** *= Society of Thoracic Surgeons Predicted Risk of Mortality;* ***TAVI*** *= transcatheter aortic valve implantation;* ***TF*** *= transfemoral. Adapted from Vahanian A et al., 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2021, by permission of Oxford University Press.*

4.1.7.2 Therapeutic approaches to asymptomatic severe aortic valve stenosis

In the past, the risk of mortality posed by AVR was considered to outweigh the risks of watchful waiting in the latent phase of AS. In practice, the therapeutic strategy for the majority of these patients consists of thorough clinical and echocardiographic evaluations at follow-ups and, once symptoms or LV systolic dysfunction present, the performance of AVR. However, deferred reporting of symptoms could lead to permanent cardiac damage and worse outcomes after AVR. Furthermore, observational studies showed a poorer prognosis for conservatively treated asymptomatic patients with severe AS compared to patients who underwent AVR. One publication showed a survival advantage of early SAVR (i.e., within 3 months of being diagnosed with severe AS) by comparing patients who underwent early SAVR to patients who underwent AVR once symptoms emerged. This finding caused the ESC/EACTS to amend their guidelines to include further recommendations regarding asymptomatic patients with a low surgical risk to optimize AVR timing (27). These amendments aim at predicting symptom progression or future adverse events in this cohort and are based on patient characteristics, echocardiographic measurements, and biomarkers. Current ESC/EACTS guidelines recommend

criteria which apply only for early SAVR, as TAVI has not yet been approved for this cohort. For patients who do not fulfill the criteria stated below, regular follow-ups with re-evaluations of the indications for AVR are recommended (1, 11).

ESC/EACTS guidelines recommend SAVR for (eligible) asymptomatic patients with severe AS and (1):

- systolic LV dysfunction (LVEF <50 %) that is not caused by a different ailment (class of recommendation I, level of evidence B)
- abnormal exercise tolerance in terms of typical AS symptom presentation during exercise (class of recommendation I, level of evidence C)

According to ESC/EACTS guidelines SAVR should be considered for (eligible) asymptomatic patients with (1):

- severe AS and abnormal exercise tolerance presenting as a fall in blood pressure (>20 mmHg) beneath baseline values (class of recommendation IIa, level of evidence C)
- severe AS and systolic LV dysfunction (LVEF <55 %) not caused by a different ailment (class of recommendation IIa, level of evidence B)
- LVEF >55 %, normal exercise tolerance, a low surgical risk and any one of the following (class of recommendation IIa, level of evidence B):
  - very severe AS (V_{max} >5 m/s or MPG ≥60 mmHg)
  - severe AVC with a progression of V_{max} of ≥0.3 m/s/year
  - more than three times higher brain natriuretic peptide (BNP) levels than the age- and gender-corrected standard range in repetitive measurements, not caused by a different ailment

However, due to a lack of substantial data the correct timing of AVR in individuals presenting with asymptomatic AS remains unclear (1, 11).

The presence of LV systolic dysfunction, defined by the ESC/EACTS guidelines as an LVEF <55 %, is associated with an increased risk of mortality and currently represents an indication for AVR in this cohort (1, 26). Studies have shown that in roughly a quarter of patients, LVEF fails to recover after AVR, which entails unfavorable long-term events. The HAVEC ('Heart Valve Clinic International Database') registry showed that the prognosis and heart failure associated mortality was significantly better in patients undergoing AVR with an LVEF of >60 % compared to those with 50-59 %. These findings prompted the scientific community to demand a change in the definition of LV systolic dysfunction to an LVEF cut-off at <60 % in future guidelines (27).

With the advent of LV STE-GLS measurements and advancements in CMR imaging, new possibilities for more accurate pre-interventional risk stratification have emerged. A reduced STE-GLS <14.7 % is associated with a significantly higher mortality risk and provides an early warning by indicating systolic dysfunction while the ejection fraction (EF) is still normal. In CMR imaging, the identification and quantification of LGE midwall patterns, representing myocardial fibrosis, correlates with LV decompensation. Once LGE midwall patterns emerge,

further fibrosis is quickly amassed and remains permanent even after AVR. This could negatively affect long-term outcomes long after the intervention. These findings led to the proposition to enhance long-term outcomes by performing AVR once midwall LGE is identified (27).

Using circulating blood biomarkers to stratify asymptomatic patients could provide an easy and accessible alternative. However, finding a specific biomarker is difficult, as adaptive and maladaptive processes are closely intertwined and differentiating between them is challenging. Recent studies show that the process of hypertrophic remodeling is too complex to be properly represented by BNP levels alone, which is secreted only when the ventricles are stretched. It has been suggested that patients with high levels of BNP could benefit from early AVR, but this remains to be proven. Other blood biomarkers could help expose maladaptive hypertrophic remodeling in asymptomatic patients, which occurs in response to the increasing narrowing of the EOA and pressure overload. This form of remodeling is associated with inferior systolic function, a reduced chance of survival, and aggravated heart failure symptoms (1, 22, 27). Preclinical studies were able to illustrate the function of biomarkers like Growth Differentiation Factor 15, soluble suppression of tumorigenicity-2, and high-sensitivity troponin in the development of hypertrophic remodeling on a cellular level, and a certain prognostic ability was observed. For example, high-sensitivity troponin was shown to correlate with the extent of hypertrophic remodeling and myocardial fibrosis, as well as offer the possibility to identify the transition from adaptive LV remodeling to heart failure. Further studies are needed to clarify the relationship between specific biomarkers and clinical outcomes before they can be implemented in routine clinical use and decision-making for asymptomatic patients. Two prospective RCTs ('EARLY TAVR' and 'EVOLVED' trials) were recently designed to enhance the understanding of the role that biomarkers play in risk stratification and to optimize the timing of AVR in patients with asymptomatic AS (22, 27).

4.1.8 Follow-up

According to ESC/EACTS recommendations, patients presenting with severe AS without current symptoms should be evaluated every 6 months with regard to changes in exercise tolerance and echocardiographic criteria. These patients should be thoroughly informed about the variable pace of disease advancement and encouraged to report symptoms as soon as they manifest. A more detailed evaluation regarding the follow-up of asymptomatic patients has already been described above. In case of mild to moderate AS or substantial calcification, checkups should be performed annually. This interval can be extended to up to three years in younger patients with mild AS and trivial calcification (1, 11).

4.1.9 Prognosis

If no AVR is performed, patients are expected to survive for up to five years following an initial occurrence of typical symptoms (17). After this 5-year time span, there is a low survival rate of 15-50 % (11).

When SAVR is performed without concomitant procedures, operative mortality lies at about 1-3 % in patients below 70 years and increases to 4-8 % in a selected older population. When

performed in over 80-year-olds, SAVR was still shown to prolong and improve quality of life (11). The median survival time post-SAVR without exclusion of concomitant procedures was 16 years in patients ≤65 years, decreasing to 12 years in patients aged between 65-75 years, 7 years in those aged 75-86 years, and 6 years in those aged >85 years (40).

Thirty-day mortality rates post-TAVI have improved significantly over the years. They dwindled from early reported findings of 5-15 % to 5-7 % in current all-comer registries, and even further to rates of 1-2 % reported for the newest available devices. In high surgical risk patients, the 1-year survival lies at 60-85 %, and reaches 95 % in intermediate risk patients (11). Recent RCTs assessing (highly) selected patient cohorts at a low surgical risk showed a 2-year survival of 96.5 % for self-expanding valves (35) and 97,5 % for balloon-expandable valves (41). Post-TAVI, the improvement in symptoms and quality of life was found to be similar to that found post-SAVR. Primary 5-year results concerning long-term valve durability have been published and show similar results to surgically deployed bioprostheses (11).

4.2 Transcatheter aortic valve implantation (TAVI)

4.2.1 Conceptualization and elaboration of TAVI

The TAVI procedure was devised by Alain Cribier and colleagues and was carried out for the first time in man in 2002 (21). Its development arose from balloon aortic valvuloplasty, which has been used to treat AS since 1985. However, balloon aortic valvuloplasty is associated with high rates of re-stenosis and shows no significant survival benefit. This led researchers to develop a large stent with an attached valve prosthesis which was positioned inside the constricted AV. Trials that were initiated after the first successful procedures confirmed the feasibility and yielded decent post-procedural outcomes. In 2004, Edwards Lifesciences acquired the start-up that developed the first THVs, leading to a rapid advancement of THV-related technology. This period also marked the development of alternative access routes that are most commonly used today, different valve sizes, as well as the first CoreValve THV (42).

In 2009 the first RCT, entitled ‘Placement of Aortic Transcatheter Valves’ (PARTNER), was carried out in 23 US centers. It included 1056 high surgical risk patients. Compared to standard treatment, TAVI deployment in inoperable patients was shown to be highly beneficial in terms of 1-year mortality and hospital readmissions. Furthermore, concerning 1-year mortality in high surgical risk patients, TAVI was shown to be noninferior or superior to SAVR. The positive outcomes resulted in the Food and Drug Administration (FDA) approving TAVI for non-surgical patients in 2011. This made TAVI a widely accepted treatment method for severe AS in patients unfit for SAVR (42).

After favorable outcomes in the PARTNER I (2017) and US Pivotal trials (first results in 2015), the number of TAVI procedures increased, and its utilization was further expanded to intermediate surgical risk patients. Further trials were conducted to show comparable results in patients with an intermediate surgical risk; these included PARTNER II (mean STS score ~5.8 % ± 2.0 %) and SURTAVI (Surgical Replacement and Transcatheter Aortic Valve

Implantation) (mean STS score ~4.5 % ± 1.6 %). The results confirmed previous findings that TAVI is equivalent to SAVR in terms of short-term outcomes. Nevertheless, a fairly high rate of paravalvular leak (PVL), vascular complications and re-interventions remained a concern (34). By 2018 more than 350,000 procedures had already been carried out in over 70 countries (28).

Following the introduction of new-generation valves, further RCTs were conducted to test them in low operative mortality risk patients (STS-Predicted Risk of Mortality (STS-PROM) <4 %). The Evolut Low Risk trial assessed self-expanding THVs including CoreValve, Evolut R, and Evolut PRO THVs. 2-year results were published in 2021 and showed that TAVI with self-expanding THVs in low-risk patients is noninferior to SAVR at 24 months regarding the primary clinical endpoint death or disabling stroke (4.3 % vs. 6.3 %) (32, 36). The PARTNER III RCT examined Edwards SAPIEN 3 balloon-expandable THVs. The 2-year results showed that TAVI with the SAPIEN 3 THV is superior to SAVR in terms of primary composite endpoint occurrence, which consisted of stroke, death, and rehospitalization at one year (11.5 % vs. 17.4 %, p=0.007) (33, 41). A recent propensity score-weighted study using data from low-risk patients in the German Aortic Valve Registry (GARY) showed similar results in terms of superior in-hospital as well as 30-day survival of TAVI versus SAVR (43).

Current publications indicate that TAVI has become a reasonable alternative to SAVR, as it enables a procedural success rate >90 % in older patients with a high or intermediate surgical risk (11). Meanwhile, the immense rise in popularity of TAVI in recent years has become apparent, as more than 800,000 procedures had already been carried out around the world by 2021 (44). The data published for the latest THVs in low-risk patients are promising and could overcome previous hesitations regarding TAVI deployment (34). In future the treatment indication for TAVI is expected to expand and it is thought that the results of current research will lead to a wider adoption in younger and healthier patients (29). One first major step in that direction is the FDA's approval in 2019 of SAPIEN 3 and SAPIEN 3 ultra THVs, as well as the CoreValve Evolut R and Evolut PRO THVs for TAVI procedures in low surgical risk patients with severe AS (45).

4.2.2 Developments in cardiovascular imaging for TAVI

Measuring native AV dimensions during SAVR is straight-forward, as it can be done directly with a sizing probe. This is not possible during TAVI, making preprocedural imaging necessary. For TAVI to be successful, a thorough preprocedural evaluation of the aortic root, the aorta, and the peripheral access vessels (iliofemoral and axillary artery) is necessary. It allows appropriate choice and sizing of the bioprosthetic, as well as reducing the occurrence of vascular complications (8).

Historically, preprocedural imaging before TAVI was performed using two-dimensional imaging techniques like TTE, TEE, and conventional X-ray angiography. Two-dimensional imaging produced imprecise measurements of the double-oblique oriented aortic root and oval-shaped annulus. Imprecise preprocedural imaging resulted in the need to frequently perform two-dimensional aortograms during TAVI, as correct THV placement requires adequate fluoroscopic orientation to attain a projection angle that is exactly parallel to the aortic annulus. The repetitive

use of two-dimensional aortograms resulted in long procedural times and high doses of radiation and contrast media being required (8).

The advent of preprocedural MDCT imaging enabled more detailed and reproducible three-dimensional assessments. It covers the complete region between the supraclavicular level to underneath the common femoral artery. This imaging technique allows submillimeter spatial resolution and is now considered the standard of care for pre-TAVI imaging. Contrast-enhanced MDCT scans allow a thorough evaluation of the endovascular delivery pathway, an accurate prediction of the THV size, and selection of a proper THV delivery system, as well as a better prediction of peri- and post-interventional adverse events. CTA deployment enables the anticipation of a suitable fluoroscopic projection angle before the procedure, which in turn reduces the need for two-dimensional aortograms during the procedure. Furthermore, MDCT allows a superior assessment of calcification in the aortic root, of the annulus, and along the endovascular delivery pathway, even when compared to other three-dimensional imaging techniques like three-dimensional TEE and CMR. This is of great importance as calcification of the AV cusps promotes post-TAVI coronary obstruction, facilitates periprocedural annulus rupture, increases the rate of permanent pacemaker implantation (PPI), and reduces the seal between the annulus and the THV, leading to more severe PVL post-TAVI. Calcification of the aortic root can hinder valve positioning and correlates with a higher rate of periprocedural post-dilatation. Finally, post-procedural MDCT, though not routinely performed, can provide helpful insights into THV positioning, leaflet mobility, and the presence of subclinical leaflet thrombosis (8).

Drawbacks of MDCT include high exposure to radiation, the need for administering iodinated contrast medium to obtain contrast-enhanced scans, and its inability to provide hemodynamic data. The contrast medium can trigger contrast-induced nephropathy, to which the average patient undergoing TAVI is more susceptible due to advanced age and the number of comorbidities. Contraindications for contrast-enhanced MSCT scans include preexisting renal disease or allergy to iodinated contrast medium (8). Precisely when preexisting renal disease qualifies as a contraindication is currently under debate. Current research suggests that patients presenting with chronic kidney disease with a glomerular filtration rate ≥45 mL/min/1.73 m^2 have an insignificant risk of contrast-induced nephropathy. In patients with a glomerular filtration rate between 30-44 mL/min/1.73 m^2, the risk is considerably lower than previously thought (46). This means that the major advantages of contrast-enhanced MSCT regarding preprocedural planning for TAVI would in most cases probably outweigh the risk of contrast medium-induced nephropathies and radiation exposure in these groups (although an individual risk-benefit analysis should be carried out for the latter group). Patients presenting with severe chronic kidney disease (glomerular filtration rate < 30 mL/min/1.73 m^2) are still thought to be at high risk of contrast-induced nephropathy; therefore, no contrast medium should be used in these patients (46). For this group and other patients with contraindications it is advised that preprocedural imaging be performed using three-dimensional TEE or CMR (8).

The latest developments regarding cardiovascular imaging before TAVI were made in the field of CMR. In addition to the advances in diagnosis and severity assessment of AS outlined earlier,

CMR use was also extended and refined in respect to TAVI planning. It is currently considered a promising alternative to MSCT for pre- and post-TAVI assessment. Today it is used mostly in instances where pre-TAVI MSCT scans are contraindicated. However, CMR is also routinely used in patients with low-gradient AS or LV systolic dysfunction, as it provides crucial information regarding pre-TAVI planning for these patients. Previous studies confirmed that, regarding preprocedural assessments, CMR provides accurate measurements of the aortic root and AV dimensions that are comparable to MSCT and TTE, while also providing functional data on the valve and ventricles. Furthermore, it offers predictive information by utilizing tissue characterization through the use of CMR-LGE and T1 mapping techniques. In a postprocedural setting, CMR is able to thoroughly assess PVL using phase contrast velocity mapping with a far lower rate of inter- and intraobserver variability compared to TTE. Postoperative CMR assessment is aided by the fact that the two main THV manufacturers (Edwards and Medtronic) offer MR-conditional bioprosthetic THVs (8).

Some shortcomings of CMR have already been discussed in section 4.1.6; however, for TAVI planning further limitations are important. The previously mentioned inability to properly detect calcification hinders the correct estimation of AV dimensions and makes TF access planning difficult, as access way calcification and AVC are frequently found in older patients and are associated with adverse events post-TAVI (1, 16, 47). This shortcoming could be overcome by using contrast medium; however, this would mean that the greatest advantage of CMR over MSCT, namely its use in patients with preexisting renal disease, would be nullified. Further shortcomings are a pronounced sensitivity of CMR image quality to heart rate irregularities and arrhythmias, as well as the need for several breath holds, which might be troublesome for older individuals. Also, CMR is often contraindicated in individuals with status post conventional PPI, which is still common in individuals undergoing TAVI (8). Nevertheless, in general the indications for CMR have been steadily expanded in the past decades to include a variety of cardiac diseases as well as the assessment of sarcoidosis, amyloidosis, and cardiac tumors (48). It is expected that CMR will take on an ever greater role in AS evaluation and TAVI planning in everyday clinical practice, not only due to the swift advances in MRI technology, like four-dimensional flow MRI, which accurately evaluates blood flow dynamics of the cardiovascular system, but also due to its potential use in risk stratification, TAVI planning in younger patients, and CMR-guided TAVI procedures (8).

4.2.3 Pre-interventional risk stratification

Pre-interventional risk assessment is a pivotal part of planning surgical or interventional procedures, not least because it is an integral component of the informed consent procedure (49). However, even though the first-in-man TAVI procedure was successfully performed two decades ago, and TAVI deployment has surged since then, no TAVI-specific pre-operative risk stratification system has been systematically validated to date. The risk stratification tools used in most publications, as well as in this study, were developed for cardiac surgeries and not for TAVI (50). Moreover, the risk stratification scores were developed for a standard surgical risk population and therefore do not adequately include patients at the extremes of the population. This is significant, as TAVI is performed most frequently in patients with a high surgical risk, who are depicted at the right of the bell curve, therefore reducing the accuracy for this cohort

(51). Furthermore, most scores fail to include disease severity and important comorbidities such as porcelain aorta and frailty, which are critical for TAVI planning (49, 52). Therefore, publications have questioned the validity of these scores regarding the risk prediction for TAVI patients (50).

Logistic EuroSCORE I

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) I was the first risk stratification score for SAVR. It was developed in 1995 and updated to the logistic EuroSCORE I in 1999. The logistic EuroSCORE I includes a total of 17 patient-related features (51). It offers an only low predictive value regarding mortality of older and/or high-risk patients (50), and overestimates 30-day mortality (3, 52). This led to its exclusion from the 2021 ESC/EACTS guidelines (1).

Using the logistic EuroSCORE I, a patient's operative risk can be categorized into three distinct levels (53):

- Logistic EuroSCORE I < 10 % = low risk
- Logistic EuroSCORE I 10-20 % = intermediate risk
- Logistic EuroSCORE I > 20 % = high risk

EuroSCORE II

The next-generation score, called EuroSCORE II, was developed in 2010 and includes 18 patient characteristics. Even though the EuroSCORE II was considered more accurate than the logistic EuroSCORE I in terms of predicting postoperative outcomes after AVR, it was shown to regularly overpredict mortality in a higher-risk population (3, 51, 52).

Similar to the logistic EuroSCORE I, EuroSCORE II also categorizes patients' operative risk into three distinct levels (8):

- EuroSCORE II < 4 % = low risk
- EuroSCORE II 4-8 % = intermediate risk
- EuroSCORE II > 8 % = high risk

STS score

The STS score was established between 2002 and 2006 in the USA to stratify risks before cardiac surgeries and is updated regularly to improve accuracy (51). It was developed to predict 30-day mortality and morbidity rates. Later research suggested that it was also useful in forecasting one-year mortality after cardiac surgeries (49). Overall, regarding TAVI deployment the score showed an enhanced predictive accuracy as opposed to the logistic EuroSCORE I (2). The common drawbacks described above also apply to the STS score, which was shown to overpredict mortality in a TAVI cohort (54).

The STS score offers risk predictions for different outcomes; the most important in this setting is the STS-PROM score, which can be used to classify patients according to their surgical risk (8):

- STS-PROM < 4 % = low risk

– STS-PROM	4-8 %	= intermediate risk
– STS-PROM	> 8 %	= high risk
– STS-PROM	> 50 % at 1 year	= prohibitive risk

Based on data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) registry, a new score was created in 2016 to predict in-hospital mortality after TAVR. This score was found to be more precise compared to previous surgical risk models. However, only in-hospital mortality can be predicted, which is somewhat inexpedient as patients seldom die during their hospital stay but rather within 30 days post-TAVI (51).

Further TAVI-specific risk models (i.e., the 'TAVI2-SCORe' and 'CoreValve model') were recently published or are currently in development. These offer additional outcome predictions like post-TAVI stroke risk, postoperative quality of life, as well as a more precise mortality prediction. Additionally, current advances in artificial intelligence enable the use of machine-learning prediction models, which were shown to outperform the newest generation of TAVI-specific risk scores in forecasting one-year mortality post-TAVI. In the future these models could help increase the accuracy of pre-AVR patient stratification and thereby ameliorate procedural outcomes and safety (51, 55).

Definition of surgical risk according to valvular heart disease guidelines
The definition of surgical risk in the valvular heart disease guidelines goes beyond the mere calculation of a patient's risk scores. According to these guidelines, a low surgical risk can be assumed in patients who meet all of the following requirements: STS-PROM <4 %, lack of frailty criteria, no dysfunction of a major organ system, and no procedural impediments. Patients who do not fulfill all of the above criteria are rated as having an intermediate surgical risk. Specifically, an intermediate surgical risk is present if patients fulfill one of the following criteria: STS-PROM 4-8 %, one mild indexed frailty criterion, dysfunction of a major organ system, or possible procedural impediments. A patient is classified as a high surgical risk candidate if any one of the following criteria apply: STS-PROM >8 %, ≥2 moderate-severe indexed frailty criteria, dysfunction of ≤2 major organ system, or possible procedural impediments. Finally, a prohibitive surgical risk is presumed if any one of the following criteria apply: forecasted risk of all-cause mortality or major morbidity after surgery of >50 % at one year, dysfunction of ≥3 major organ systems, or severe procedural impediments (56).

4.2.4 Treatment indications for TAVI

TAVI indications are regularly expanded due to cumulating evidence that TAVI is not only superior to SAVR in high surgical risk patients, but also non-inferior or superior to SAVR in those at an intermediate to low risk. As further experience with TAVI is gained, it has crystallized that relying solely on age and risk scores for pre-interventional risk stratification is not sufficient in most cases due to their numerous limitations (57). According to the ACC/AHA and ESC/EACTS guidelines the decision should be guided by a more holistic patient evaluation, which should include AV morphology (including the degree and extent of AVC), anatomical

considerations (including coronary ostial height), intervention-specific procedural risks and impediments (including the feasibility of TF access for TF-TAVI), lifetime management, age, comorbidities, frailty, future therapeutic options once the prosthesis deteriorates, and objectives of care (1, 26).

According to the current ESC/EACTS guidelines published in 2021, SAVR is still preferred in low surgical risk patients (age <75 years and STS-PROM/EuroSCORE II <4 %) (class of recommendation I, level of evidence B); however, certain comorbidities are not included in these scores (see section 4.2.3). In intermediate surgical risk patients, SAVR or TAVI is recommended depending on a patient's specific procedural hazards. Both guidelines recommend TAVI for patients unsuitable or at high surgical risk for SAVR (class of recommendation I, level of evidence A) unless the post-TAVI outcome is not expected to improve the patient's survival or quality of life. The guidelines recommend TAVI in patients aged ≥75 years or PROM/EuroSCORE II >8 % (class of recommendation I, level of evidence A) (1).

According to the current ESC/EACTS guidelines the decision between TAVI and SAVR in the rest of the patient population should be based on anatomical considerations (e.g., porcelain aorta, unfavorable chest anomalies, residues of thoracic radiation), technical aspects, and clinical characteristics. Table 1 offers an overview of patient characteristics favoring TAVI or SAVR according to the current ESC/EACTS guidelines (1, 52).

	Favours TAVI	Favours SAVR
Clinical characteristics		
Lower surgical risk	–	+
Higher surgical risk	+	–
Younger age	–	+
Older age	+	–
Previous cardiac surgery (particularly intact coronary artery bypass grafts at risk of injury during repeat sternotomy)	+	–
Severe frailty	+	–
Active or suspected endocarditis	–	+
Anatomical and procedural factors		
TAVI feasible via transfemoral approach	+	–
Transfemoral access challenging or impossible and SAVR feasible	–	+
Transfemoral access challenging or impossible and SAVR inadvisable	+[a]	–
Sequelae of chest radiation	+	–
Porcelain aorta	+	–
High likelihood of severe patient–prosthesis mismatch (AVA <0.65 cm^2/m^2 BSA)	+	–
Severe chest deformation or scoliosis	+	–
Aortic annular dimensions unsuitable for available TAVI devices	–	+
Bicuspid aortic valve	–	+
Valve morphology unfavourable for TAVI (e.g. high risk of coronary obstruction due to low coronary ostia or heavy leaflet/LVOT calcification)	–	+
Thrombus in aorta or LV	–	+
Concomitant cardiac conditions requiring intervention		
Significant multi-vessel CAD requiring surgical revascularization	–	+
Severe primary mitral valve disease	–	+
Severe tricuspid valve disease	–	+
Significant dilatation/aneurysm of the aortic root and/or ascending aorta	–	+
Septal hypertrophy requiring myectomy	–	+

*Table 1. Characteristics of patients taken into account by the Heart Team when deciding between SAVR or TAVI (1). **AVA** = aortic valve area; **BSA** = body surface area; **CAD** = coronary artery disease; **ESC** = European Society of Cardiology; **LV** = left ventricle; **LVOT** = left ventricular outflow tract; **SAVR** = surgical aortic valve replacement; **TAVI** = transcatheter aortic valve implantation. [a]Using non-femoral access. Adapted from Vahanian A et al., 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2021, by permission of Oxford University Press.*

The factors discussed above must be evaluated for each TAVI patient individually. This evaluation should be performed by a multidisciplinary heart team, which adjudicates upon the final therapeutic procedure (class of recommendation I, level of evidence C). The heart team is a multidisciplinary group of health care specialists with expertise in all fields relevant to TAVI (1, 29). As defined by the VARC-2 (Valve Academic Research Consortium) criteria, the heart team must convene with at least the following participants present: cardiac surgeons, imaging

professionals, interventional cardiologists, and anesthesiologists (2, 28). The multidisciplinary approach also helps avoid high-risk and high-cost procedures in patients suffering from conditions due to which they are not expected to benefit from AVR. In addition to an expected minor or lack of improvement in survival and quality of life mentioned above, these conditions can include severe pulmonary disease, advanced dementia, irreversible LV dysfunction, and others (9).

The 2021 ESC/EACTS guidelines exhibit some potential shortcomings. One drawback is that they introduced age cut-offs to allocate patients to the different interventions. This is problematic as age is only one of many factors that can influence pre-operative fitness as well as post-operative survival and quality of life. This could, for example, lead to over 75-year-olds being allocated to TAVI because of their age even though they might benefit more from SAVR. Furthermore, the introduction of age cut-offs has led to ambiguities between different guidelines. Unlike the ESC/EACTS guidelines, the ACC/AHA guidelines recommend SAVR for patients <65 years and state that the decision on which intervention should be performed in patients aged 65-80 years should be made individually. A 2020 consensus paper on the indication for SAVR versus TAVI in Germany recommends SAVR in low-risk patients <70 years, while patients aged 70-75 years can receive either TAVI or SAVR (26, 58, 59). Future guidelines should include more objective criteria to allow a valid allocation of patients to the different interventions. Another limitation is that the new ESC/EACTS guidelines' recommendation to allocate low-risk patients over 75 years to either the SAVR or the TAVI group is based on the PARTNER-III and Evolut Low Risk trials. However, the outcomes of these trials (i.e., that TAVI with self- and balloon-expandable THVs is noninferior or even superior to SAVR in low-risk patients) are based on a highly selective patient cohort that excluded patients with severe LVOT calcification and other relevant criteria (32, 33, 60, 61). The shortcomings of the PARTNER-III and Evolut Low Risk trials are discussed in detail in section 4.3.

4.2.5 Modus operandi for transcatheter aortic valve implantation

4.2.5.1 Diagnostic workup before TAVI and choice of prothesis

Previously, only CT imaging was used for assessing the access vasculature. However, today MSCT is the gold standard for 'annular sizing, determination of the risk of annular injury and coronary occlusion, and to provide co-planar fluoroscopic angle prediction in advance of the procedure' (14). Crucial to an artifact-free assessment of the aortic root and heart is an ECG-synchronized CTA, which is simultaneously complemented by a non-ECG-synchronized CTA of the aortic and iliofemoral vasculature. Assessment of both the aortic root and the vasculature is an essential part of MSCT-based pre-TAVI planning (14). Pre-TAVI MSCT is performed whilst administering only minor volumes of contrast media. This volume can be further reduced at the cost of reduced image quality when patients present with renal insufficiency (28).

In this pre-TAVI setting, both CMR and TEE are currently inferior to MSCT for various previously mentioned reasons. Recently, TEE deployment has been reduced as TAVIs are increasingly performed under conscious sedation; however, in patients under general anesthesia (GA) it remains essential for procedural monitoring and is especially important for assessing peri- and post-procedural complications (11). Novel CMR techniques are currently under

investigation to enhance its role in TAVI planning and might at some point be deployed to guide a TAVI procedure (8).

4.2.5.2 Local versus general anesthesia

The standard protocol for patients undergoing major surgical procedures is GA. However, the standard use of GA for TAVI is questionable. It was found that use of GA in patients with severe AS can increase the periprocedural risk. Furthermore, use of GA in itself poses a risk of 0.03 deaths per 1000 patients, which is further increased when used in an older and sicker population, which is generally in whom TAVI is currently indicated (62).

On the one hand, GA provides the benefits of using TEE intraoperatively, thus offering more stable operating conditions. In the rare event of major peri-procedural complications, GA permits a quick conversion to open-heart surgery. On the other hand, patients benefit more from local anesthesia with conscious sedation as it shortens the procedural duration and permits an earlier discharge from hospital (62).

The randomized SOLVE-TAVI (compariSon of secOnd-generation seLf-expandable vs. balloon-expandable Valves and gEneral vs. local anaesthesia in Transcatheter Aortic Valve Implantation) trial compared outcomes of GA and local anesthesia with conscious sedation in 447 randomly assigned high-to-intermediate surgical risk patients undergoing TF-TAVI. The trial showed that outcomes were comparable between the two groups regarding the most relevant outcomes; however, GA deployment necessitated a greater use of catecholamines. Similar rates of PVL were found between the groups, suggesting that increased procedural experience and THV refinement compensated the absence of intraprocedural TEE deployment (63).

In the past years, an increasing number of centers has adopted local anesthesia with conscious sedation. Data from GARY show that local anesthesia with conscious sedation was used in almost half of all patients undergoing TAVI. The data also suggest that this method was well tolerated, showing fewer adverse events post-TAVI and reduced early mortality (64). Similar results were observed in the STS/ACC TVT registry. Local anesthesia with conscious sedation is currently the ‘contemporary gold standard’ for TAVI in most clinics (65).

A pivotal study included 321 consecutive patients between 2015 and 2018 who underwent TAVI under local anesthesia without conscious sedation. The result showed that local anesthesia without conscious sedation was safely accomplished in 96.8 % of patients. Local anesthesia alone has many advantages, as it was well tolerated by patients, simplified patient management, showed excellent clinical outcomes, and avoided the side effects of conscious sedation. These advantages could enable hospitals to further increase the numbers of procedures they can perform, which will be necessary as TAVI is indicated in an ever increasing number of patients (65).

4.2.5.3 Access routes

Several different access routes are feasible for bioprosthetic valve implantation in the context of TAVI. Each approach is described in the following. Figure 4 shows the most common access

routes currently used in clinical routine. They include the transfemoral (Figure 4 a), transapical (Figure 4 b), transaortic (Figure 4 c), and axillary access route (Figure 4 d). Additional access routes have been developed more recently, including the transcarotid, transcaval, and suprasternal approach (not pictured in Figure 4). The efficacy and safety of these new access routes has not yet been tested in RCTs and was only shown in small studies, which impedes their routine clinical use. The variance in complication rates could also be partly due to patient allocation to the various access routes based on their individual risk profiles (66).

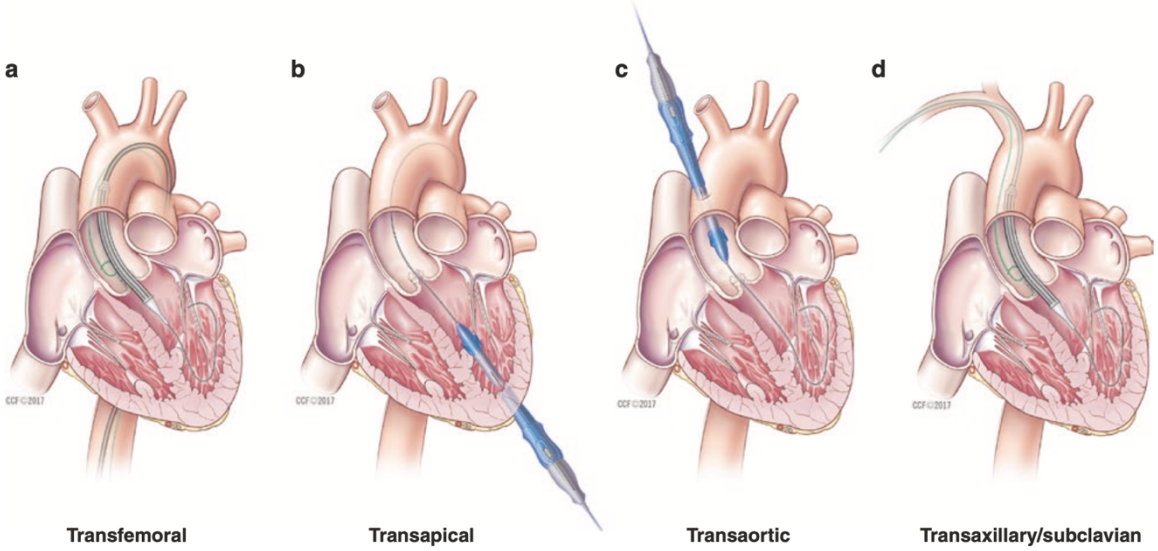


Figure 4. Access routes used for TAVI implantation (4). Reprinted by permission from Springer Nature: Springer, Cardiac Surgery: A Complete Guide, Transcatheter Aortic Valve Therapies, Hamandi M, Mack MJ (2020).

Transfemoral TAVI

The standard and optimal access route for TAVI is the TF method (Figure 4 a). This method uses the femoral arteries as access sites and delivers the THV in a retrograde approach to the AV annulus (4). A more detailed description of the TF-TAVI approach can be found in section 4.2.5.5. Unfortunately, this route is not feasible in some patients due to a decreased vessel caliber (<5 mm), diseases like peripheral artery disease (PAD), substantial access vessel tortuosity, or sizeable infrarenal aneurysms. Even though TAVI delivery systems are becoming ever smaller, it is still expected that 10-15 % of patients will have an unfavorable anatomy for TF-TAVI in the near future (66, 67).

This predicament called for establishing alternate access routes for THV implantation, primarily the transapical, subclavian, and direct aortic access. Unlike in TF-TAVI, GA is commonly used in all three approaches. Furthermore, only the transaxillary route shows similar long-term outcomes, while the transapical and the direct aortic access routes entail a higher mortality. The higher mortality risk remains questionable, as patients undergoing non-TF TAVI usually present with worse risk profiles (66, 67).

The current ECS/EACTS guidelines state that a different percutaneous access route may be considered in individuals who are unfit for SAVR and in whom TF-TAVI is not feasible (class

of recommendation IIb, level of evidence C) (1). The decision on which access route is best suited for a patient should be evaluated by the heart team based on several factors. These can include tortuosity, dimensions, and degree of calcification of the different arteries used by each access route, as well as the presence of a porcelain aorta and other contraindications to specific access routes. Furthermore, the surgeon's experience with access routes and THV types plays a major role regarding the procedural choice (66).

Transapical TAVI

Transapical TAVI was the first approach to be developed for patients with unsuitable peripheral access (67). It requires the use of GA as well as a small left anterior thoracotomy to directly access and open the LV apex (Figure 4 b). Balloon-expandable THVs are most commonly used in this approach. Following valve implantation, ventricular pacing is deployed to reduce pressure until the apex incision is closed (66, 68). This non-TF-TAVI approach avoids a full sternotomy and does not require cardiopulmonary bypass (which, however, should always be on standby). Its advantages include a reduced occurrence of PVL, absence of vascular complications, and a reduction in contrast media volumes. Disadvantages include a high degree of invasiveness, potentially life-threatening bleeding complications from the puncture site, and a high rate of acute kidney injuries (AKI). This approach entails a significantly higher mortality risk than TF-TAVI; however, at 2 years similar rates were found when compared to SAVR (66). When transapical TAVI is performed more frequently, single-center studies have reported more favorable mortality rates closer to those of the TF-TAVI method (67). The disadvantages of this approach and the increased variety of alternative non-TF-TAVI methods have led to a steep decline in transapical TAVI deployment (14.5 % in 2012 vs. 6.1 % in 2015 in the USA) (66).

Transaxillary/transsubclavian TAVI

This approach can be carried out in a completely percutaneous manner by puncturing and placing a sheath into the axillary artery (69). From here, the THV is advanced towards the subclavian artery and then subsequently delivered to the AV annulus in a retrograde approach (Figure 4 d) (67). This approach is currently limited to self-expandable THVs. It allows a quicker procedure, reduced GA use, and is considered the least invasive of all non-TF access routes. Due to a higher frailty of the axillary and subclavian artery, vascular complications are common. Additionally, a higher risk of stroke was observed (66, 67). Of all the non-TF TAVI approaches, the transaxillary approach is the only one to achieve a 1-year survival rate comparable to that of TF-TAVI (80.5 ± 3 % vs. 84.6 ± 0.7 %) and similar complication rates. In cases where the transaxillary approach is feasible, it might be the favored alternative access site (66).

Transaortic TAVI

The direct aortic access is a possible option when both the subclavian and the TF access routes are not feasible. While this approach always requires GA, it is not limited to a specific THV type. A small right anterior thoracotomy or hemisternotomy exposing the proximal ascending aorta is usually performed (Figure 4 c) (68). This method favors direct access to the aorta without injuring the LV myocardium and avoiding pleural separation, which would be necessary during transapical TAVI. As a result, it alleviates postoperative pain and respiratory adverse

effects that are common for other non-TF TAVI approaches, and the risk of vascular and bleeding complications is significantly lower (66, 67). The drawbacks of this approach are that it is challenging to perform, requires having cardiopulmonary bypass on standby, and that numerous contraindications apply to post-SAVR patients. Recent studies have suggested that, in suitable patients, transaortic TAVI should be given preference over a transapical approach; however, RCTs directly comparing both modes are still warranted (66).

Transcarotid TAVI

This approach favors the use of the left carotid artery as access site (not shown in Figure 4, but similar to Figure 4 d); it can be performed under conscious sedation and is limited to self-expanding THVs. The carotid artery lies in close anatomical proximity to the vagus and the laryngeal nerve, as well as to the trachea, making the presence of a vascular surgeon during the intervention obligatory. A higher chance of periprocedural stroke and other adverse events make it a riskier approach. Comparable 2-year mortality rates to TF-TAVI were shown, with an altogether lower rate of vascular events following transcarotid TAVI. On the other hand, a higher rate of cerebrovascular incident, acute myocardial infarction, bleeding, renal failure, and start of dialysis was found for this mode. Contraindications include ≥50 % arctation of the carotid artery or presence of carotid plaques, as well as absence of collateral blood flow in the circle of Willis. Due to a lack of large-scale trials and limited reliable data, transcarotid TAVI is currently only employed in patients in whom no other access route is feasible (66).

Transcaval TAVI

Transcaval TAVI is a challenging procedure of last resort (not shown in Figure 4, but similar to Figure 4 a). It permits a completely percutaneous TAVI and implantation of any THV type. The THV delivery system is introduced into the femoral vein and navigated into the aorta by creating an aortocaval fistula. Post-TAVI this fistula is sealed using an Armplatzer device. Due to its recent development and procedural complexity, not many studies have been performed yet. In a small prospective US study comprising 100 patients, a high rate of device success and decent 30-day survival rates were achieved, but also a higher rate of periprocedural vascular complications compared to TF-TAVI. This approach is currently used only in high-risk patients with contraindications to all other non-TF TAVI approaches (66).

Suprasternal TAVI

The latest TAVI access route is the suprasternal approach. Here, either of the THV types is implanted via the brachiocephalic artery (not shown in Figure 4, but similar to Figure 4 d). Its main advantages include that it enhances implant site accuracy, does not require thoracotomy, and can be performed under conscious sedation. Just a very small number of suprasternal TAVI studies have been published. The studies comparing suprasternal TAVI with other non-TF approaches showed a high rate of device success, a reduction in stroke rates, as well as a reduction in procedural and hospitalization time. In these small studies, adverse events rates were similar to those of other non-TF-TAVI approaches. According to these studies, suprasternal TAVI appears to be a reasonable and safe procedure. More trials are warranted to further evaluate its merits compared to other non-TF access sites (66).

4.2.5.4 Types of transcatheter heart valves

First-generation TAVI devices like the Edwards SAPIEN, the Edwards SAPIEN XT, and the CoreValve system enabled good clinical outcomes and solid valve performance. However, their success was limited by drawbacks including a high incidence of stroke, PVL, vascular complications, and valve malpositioning. This triggered further development, which resulted in the release of newer-generation devices. The developmental pathway taken by most manufacturers included decreasing introducer sheath dimensions, lowering the THV delivery system profile, developing different THV sizes, improving positioning, enabling retrievability, enhancing deployment controllability, as well as enabling THV implantation in a supra-annular position, and fine-tuning THV designs to counteract PVL and reduce PPI rates (70-73).

The design of a bioprosthetic AV relies on six fundamental principles: '(a) hemocompatibility, (b) hydrodynamics, (c) nonthrombogenicity, (d) high durability, (e) low calcification susceptibility, and (f) crimping & deployment stability. Aspect (f) makes the engineering of TAVR devices even more challenging compared to the surgical valve designs' (74). An example for how adequate durability is verified is the 'accelerated wear testing' (in which 5 million cycles are simulated), which must be passed in order to obtain the Conformité Européenne (CE) safety mark (75).

Figure 5 shows a selection of THV designs currently used in clinical practice. They can be classified according to their mode of deployment into balloon-expandable THVs (top part of Figure 5), self-expandable THVs (middle part of Figure 5) and THVs utilizing a mechanical-expandable approach (bottom part of Figure 5). FDA-approved THVs are the SAPIEN XT, SAPIEN3, SAPIEN 3 Ultra, CoreValve Evolut R, CoreValve Evolut PRO, and LOTUS Edge. Recently, the FDA extended the approval of the SAPIEN 3, SAPIEN 3 Ultra, CoreValve Evolut R and CoreValve Evolut PRO for use in low surgical risk patients (5, 74, 76). Additionally to the FDA-approved valves, the ACURATE neo, Portico, ALLEGRA THVs and several others were given the CE mark (77). Due to the vast number of THVs that could potentially be explored here, only the ones that are currently in clinical use and regularly implanted in this study population (section 5.1) are discussed below.

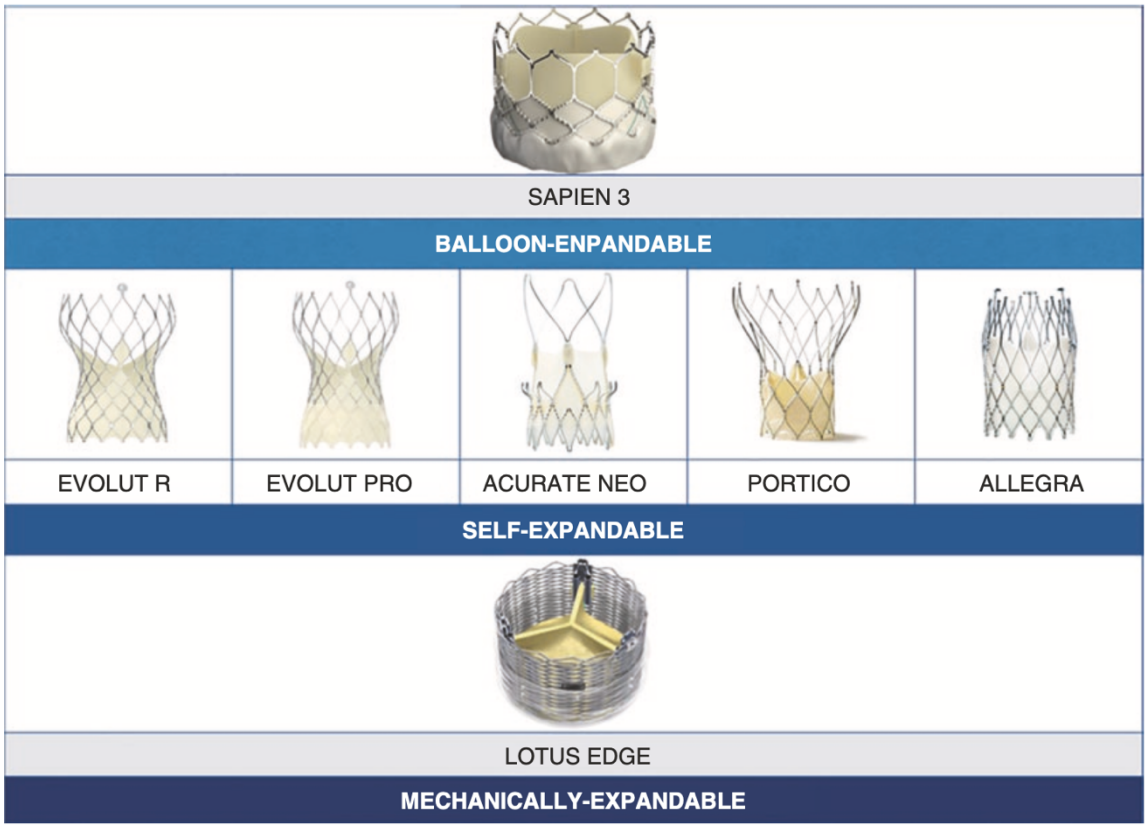


Figure 5. Overview of THVs for TAVI currently used in clinical practice, sorted by mode of deployment (5). Reprinted by permission from Springer Nature: Springer International Publishing, Transcatheter Aortic Valve Implantation: Clinical, Interventional and Surgical Perspectives, Self-Expanding vs. Balloon-Expandable Devices for Transcatheter Aortic Valve Implantation, Todaro D, Picci A, Tamburino C, Barbanti M (2019).

Edwards Lifesciences SAPIEN 3

The SAPIEN 3 THV was developed to overcome the shortcomings of previous generations of balloon-expandable THVs including the Cribier-Edwards valve, the Edwards SAPIEN, and the Edwards SAPIEN XT THV. The SAPIEN 3 THV comprises a cobalt chromium alloy frame with an attached intra-annular trileaflet valve sutured from bovine pericardium tissue. An external seal made of polyethylene terephthalate is affixed to the bottom of the THV to reduce PVL occurrence. Furthermore, the outer skirt of the lower part is divided into pouches, allowing retrogradely coagulating blood to accumulate there, resulting in an enhanced seal between the THV and the aortic root. Apart from improvements in paravalvular sealing, the SAPIEN 3 was also enhanced in the following ways compared to its precursors: increased radial force, low profile access, and open-cell geometry supporting coronary access in future interventions. It should be mentioned that repositioning this THV is not possible. It comes in the sizes 20 mm, 23 mm, 26 mm (crimped size: 14 French (Fr)) and 29 mm (crimped size: 16 Fr), suiting annulus widths of 16-28 mm. The small crimped size enables its deployment via peripheral vessels with diameters of merely 5 mm (74, 78, 79).

The standard SAPIEN 3 procedure is TF-TAVI (~85 % in a 2019 review (78)), though transapical, transaortic, transaxillary and transcaval access ways are also possible. The rate of complications post-SAPIEN 3 implantation have mostly decreased, specifically the rate of PVL >mild (currently <7 % in a 2019 review (78)) and major vascular complications (<6 %). Thirty-

day mortality (<5 % in most studies) and PPI rates (4-13.3 %) remain similar to its predecessor. After the PARTNER 2 RCT successfully showed noninferiority of the SAPIEN XT THV to SAVR in intermediate risk patients, use of the SAPIEN 3 in low-risk patients is currently being evaluated in the PARTNER 3 RCT (see section 4.3). The SAPIEN 3 THV has been accepted for intermediate risk patients, and in mid-2019 the FDA approved it for low surgical risk patients (74, 78-80).

The SAPIEN 3 Ultra THV is the latest prosthetic valve by Edwards Lifesciences and obtained its CE mark in late 2018. Its amendments include an extension of the polyethylene terephthalate skirt resulting in an increased contact area with the AV device landing zone (DLZ). This refinement is aimed at further reducing PVL occurrence. Available sizes include 20 mm, 23 mm and 26 mm (crimped size: 14 Fr) (79).

Medtronic Evolut R, Evolut PRO and Evolut PRO+
The first-generation CoreValve THV was the first self-expanding valve used for severe AS treatment. The second generation of Medtronic THVs is called Evolut R. It comprises a self-expanding nitinol alloy frame appended to a porcine pericardium trileaflet in a supra-annular position. The supra-annular position avoids confinement of the THV within the replaced aortic cusps, which results in a shorter blood residence time near the replaced cusps and thus decreases thrombogenicity. Furthermore, this position enables enhanced circularity of the THV orifice than previously observed after intra-annular THV placement. Similar to SAPIEN 3 developments, the radial strength was enhanced, while paravalvular sealing was further increased by lengthening the porcine pericardial skirt. What distinguishes this THV is the possibility to reposition and even partially 'recapture' the valves until shortly before final THV placement. It comes in the sizes 23 mm, 26 mm, 29 mm and 34 mm (crimped size: 14 Fr), which fits annulus widths of 17-30 mm. A vessel diameter of ≥5 mm is required to implant the Evolut R THV. TF-TAVI is the standard approach for Evolut R implantation; however, other alternative routes are possible (subclavian, transaortic, and trans-carotid). The SURTAVI trial attested noninferiority of the Evolut R to SAVR in intermediate risk patients. According to a 2017 report from the STS/ACC TVT registry, this design has above all improved PPI rates (18.3 %) compared to its predecessors (20.1 %), whereas the outcome regarding the incidence of other complications remained similar (74, 78, 79).

First results of SOLVE-TAVI, a RCT (n=447) that included intermediate and high surgical risk patients, enabled a direct comparison of outcomes concerning SAPIEN 3 and Evolut R. The only major difference between the devices was the incidence of stroke, as the Evolut R posed a significantly lower stroke risk at 30 days (0.5 %) compared to the SAPIEN 3 (4.7 %). Other incidence rates at 30 days were similar, including >mild PVL (1.9 % vs. 1.4 %), mortality (2.8 % vs. 2.3 %), and novel PPI (22.9 % vs. 19.0 %) (78).

The next Medtronic THV generation was the Evolut PRO THV. The main improvement was targeted at reducing PVL occurrence by complementing the first 12 mm of the ventricular portion of the THV with an external porcine pericardial wrap (flared annulus design), thus allowing more accurate matching with the aortic root morphology. This was accomplished, while

simultaneously maintaining all benefits of the Evolut R (repositionability, partial 'recapturability', low profile and more). Available sizes are 23 mm, 26 mm and 29 mm (crimped size equivalent to 16 Fr in the SAPIEN 3 system), suiting an annulus width of 17-26 mm. In a small pivotal study (n=60) the Evolut PRO device was shown to further decrease PPI rates (11.8 %) and lower the rate of PVL (in this small study, no patient had PVL >mild) compared to the Evolut R (74, 78). These results have prompted further studies including the FORWARD PRO study to assess the five-year performance of the Evolut PRO THV in high-risk patients, and the Evolut Low Risk RCT to evaluate its use in low-risk patients (79).

In the newest Medtronic THV generation Evolut PRO+, the Evolut PRO THV was further amended by enhancing the external porcine pericardial wrap to further reduce PVL occurrence. Furthermore, this THV is available in a larger size (23 mm, 26 mm, 29 mm, and 34 mm), whereby the 34 mm size requires an 18F delivery system (81, 82). A single-center study (n=239) comparing the 34 mm Evolut R with the 34 mm Evolut PRO+ was conducted. Here, compared to the Evolut R, the 34 mm Evolut PRO+ showed a lower rate of PPI (16.2 % vs. 10.8 %, p=0.41) and a slightly lower PVL rate (PVL≤mild: 96.6 % vs. 100 %, p=0.27), however with a considerably greater incidence of vascular adverse events (1.6 % vs. 23.3 %, p<0.001) (82).

Boston Scientific ACURATE neo
The ACURATE NEO comprises a trileaflet structure made of porcine pericardial tissue situated within a self-expanding nitinol alloy stent and is covered on the interior and exterior with a mounting made of porcine pericardial tissue. The device also uses a flared annulus design, similar to the Evolut PRO THV, to minimize PVL occurrence (5, 8, 74). Unlike the Evolut R and Evolut PRO, it is not repositionable and cannot be fully retrieved. The THV is deployed using the TF access route (crimped size: 18 Fr) and fits annulus widths of 21-27 mm. A vessel diameter of ≥6 mm is mandatory to implant the ACURATE neo device (8).

The SCOPE I (Safety and Efficacy Comparison Of Two TAVI Systems in a Prospective Randomized Evaluation) RCT was set up to assess noninferiority of the self-expandable ACURATE neo to the balloon-expandable SAPIEN 3. The primary early safety and clinical efficacy composite endpoint showed no advantage of the ACURATE neo compared to the SAPIEN 3 at 30 days (24 % vs. 16 %, p=0.42 for noninferiority). Noninferiority regarding the primary composite endpoint was thus not achieved. At 30 days the ACURATE neo showed a significantly higher incidence of AKI (3 % vs. 1 %, p=0.034) and moderate-to-severe PVL (9 % vs. 1 %, p<0.0001), while achieving a lower mean transvalvular gradient (median: 7 mmHg vs. 11 mmHg, p<0.0001) and a larger mean AVA (median: 1.73 cm^2 vs. 1.47 cm^2, p<0.0001). At 30 days no difference was found regarding stroke (2 % vs. 3 %, p=0.33), PPI rate (2 % vs. 3 %, p=0.76), as well as cardiovascular (2 % vs. 1 %, p=0.13) and all-cause mortality (2 % vs. 1 %, p=0.09). These results suggest that the SAPIEN 3 is superior to the ACURATE neo in terms of the outcomes assessed (83). At the same time the SCOPE II trial was conducted, which had a randomized design aimed at demonstrating noninferiority of the ACURATE neo to the CoreValve Evolut. In this study, comparability between the devices was higher, as both THVs are self-expanding and have a supra-annular implantation mode. The primary composite endpoint comprising mortality and stroke at 1 year was unable to show noninferiority of the

ACURATE neo to the CoreValve Evolut (15.8 % vs. 13.9 %, p=0.0549 for noninferiority). In this trial, implantation of the ACURATE neo resulted in significantly higher moderate-to-severe PVL at 30 days (10 % vs. 2 %, p=0.002), higher cardiac mortality at 30 days (2.8 % vs. 0.8 %, p=0.03), and increased all-cause mortality at 1 year (8.4 % vs. 3.9 %, p=0.01), while achieving a lower PPI rate at 30 days (10.5 % vs. 18 %, p=0.0027) (84).

The significantly higher rates of PVL in the SCOPE I and II trials led to modifications of the ACURATE neo. The outcome of this development process was the ACURATE neo2, which boasts an additional annular sealing skirt to reduce PVL occurrence and enhances adaptability to an irregular calcified DLZ. Furthermore, a radiopaque indicator to assist THV positioning was added. It's very recent release has enabled only preliminary accelerated wear testing, which indicated superb long-term durability corresponding to 25 years of biomechanical strain. Further trials are necessary to evaluate the feasibility of this device in an in-vivo setting (85).

4.2.5.5 Procedural technique of transcatheter aortic valve implantation

If permitted by the iliofemoral vasculature, TF access is the standard procedure for TAVI implantation in most centers. In the PARTNER II SAPIEN 3 registry, nearly 90 % of patients underwent TAVI via the TF access (70). As it is the main access route used in general as well as in this study in particular, only TF access will be discussed in this section.

Knowledge of the femoral luminal size, the extent of vessel calcification and tortuosity derived from MSCT scans is essential for TF-TAVI planning and execution. For the percutaneous TF approach both femoral arteries are punctured using fluoroscopy and a safety wire for guidance (68). To allow right ventricular pacing, a venous access site is used for wire placement (86). A 6 Fr sheath is first introduced into one vessel, allowing a 5 Fr pigtail catheter to be positioned into the noncoronary sinus after fluoroscopic confirmation of the correct position. The pigtail catheter's position equates to the later placement site of the bioprosthetic valve and permits the use of arteriography to correctly place the valve. Pre-closure of access sites, with vascular closure devices (VCD), should be performed immediately after sheath placement (see section 4.2.5.6). The opposite femoral artery is used to place the 18 Fr sheath, which is later used for balloon valvuloplasty and device placement (68).

Prior to THV implantation, balloon valvuloplasty of the aortic annulus is mostly restricted to patients with a BAV or severely calcified AV. It can fracture the calcific deposits and can allow the prosthesis to pass through a heavily calcified AV. It is performed utilizing an undersized balloon to decrease damage to the aortic annulus and to reduce PVL occurrence. Balloon valvuloplasty is executed during ventricular pacing (160-220 beats per minute) to minimize unintended balloon ejection from the annulus area and to prevent annulus rupture. Following effective balloon pre-dilatation, the balloon is replaced with the THV implant (86).

Most THVs are placed directly at the aortic annulus, beneath the coronary arteries. Once correct positioning is achieved, a self-expanding device or high-pressure balloon dilatation and subsequent THV implantation alongside deployment of rapid ventricular pacing is utilized. The new implant regains the pre-stenosis valve function immediately after delivery by distending the

native valve and replacing it with the bioprosthetic counterpart (21). To detect THV dysfunction the newly updated VARC-3 document refers to the VARC-2 consensus document, which recommends use of an algorithm. This algorithm begins with the direct evaluation of patient hemodynamics after the procedure, offering first insights regarding correct valve positioning and function. Next, a thorough hemodynamic evaluation should be performed, including a flow-dependent (i.e., MPG) and flow-independent criterion (i.e., EOA). If the measured data are dissonant, further calculations are made to detect prosthesis-patient mismatch as early as possible (2, 57). If PVL ≥moderate is detected during the procedure, balloon post-dilatation can be performed to reduce the presence of PVL ≥moderate. This should be performed cautiously as it was shown to increase the incidence of perioperative cerebral embolization (87). Contingent on successful THV implantation and function, the catheters, guidewires and sheaths are removed, and closure of the access sites is accomplished surgically or using the preplaced VCD (86).

In most cases, patients need not be admitted to the ICU post-TAVI. Instead, they are monitored for four hours in a coronary care unit before returning to a normal care unit. Here, patients are continuously monitored for cardiac conduction abnormalities using telemetry. Discharge within 48 hours after the procedure is common if no post-TAVI complication occurs (21). The 2021 ESC/EACTS guidelines recommend lifelong treatment with acetylsalicylic acid for post-TAVI patients without a baseline indication for oral anticoagulation (class of recommendation I, level of evidence A). However, if post-TAVI patients have underlying ailments necessitating oral anticoagulation, lifelong treatment with oral anticoagulants is recommended (class of recommendation I, level of evidence B) (1).

4.2.5.6 Vascular closure devices

As sheath placement in the common femoral artery requires a large-bore access, TF-TAVI procedures are prone to vascular complications. VCDs were developed to resolve this weakness. Nevertheless, access site complications still occur frequently after TAVI and heart catheterization (88) and can have dire consequences on mortality and morbidity (89). The two most frequently used VCDs today are Perclose ProGlide® and MANTA®. Several publications indicated comparable outcomes for the MANTA and the ProGlide VCDs (88, 90). A recent propensity-matched study found a non-significant difference between the MANTA and the ProGlide in respect to the occurrence of ≥major bleeding (3.1 % vs. 5.4 %, p=0.540), pseudoaneurysm (0.8 % vs. 2.3 %, p=0.622), need for endovascular bailout intervention post-VCD placement (9.3 % vs. 5.4 %, p=0.341), and dissection or stenosis of the femoral artery (6.2 % vs. 3.1 %, p=0.376) (90).

4.2.5.7 Valve Academic Research Consortium-2 criteria

The VARC-2 consensus document offers a definition of clinical and composite endpoints for TAVI procedures. This ensures an increase in comparability between devices and approaches, as well as an improved interpretability of results (2, 11). A detailed description of the criteria can be found in section 5.3. In 2021 the VARC-3 consensus document was published, which offers further (and more precise) definitions of clinical and composite endpoints. The endpoints defined in this new document mostly set a framework for future clinical research while also offering

valuable information for everyday clinical routine (i.e., more precise definitions of bioprosthetic valve dysfunction and failure) (44). As the present study is based on the VARC-2 definition, these will be extensively examined in the following and, where appropriate, novelties from the VARC-3 document will be discussed.

4.2.6 Complications post-TAVI

Possible adverse events after TAVI are plentiful; however, incidence rates of severe complications are low. According to the VARC-3 consensus document, any adverse events occurring within 30 days post-TAVI are likely caused by the THV or procedure, unless a different underlying cause is apparent, whereas those occurring >30 days post-TAVI are more likely influenced by patient-specific features (44). Severe post-TAVI adverse events associated with mortality include multiple organ failure, acute myocardial infarction, sudden death, life-threatening bleeding, severe respiratory dysfunction, and extensive cerebrovascular insult. Furthermore, the VARC proposed major TAVI-associated adverse events such as left coronary artery (LCA) occlusion leading to acute myocardial infarction, AKI necessitating dialysis, and cerebrovascular insults. However, not all post-procedural complications necessarily entail an immediate risk of mortality; instead, they are more likely to impact long-term survival and quality of life. Both short- and long-term risks to survival will be discussed below with examples (2, 44, 91).

In the early stages of TAVI, post-procedural occurrence of most complications was higher at 30 days compared to SAVR. In a 2014 summary of RCTs, the most common complications of TAVI compared with SAVR were moderate-to-severe PVL (10.0-12.2 % vs. 0.9-1.3 %), major vascular complications (5.9-11.0 % vs. 1.7-3.2 %), post-procedural cardiac arrhythmia necessitating PPI (3.8-19.8 % vs. 3.6-7.1 %), and stroke (4.9-5.5 % vs. 1.7-3.2 %). The rate of post-procedural complications had already significantly improved in 2014 compared to the very early days of the technique and further enhancements were anticipated (9).

As expected, with a newer generation of THVs, higher intervention numbers and a greater clinical routine in performing TAVI, for most events the complication rate had declined in 2018. Moderate-to-severe PVL, which was shown to affect long-term outcomes, had become rarer (3-4 %) as newer devices were being implanted. Mild or trace PVL remained a common complication. Vascular complications had been reported at a rate of up to 20 %, which subsequently decreased to about 5 % thanks to reduced sheath dimensions. The rate of PPI differed between devices; in the balloon-expandable system it occurred in up to 13 % of cases, whereas use of the self-expanding system led to a rate of up to 40 %. The incidence of stroke (~1-5 %) had also decreased, but not as significantly as the other negative outcomes (11).

Severe complications post-TAVI were common in the past and included coronary obstruction, ventricular perforation, annular rupture, valve embolization, and more. However, today they have become very rare and are each below 1 % (11). This can be somewhat attributed to the use of MSCT scans, which offer better pre-intervention identification of potentially hazardous anatomical circumstances (21).

In current trials and present-day registries the rate of complications has fallen significantly; nevertheless, about 1-2 % of patients still need a prompt switch to cardiac surgery due to life-threatening complications post-TAVI (11). In the Low Risk Evolut trial, which compared TAVI with SAVR, only few deaths (0.5 % vs. 1.3 %) and disabling strokes occurred at 30 days (0.5 % vs. 1.7%). Furthermore, many complication rates post-TAVI were significantly lower compared to previous studies. After 30 days, low-risk patients in the TAVI arm showed fewer vascular complications (2.4 % vs. 7.5 %), fewer AKI (0.9 % vs. 2.8 %), a faster recovery according to the Kansas City Cardiomyopathy Questionnaire, a reduced occurrence of disabling strokes (0.5 % vs. 1.7 %) and AF (7.7 % vs. 35.4 %), but rather a higher rate of PPI (17.4 % vs. 6.1 %) and moderate-to-severe PVL (3.5 % vs. 0.5 %) (32). Recently, 2-year results were published that show similar results. At 2 years, TAVI showed fewer deaths (3.5 % vs. 4.4 %), disabling strokes (1.5 % vs. 2.7 %) and rehospitalizations due to cardiac ailments (5.3 % vs. 7.1 %) when compared to SAVR. The rate of ≥moderate PVL and THV thrombosis in the TAVI arm was very low (1.7 %) at 2 years. Contrariwise, at 2 years a significantly greater incidence of PPI (21.1% vs. 7.9 %) and mild PVL (26.6 % vs. 2.6 %) was found for TAVI compared to SAVR (35-37).

The PARTNER III trial has also recently published results up to 2 years. After 30 days, Kaplan-Meier estimates for low-risk patients in the TAVI arm showed fewer strokes (0.6 % vs. 2.4 %, $p=0.02$), AF (5 % vs. 39.5 %, $p<0.001$), shorter hospitalization (3.0 days vs. 7.0 days, $p<0.001$), and a faster recovery according to the Kansas City Cardiomyopathy Questionnaire ($p<0.001$) compared with SAVR. No significant disparities of the Kaplan-Meier estimates were found at 30 days between TAVI and SAVR in respect to PPI (6.6 % vs. 4.1 %), major vascular complications (2.2 % vs. 1.5 %), and moderate-to-severe PVL (0.8 % vs. 0 %) (33). In the 2 years since the index procedure, the prevalence of PVL remained stable after both TAVI and SAVR, particularly moderate-to-severe PVL (0.5 % vs. 0 % at 2 years) and mild PVL (26 % vs. 2.3 % at 2 years). However, the incidence of some secondary endpoints within the second year post-AVR was higher post-TAVI compared to post-SAVR. This resulted in the difference between TAVI and SAVR not being statistically significant anymore at 2 years for mortality (2.4 % vs. 3.2 %, $p=0.47$) and stroke (2.4 % vs. 3.6 %, $p=0.28$). The diverging rate of valve thrombosis between TAVI and SAVR has further increased over the 2 years of follow-up (2.6 % vs. 0.7 %, $p=0.02$) (41).

Even though the incidence rate of some adverse events has increased in the TAVI group compared to the SAVR group, both current RCTs show non-inferiority or superiority of TAVI compared to SAVR for the primary endpoints of their studies at 2 years. Nevertheless, the results of the Low Risk Evolut trial and PARTNER III trial should be interpreted with caution as they do not reflect real-world data. Instead, these trials are based on an unrepresentative (<35 % women included) and highly selective patient cohort in which patients presenting with features highly relevant to the success of TAVI were excluded (including severe LVOT calcification and frailty) (32, 33, 60, 61). A detailed examination of the limitations of the Evolut Low Risk and the PARTNER III trials can be found in section 4.3. Even though most complications have become rarer, further exploration and prevention of long-term complications is necessary as ever younger patients are undergoing TAVI procedures (92).

4.2.6.1 Cerebrovascular events

Cerebrovascular complications are morbid, life-limiting adverse events following TAVI. They pose a significant risk of both short-term mortality and long-term disability (21). Strokes can be categorized into early (≤7 days post-TAVI) and late strokes (>7 days post-TAVI), whereby the former arises from debris embolization and the latter is attributed to patients' individual risk factors (93). Early stroke is more common: 85 % of all post-TAVI strokes occur within the first seven days after the procedure, with the incidence peaking on the second day (94). Additionally, the VARC-2 criteria distinguish between disabling and non-disabling stroke, as determined by the modified Rankin Scale (see section 5.3) (28). The updated VARC-3 criteria distinguish between periprocedural (≤30 days post-TAVI) [a further subdivision into acute and subacute neurologic events is recommended], early (≤1 year post-TAVI), and late (≥1 year post-TAVI) neurologic events (44).

A higher AV peak gradient measured pre-TAVI has been established as a significant risk factor concerning early stroke following TF-TAVI. Additional patient-related predictors of early stroke include status post cerebrovascular events or PAD (94), as well as female gender, low body mass index (BMI), newly acquired AF post-TAVI, and chronic kidney disease (93). Other procedural hazards for early stroke are the need for prosthesis repositioning, total procedural time, deployment of rapid pacing (94), AV annulus size and, finally, balloon pre- and post-dilatation (93). As mentioned earlier, post-procedural strokes can also occur with a delay to the index procedure, also well after the early post-implantation period has ended (2). This can mostly be predicted on the basis of patient characteristics, like presence of arteriosclerotic disease, chronic AF, and frailty. Unlike early stroke, late stroke is determined less by procedural variables (93).

Worryingly, novel cerebral lesions (clinically silent foci of limited diffusion) detected using diffusion-weighted MRI scans present in 60-100 % of patients post-TAVI, compared to barely half this rate post-SAVR. Previous publications showed that a process called embolic showering, where many silent cerebral foci occur post-TAVI, can result in acute cerebral failure (e.g., delirium) or chronic cerebral failure (e.g., dementia). In a recent study where multiple head MRI scans of 96 patients were performed pre- and post-TAVI, silent cerebral foci were detected in 76 % of patients one week post-TAVI. Of these, the ischemic foci disappeared entirely in 70 % of the patients after three to five months. In patients where the ischemic foci remained after three to five months, their size and number decreased in 70-80 % of cases, whereas in the other quarter they progressed to a gliotic scar. The presence of persistent silent cerebral ischemic foci doubled the chances of developing dementia and reduced the Mini-Mental State Examination score post-TAVI. At one to two years post-TAVI, 10 % of patients showed a decline in cognitive function. Furthermore, the dimensions of the remaining silent cerebral ischemic foci correlated positively with the reduction in neurocognitive function. This positive correlation could be due to the fact that half of the silent cerebral ischemic foci were found in cortical and subcortical structures. In this study, non-balloon-expandable THVs showed a very high incidence of silent cerebral foci (mechanical THVs: 100 %, self-expanding THVs: 82 %), whereas the rate in balloon-expandable THVs was much lower (50 %). This striking difference is possibly due to elongated friction between the non-balloon-expandable THV and the beating heart. Additionally, the main embolic sources identified using histopathological studies of debris obtained through cerebral protection

devices were arterial wall segments (94 % of cases). The authors theorized that these segments originated from the atheromatous aortic arch, through which the prosthesis delivery system must be advanced (95, 96). The VARC-3 writing committee acknowledges that silent cerebral infarction may lead to a decline in cognitive function; however, no recommendations or definitions for this entity were included in the document. Instead, the document states that the assessment of cognitive impairment is not standardized and thus findings might not be transferable. Moreover, insufficient evidence links this type of neurologic event to endpoints like mortality or a reduction in quality of life. The VARC-3 document states that further research in this field is required before silent cerebral infarction is included in their clinical endpoints (44).

The higher rate of strokes compared to SAVR and the exceedingly high incidence of silent cerebral ischemic foci triggered extensive research into the development of cerebral embolic protection devices. Currently, the only CE-approved system is the dual-filter Claret Sentinel. Its release had raised hopes of reducing cerebrovascular events post-TAVI (94). A study by Stachon et al., which included 41,654 TAVI patients from a German nationwide database, showed that between 2015 and 2017 this device was merely used in 3.8 % of TF-TAVIs in Germany. Furthermore, a reduction in embolic showering and delirium rates, as well as a decreased stroke frequency post-TAVI were not identified. The authors listed several limitations of the dual-filter Claret Sentinel, which might explain the discouraging results. The device allows only partial concealment of the cerebral vessels, the left vertebral artery is not protected, and thrombus formation on the protection device is also conceivable. Additional refinements and further RCTs are necessary before this device or future cerebral embolic protection devices can be routinely used in the clinical setting. Further refinement of these devices is of increasing significance as ever younger patients are undergoing TAVI (96).

4.2.6.2 Cardiac arrhythmias

During THV implantation, direct compression of the patient's native conductive tissue occurs. Especially the atrioventricular node, interventricular septum and left bundle branch are at risk of suffering mechanical injury (94). In most cases this is the underlying cause of newly acquired conduction disturbances post-TAVI (i.e., atrioventricular block). Two advances have slightly improved outcomes as of late: the development of repositionable valves and general enhancement of TAVI devices (21). Besides independent predictors of PPI, like pre-existing right bundle branch block and age above 82.7 years, the advent of MSCT revealed an association between an increased risk of PPI and LVOT calcium located at the left coronary cusp (LCC) (>41.4 mm^3 at a threshold of 500 Hounsfield Units (HU) in CTA data) in a recent study with ACURATE neo valves (97). In a recent meta-analysis, which included only new generation devices, it was discovered that calcium depots located in the non-coronary cusp (NCC), LCC and LVOT, measured by MSCT, correlated with the need for PPI post-TAVI (98).

PPI mostly has beneficial effects, as it protects patients from bradyarrhythmia, which is common in the patient population in whom TAVI is currently indicated (21). Also, compared to patients who did not require PPI post-TAVI, PPI was shown not to affect all-cause mortality or symptom severity at 30 days and 1 year post-PPI (94). However, it increases the risk of peri-operative complications and comes at a high general cost (21). Additionally, it entails a longer hospital

stay and an increased rate of rehospitalization at 30 days and 1-year post-PPI. As mentioned above, PPI is required more often after implantation of a self-expanding valve. It should be mentioned that rates have dropped significantly in recent studies, due to the introduction of the new CoreValve Evolut R self-expanding valve (94). Nevertheless, PPI rates and long-term effects of PPI should be evaluated persistently, as the rate of PPI might increase again subsequent to additional device amendments (11).

4.2.6.3 Vascular complications

Vascular complications are associated with a higher degree of morbidity and mortality (21). However, patients presenting with a minor vascular complication as defined by VARC-2 are just as likely to suffer from further complications or premature death as those without vascular impediments post-TAVI. Occurrence of major vascular complications as defined by VARC-2 often entails an elongated procedure, a longer hospital stay, and higher mortality (99). The former VARC-2 classification has been extended in the VARC-3 document to differentiate between 'vascular complications' and 'access-related non-vascular complications'. The latter mostly refers to non-TF TAVI access routes and includes complications like pneumothorax after transaxillary TAVI (44).

The underlying pathologies are plentiful and range from access site hematoma through arterial perforation and annulus rupture to aortic dissection. They can be subdivided into vascular access site and access-related complications, as well as into iliofemoral and aortic complications. Iliofemoral complications are the most common post-TAVI, which are today primarily treated using catheter-based approaches. Predictors for vascular complications include a larger sheath-to-femoral artery ratio (≥1.05), as well as patient-related factors, which comprise renal insufficiency, female gender, iliofemoral arterial calcification (particularly if circumferential), and coexistent PAD. VCD failure is an independent predictor of vascular complications (incidence rate: 2.7-12 %) (99).

The most feared but seldom vascular complication is annulus rupture (incidence rate: 0.4-2.3 %). It entails a prompt hemodynamic collapse and a high level of mortality (30-day mortality: 49-67 %) due to the rapid occurrence of cardiac tamponade. The risk of annulus rupture during TAVI is thought to be strongly determined by subannular calcification, excessive THV oversizing, aggressive post-dilatation, and use of balloon-expandable THVs. Using MDCT for preprocedural imaging can drastically reduce the likelihood of annulus rupture, due to enhanced balloon and THV size selection. In instances where preprocedural imaging shows severe annular or subannular calcification, undersizing the THV is the method of choice. When an annulus rupture is suspected, angiography and echocardiography should be performed instantly. If confirmed, an immediate conversion to open surgery including cardiopulmonary bypass is usually necessary (100).

The overall incidence rates of all vascular complications have recently dropped due to pre-operative MSCT reconstruction offering detailed three-dimensional reconstruction, but also due to the increased use of balloon cross-over methods, which safeguard vessel hemostasis, as well as smaller access sheaths and other advances. Nevertheless, vascular complications are

inextricably linked to TAVI, and further refinements are warranted in order to further reduce incidence rates (21).

4.2.6.4 Paravalvular leak

Moderate-to-severe PVL post-TAVI is linked to higher mortality (in-hospital mortality: 14.5 %; 1-year mortality: 30.8 %) and limited long-term survival (5-year mortality:72.7 % vs. 56.5 % in patients with PVL ≥mild) (101). The rate of more than mild PVL has dropped in recent years. This is mainly due to an increase in measurement precision achieved by using MSCT scans for device selection and pre-TAVI planning, as reported above (21). Furthermore, MSCT scan analyses enabled identification of new risk factors for PVL ≥mild. They include extensive upper LVOT calcium volume (≥21 mm^3 using an individual HU threshold in CTA (102)), a high AV cusp calcium burden (>410.6 mm^3 at a 500 HU threshold in CTA data) for ACURATE neo valves (97), an increased calcium burden in the annulus region for SAPIEN 3 valves (103), as well as asymmetrically calcified aortic cusps (particularly when presenting with increased annulus dimensions and an oval annular outline) in a TA-TAVI cohort (104).

Recently, mild PVL post-TAVI has become a matter of concern due to its high incidence rate of about 30 % (91). Independent predictors of mild PVL, when using SAPIEN 3 THVs, comprise LVOT eccentricity, calcification of all three aortic leaflets, and inappropriate valve sizing (105). Although the specific long-term effects remain undetermined, recent studies have suggested adverse outcomes for patients with mild PVL post-TAVI. A meta-analysis by Ando et al. found that mild PVL is associated with a 26 % higher all-cause mortality (follow-up range: 6 months to 5 years) and a 28 % higher cardiovascular mortality (follow-up range: 1 to 3 years) compared to <mild PVL. The increased all-cause mortality associated with mild PVL was most pronounced after balloon-expandable THV implantation but was not observed with self-expanding THV implantation. The possible negative effect of mild PVL on mortality could be prompted by several factors. The slightly increased preload and hemodynamic wall stress caused by mild PVL could be too much of a burden on the already stiffened and incompliant ventricle. The increased risk of mortality might not be caused by mild PVL, but rather by an increased calcium burden, which is associated with the emergence of mild PVL. Another possible explanation is that the severity of PVL was misjudged by the echocardiographer, resulting in moderate PVL being falsely interpreted as mild PVL (106). The findings of this meta-analysis should be evaluated by further studies to assess the actual long-term impact of mild PVL on mortality and other adverse events. It should be noted that worsening of PVL based on measurements acquired immediately post-TAVI is rare, suggesting a good durability of the TAVI valves (91).

Once PVL is detected, several therapeutic options exist. Deployment of balloon dilatation immediately after THV implantation can close a paravalvular defect, but at the risk of aortic root hematoma or rupture if performed too aggressively. Other options include transcatheter aortic valve in transcatheter aortic valve implantation (TAV-in-TAV), a percutaneous transcatheter method to stall aortic regurgitation, as well as slight repositioning of the valve using a snaring device (94). The newest THV generations were specifically designed to address this complication. The SAPIEN 3 was supplemented with an outer skirt adaptive seal, whereas the

Evolute R and Evolute PRO were devised to optimize positioning by creating repositionable valves (21).

4.2.6.5 Other complications

The types of further complications after TAVI are ample. The most relevant and frequent complications are described above; nevertheless, other severe and life-limiting conditions should be mentioned. They include unplanned coronary bypass, ventricular septal perforation, cardiac tamponade, valve malpositioning, valve thrombosis, TAV-in-TAV deployment, damage to the mitral valve apparatus, and more (2). Most of these complications are rare. Some of the more prevalent further complications and those included in the combined clinical endpoint of this study are detailed below.

The incidence of myocardial infarction within 30 days post-TAVI lies at roughly 0.5 %, compared to 1 % after 30 days for SAVR (107). It is caused by part of the THV or valve tissue covering the coronary ostia, subsequently resulting in partial stenosis or complete coronary obstruction (91). A recent study evaluating MDCT scans post-TAVI discovered that one or both coronary ostia were obstructed by the neo-commissures of the THV in 51 % of patients. This makes a TAV-in-TAV procedure problematic, as a second set of neo-commissures could lead to total obstruction of one or both coronary ostia (61). To enable a better detection of myocardial infarction post-TAVI, the VARC-3 document recommends determining cardiovascular biomarkers pre-TAVI as well as twice in the 24 hours post-TAVI. A 12-lead ECG should be recorded before the procedure as well as daily until discharge (44).

Onset of AKI post-TAVI is common, ranging from 4.1-57.7 % according to a recent meta-analysis. Its multifactorial pathogenesis includes peri-operative hemodynamic instability, nephrotoxic levels of medication or contrast media, and atheroembolization of cholesterol in kidney vessels caused by advancing a catheter through a calcified aorta (108). AKI can lead to a threefold increase in 12-month mortality after the index procedure. However, it is more frequent post-SAVR than post-TAVI. Ultimately, if renal insufficiency is severe, only renal replacement therapy can alleviate symptoms and increase survival (21).

Movement of the THV, mostly occurring within minutes or hours and sometimes days after the procedure, is called device migration or device embolization. Most THVs move cranially towards the ascending aorta, while about 20 % move caudally into the left ventricle (109). THV migration is mostly caused by THV malpositioning, which can be facilitated by many factors including the absence of AVC. Furthermore, post-dilatation and rapid pacing failure can lead to THV migration (110). THV migration ensues a 9-fold rise in mortality compared to average mortality rates post-TAVI. The incidence of THV migration has fallen drastically in the past decades (about 1 % of cases in a recent multicenter study (110)) due to enhanced preprocedural imaging, including pre-interventional MSCT deployment, and implantation of next-generation valves. Once it occurs, the approach utilized depends on the hemodynamic situation and surgical risk of the patient, but typically either a second valve is deployed or a fast conversion to open heart surgery is necessary (110, 111).

A complication that poses a high risk of in-hospital mortality is post-procedural endocarditis (mostly due to Enterococcus or Staphylococcus species) (21). It leads to the development of fistulas (15 % of affected patients), heart failure (33 % of affected patients), and cerebral embolisms (18 % of affected patients) (91). Treatment of endocarditis can be challenging and is often limited to antibiotic therapy (21).

4.2.7 Long-term outcomes

A systemic review published in 2017 assessed the long-term survival of high surgical risk patients (mean STS score: 9.2±6.6). Most of the patients included received an Edwards THV (SAPIEN, SAPIEN XT and SAPIEN 3) or a Medtronic THV (CoreValve, Evolut R). A total of 83 % of patients were still alive after 1 year, 75 % after 2 years, 65 % after 3 years, 48 % after 5 years, and merely 28 % after 7 years (34). Similar results were reported in an update of the PARTNER-2 RCT published in 2020, which compared 5-year outcomes of the SAPIEN XT THV implantation to SAVR in patients with an intermediate surgical risk (mean STS score: 5.8 %). After this period there was no significant difference between TF-TAVI and SAVR in terms of all-cause mortality (46 % vs. 42.1 %), disabling stroke (9.8 % vs. 8.6 %), valve hemodynamics and enhancement of health status (89 % vs. 92.7 %); however, significantly more patients who underwent TAVI experienced ≥mild PVL (33.3 % vs. 6.3 %), rehospitalization (33.3 % vs. 25.2 %), and AV reinterventions (3.2 % vs. 0.8 %). These results showed that the SAPIEN XT is also a reasonable alternative to surgical bioprosthetic valves in the long term (112).

The long-term durability of THVs has been a matter of concern since the advent of TAVI. It entails an unclear preference as to which AVR intervention is best suited for patients with a longer anticipated lifespan. Currently it is recommended that patients <55 years without contraindications undergo SAVR with a mechanical valve, as this group showed superior survival at 15 years compared to those receiving a bioprosthetic surgical valve (61). However, mechanical surgical heart valve implantation is associated with an increased risk of thromboembolic complications and thus necessitates lifelong anticoagulation (73).

Bioprosthetic valves, on the other hand, imitate the native AV function, thus obviating the need for lifelong anticoagulation. However, this comes at the price of inferior durability when compared to mechanical heart valves (113). Current bioprosthetic valves are constructed from xenogeneic tissue treated with glutaraldehyde fixation. This method greatly reduces the antigenicity of the xenogeneic tissue; however, complete prevention of xenogeneic antigen exposure is not possible, thus resulting in chronic inflammation. Glutaraldehyde fixation of xenogeneic tissues also leads to stiffening of the bioprosthetic leaflets, altering their mechanical features. The consequences include more rapid calcification and valve deterioration, which in turn promotes valve restenosis and/or regurgitation. Collectively, these issues result in reduced durability and eventually in a loss of valve function, which can make a re-intervention necessary (73). The issue of bioprosthetic valve failure has been thoroughly addressed in previous publications and lies at about 23 % at 15 years. The rate at which bioprosthetic valve failure occurs depends on the age at which the intervention is performed. After 15 years, the rate of bioprosthetic valve failure seen in patients who undergo bioprosthetic SAVR <65 years lies at

26 %, whereas in patients ≥65 years it occurs in 9 % of cases. It is important to understand how bioprosthetic valve failure is defined, as it is only referred to as 'failure' if re-SAVR is required. This means that patients with a prohibitive surgical risk for re-SAVR are not counted as bioprosthetic valve failures, even if they could today be treated by implanting a THV into the degenerated bioprosthetic valve. This is performed routinely today: On average, a THV is implanted into a surgical valve about 9 years after a bioprosthetic surgical valve was placed (61).

Bioprosthetic THVs come with shortcomings similar to the drawbacks of bioprosthetic surgical heart valves mentioned above. Additionally, the obligatory crimping of the bioprosthetic valve before THV implantation was found to further limit durability. It causes microstructural damage to the THV leaflet surface and collagen fibers, which are often not recuperated upon deployment. This structural damage further promotes calcification and leads to an increased accumulation of platelets on the THV surface (73). Many different definitions have been suggested for structural valve degeneration post-TAVI. The newest and most extensive definition of bioprosthetic valve dysfunction was included in the VARC-3 document. Unlike previous classifications, the VARC-3 definition requires more than one post-TAVI assessment of THV function (i.e., through TTE or increasingly also cardiac CTs) using >1 hemodynamic parameter and the patient's clinical condition. The VARC-3 definition differentiates between four etiologies of bioprosthetic valve dysfunction: structural valve degeneration (intrinsic alterations to the THV, i.e., calcification of THV leaflets), non-structural valve degeneration (i.e., PVL leading to THV dysfunction), thrombosis (including hypo-attenuated leaflet thickening, reduced leaflet motion and valve thrombosis), and endocarditis. In the next step the degree of dysfunction is classified into three categories according to morphological and hemodynamic aspects. In the final step bioprosthetic valve failure can be assumed when severe hemodynamic valve degeneration has occurred and the clinical status has worsened, or other consequences have arisen (i.e., reintervention) (44). Several reasons can lead to decreased THV durability compared to surgical bioprosthetic valves. They include higher PVL rates, post-dilatation, and leaflet thrombosis. For instance, subclinical leaflet thrombosis rarely occurs after SAVR, but occurs frequently post-TAVI (≤40 %) and is associated not only with structural valve degeneration, but also with postprocedural stroke (61).

Many publications have suggested a good durability and low structural valve degeneration of THVs in a timespan of 5-10 years. A durability of up to 10 years was assessed in 2019 by Blackman et al., who studied outcomes of the SAPIEN, SAPIEN XT, CoreValve and Portico THV in 241 patients. Of all patients included, fewer than 0.5 % showed severe and about 9 % showed moderate structural valve degeneration. The systolic peak gradient did not increase and PVL rates had even declined by the follow-up. A decline in PVL rates and systolic peak gradient was most pronounced in self-expanding THVs, probably due to a continuous expansion of the THV (114). These are promising results, but publications regarding structural valve degeneration beyond a 10-year period are warranted, as they are essential to further evaluate TAVI indications in younger and low-risk patients (39). One possibility to counteract this issue is TAV-in-TAV deployment. However, unlike THV placement into a bioprosthetic surgical valve, TAV-in-TAV is not yet routinely performed, there is thus not enough reliable data currently available to judge its (long-term) outcomes. As more trials focus on the durability of THVs and more experience

with TAVI is gained, it should become clearer which kind of heart valve should be implanted first when younger and lower-risk patients undergo AVR (61).

The above outcomes are mostly based on first-generations THVs, which are no longer in clinical use. As discussed above (section 4.2.1) new RCTs studying the newest generation of valves are currently ongoing. The results are expected to show a further improvement in long-term outcomes due to improvements of the valves themselves and the fact that healthier patients are being treated compared to previous studies (34).

4.3 Current state of research

A decade ago, SAVR was the undisputed gold standard to treat symptomatic, severe AS. This perception has changed in recent years due to further refinements of the TAVI technique and the extensive research performed in this field. When considering all available trials, a clearer picture emerges of the hazards posed by each method. Patients undergoing SAVR mainly experience more severe bleeding, a higher in-hospital mortality, as well as an increased rate of newly acquired AF and AKI. Patients after TAVI are at a greater risk of PPI, ≥mild PVL and vascular complications, the degrees of which depend on the device used. The rates of cerebrovascular events are comparable between the two groups (11, 39).

In their study published in 2021, Ando et al. evaluated a total of 15,100 propensity-matched patients from a US nationwide databank who underwent TF-TAVI or isolated SAVR in 2018. In 2018 the newest-generation THVs were already being used in clinical routine. They found that in-hospital mortality (1.5 % vs. 2.5 %, $p<0.001$), transfusions (5.7 % vs. 16.4 %, $p<0.001$), AKI (9.4 % vs. 17 %, $p<0.001$) and time hospitalized (4.4 vs. 8.1 days, $p<0.001$) were considerably lower in the TF-TAVI group compared to the isolated SAVR group. New PPI (10.3 % vs. 6.1 %, $p<0.001$) was found to be significantly higher post-TAVI than after isolated SAVR, while stroke (1.4 % vs. 1.1 %, $p=0.25$) and hospitalization costs (51,335 vs. 48,525 U.S. $, $p=0.053$) were similar between the two groups. These outcomes are remarkable as TAVI patients in this cohort were older and presented with more comorbidities. Another finding was that TAVI deployment has surpassed the rate of SAVR procedures in the US (39). This is supported by a study which included 19,317 patients from an all-comers registry who underwent AVR in Germany in 2018. Furthermore, in 2018 twice as many TAVI procedures were performed in Germany compared to isolated SAVR. The risk of in-hospital mortality (2.5 %) was lower for TAVI than for isolated SAVR (3.1 %) (115). Regarding mild PVL at 30 days, published incidence rates are very heterogeneous. The rate of mild PVL in current studies varies widely and ranges from 5.9 % to 63.4 %, which is drastically higher than rates found post-SAVR by Makkar et al. (3 %) (106, 112). More reliable data are available for ≥moderate PVL rates. A recent meta-analysis, which included a total of 6,293 patients, compared ≥moderate PVL rates published by the PARTNER 3 and Low Risk Evolut RCTs with current data on SAVR. Even though the newest THV devices were used in low-risk patients, a significantly higher rate of ≥moderate PVL was observed post-TAVI compared with SAVR (1.5 % vs. 0.33 %; OR=3.5; 95 % CI 0.64 to 19.10, I^2=54 %) (116). Another meta-analysis evaluated the rate of short-term vascular complications in current RCTs and propensity-matched studies (n=26,456). The pooled results showed that TF-TAVI is

associated with a significantly higher risk of major vascular complications compared to SAVR (5.5 % vs. 1.4 %, p=0.01) (117).

As mentioned before, current RCTs (PARTNER 3 and Evolut Low Risk trials) found TAVI with self- and balloon-expandable THVs to be non-inferior or even superior to SAVR in low-risk patients at 2 years (32, 33, 35, 41). However, these RCTs and other currently ongoing trials excluded individuals due to frailty, severe LVOT calcification, BAV and other significant criteria (60). Also, women (Evolut Low Risk trial: 34.9 % women, PARTNER 3 trial: 30.7 % women) and patients <65 years were underrepresented in both studies (26, 32, 33). In other words, the results of these trials were obtained in a very carefully controlled setting and lack generalizability to all low-risk patients requiring AVR. For example, the presence of severe LVOT calcification led to the exclusion of many patients from the PARTNER 3 (38 %) and the Low Risk Evolut (9 %) trials. The reason for the exclusion was that DLZ calcification is associated with a higher risk of annular rupture, cardiac arrhythmias, moderate-to-severe PVL, strokes caused by atheromatous embolization, and other adverse events post-TAVI. In both low-risk trials, the rate of moderate-to-severe PVL was very low (0.6-3.6 %), probably in part due to the exclusion of patients with severe DLZ calcification, repeated post-dilatation (20-30 %), and further device improvements. Interestingly, an analysis of low-risk patients in a subgroup of the Nordic Aortic Intervention ('NORDIC') trial, in which patients with severe DLZ calcification were not excluded, showed a significantly higher rate of moderate-to-severe PVL (15 %). The stroke rate in the low-risk RCTs was also exceptionally low (0.6-2.2 %), which is also partly attributable to the exclusion of patients with severe DLZ calcification. Currently, SAVR is still strongly recommended in patients with severe DLZ calcification, due to the feasibility of direct visualization and surgical extraction of substantial calcification. This emphasizes the major significance of DLZ calcification on the indication and the outcomes of TAVI. Therefore, it should be of great concern that no standardized objective criteria are available –at least to date– to quantify calcification and to define the severity of DLZ calcification (61, 97).

As TAVI deployment is becoming increasingly accepted in low-risk patients and is surpassing the rate of isolated SAVR in many countries, there is an increasing urgency to resolve the remaining TAVI-related concerns. Among other unresolved questions, a standardized methodology for quantifying AVC using MDCT data remains unclear. This is crucial as AVC quantification was shown to be highly relevant for predicting adverse events post-TAVI. In the last two decades, much attention has been given to the measurement and quantification of calcification using MDCT data, and three different methods to quantify calcification have evolved. These include the Agatston score, which uses NECT imaging, as well as quantification based on CTA data using either a fixed threshold cut-off or a threshold relative to luminal attenuation (LA) measured in a pre-specified anatomical region. These are currently the most frequently used methods both in research and in the clinical context (16).

The oldest and most firmly established method is the Agatston score, which was initially developed for coronary calcium scoring and is currently regarded as the gold standard for AVC quantification. It is used to estimate the density of AVC using NECT imaging with a calcium detection threshold of 130 HU. The maximum attenuation measured is used to weigh the level of

attenuation into four categories. This weighting is then multiplied by the area of the calcified region. The sums of each calcified region can then be added to form the total Agatston score. The NECT images of the aortic root are acquired before performing a contrast-enhanced CT scan, thus increasing a patient's exposure to radiation as well as the examination time (8, 16, 118).

Current research focuses on assessing calcification in CTA images. Compared to NECT scans, strengths of this imaging modality include smaller slice thickness, higher spatial resolution, and less radiation exposure, as no NECT scan has to be performed additionally to the required pre-TAVI CTA. However, regarding the pursuit of a method to accurately quantify calcification, there is one major downside to CTA scans: The use of contrast media in CTA scans complicates the characterization of an appropriate calcium detection threshold, as the images are a product of complex interactions between many variables including the speed of contrast media administration, patient weight, radiation dose by the MDCT scanner, and several more. This results in a varying degree of opacification between patients, which influences the detection of AVC in CTA scans. A standard method regarding the thresholds at which AVC should be quantified when using CTA images is yet to be established. However, most measurements of AVC using CTA data focus on assessing calcium volume, as research suggests that CTA achieves greater interscan reproducibility than calcium density measurements using the Agatston score (16, 119).

Setting a fixed calcium detection threshold (i.e., 450, 850 or 1050 HU) for CTA data is challenging due to a high interscan variability regarding the LA measured (16, 119). Current literature suggests that quantifying AVC at a threshold of 850 HU is able to predict PVL ≥mild and the need for balloon post-dilatation better than other fixed HU thresholds, as well as equally or slightly better than the traditional Agatston score. The relatively high threshold of 850 HU indicates that only the densest calcification influence the adverse events mentioned above (120, 121).

The use of individual thresholds, depending on the patient's mean LA of a pre-specified anatomic region (i.e., the annulus or the ascending aorta) in the CTA dataset, can neutralize certain interactions in CTA scans as mentioned above (16). Bettinger et al. demonstrated that threshold adjustment based on individual LA (measured at the aortic annulus) showed a stronger association between AVC and PVL ≥mild than fixed HU thresholds. Furthermore, they found that setting a threshold by adding an individual's average LA plus 100 HU with a calcium volume cut-off of 1200 mm^3 showed the highest predictive power for PVL ≥mild in their study, even though the HU thresholds calculated were comparable to other tested threshold protocols (including fixed thresholds). In contrast to publications that used a fixed threshold, the high calcium cut-off suggests that not just the densest calcification is relevant, but that the volume of calcification is also of importance (119). Jochheim et al. recently refined this method by showing that multiplying the mean LA (measured in the ascending aorta) by two can significantly improve automatic AVC detection as contrast medium was not mistaken for AVC (122).

4.4 Working hypothesis

As TAVI deployment is extended to low surgical risk and ever younger patients, the importance of understanding the causes of life-limiting operative adverse effects like PVL and others is growing. The role of valvular calcification on adverse events has been assessed in multiple studies; however, our understanding of the relationship between the degree of calcification and its pathological as well as procedural consequences is only superficial. Recently, studies were able to identify certain calcification volumes and locations with a positive correlation to PVL, PPI, cerebrovascular events, annular injury, device migration, mortality and more (70, 97, 98, 103, 110, 119, 120, 122-126).

Numerous publications have suggested different calcification volumes and their respective anatomical location to predict PVL occurrence post-TAVI. In a study by Kaneko et al., calcification was quantified at a fixed detection threshold of 850 HU using CTA scans. Using multivariate regression, they found that greater annular calcification independently predicted ≥mild PVL (OR=1.009, 95 % CI 1.002 to 1.017, p=0.018) after SAPIEN 3 deployment (103). Similar results were published by Fonseca et al., who used the same imaging modality and HU threshold, but with a wider range of balloon- and self-expandable THVs. Using multivariate regression, they determined that an AVC volume of ≥157 mm^3 independently predicted ≥mild PVL (OR=3.83, 95 % CI 1.81 to 8.10, p<0.001) (121). Factors influencing the development of ≥moderate PVL post-TAVI have been investigated even more closely. Jilaihawi et al. used CTA scans and found, by means of multivariate regression, that both AVC quantity ≥235 mm^3 quantified at a set threshold of 850 HU as well as the presence of calcification in the LVOT were independent predictors for ≥moderate PVL (OR=2.8, 95 % CI 1.2 to 6.7, p= 0.023; OR=2.8, 95 % CI 1.2 to 7.0, p=0.022; respectively) when using balloon-expandable THVs (120). All the aforementioned studies used a fixed HU threshold to quantify calcium volume. In contrast, Bettinger et al. and Jochheim et al. used individual thresholds based on the average LA of a pre-specified anatomical region for calcium load quantification in CTA scans (119, 122). Bettinger et al. assessed a variety of fixed and individual HU threshold protocols. They found that the strongest positive correlation between AVC and ≥moderate PVL was obtained at a threshold set 100 HU above the mean LA detected in the LVOT (OR=1.15, 95 % CI 1.06 to 1.24, p=0.0006) (119). Using a slightly different approach, Jochheim et al. set an individual threshold by multiplying the average LA detected in the lumen of the ascending aorta by two. Using multivariate regression analysis, they determined that a total LVOT calcification volume ≥609 mm^3 independently predicted the composite clinical endpoint of their study, which consisted of all-cause mortality, device migration, any cerebrovascular complication, annulus rupture, or ≥moderate PVL after 1 month (hazard ratio= 2.44, 95 % CI 1.26 to 4.73) (122).

The occurrence of TAVI-related cardiac conduction abnormalities requiring PPI has been shown to correlate with calcification volume and certain calcification patterns in the DLZ. Fujita et al. employed CTA scans and a fixed detection threshold of 500 HU to quantify calcium volume. They found that LCC calcification >209 mm^3 independently predicted new PPI (OR=7.45, 95 % CI 1.54 to 36.12, p=0.01) (124). Using the same MDCT modality and HU threshold, Mauri et al. determined by means of multivariate regression that LVOT calcium volume underneath the LCC

>41.4 mm^3 was an independent predictor of new PPI (OR=5.0, 95 % CI 1.5 to 17.1; p=0.010) (97). Similarly, Maier et al. assessed MDCT scans before implantation of second-generation THVs and found that a higher calcium volume at the NCC, LCC and overall LVOT was significantly associated with new PPI (mean difference = 39.76 mm^3, 95 % CI 18.60 to 60.93 mm^3, p=0.0002; mean difference = 47.60 mm^3, 95 % CI 19.40 to 75.81 mm^3, p=0.0009; mean difference = 19.17 mm^3, 95 % CI 6.68 to 31.66 mm^3, p=0.003; respectively) (98).

The link between DLZ calcification and the risk of stroke post-TAVI has generally been acknowledged, as calcific embolic material is persistently found in histopathological studies of embolic debris (95). Furthermore, Pollari et al. evaluated calcification volume in pre-TAVI CTA scans by setting an individual HU threshold depending on the mean LA of the ascending aorta. They found that higher LVOT calcification beneath the right coronary cusp (RCC) significantly correlated with post-procedural stroke (OR=1.2, 95 % CI 1.03 to 1.3, p=0.0019) (60).

Only a limited number of studies have been published with regard to the impact of calcification on the risk of annulus rupture and device migration post-TAVI. Barbanti et al. used NECT scans and the Agatston score to quantify LVOT calcification and found a highly significant correlation between high calcium burden and periprocedural annulus rupture (OR=10.92, 95 % CI 3.23 to 36.91, p<0.001) by means of conditional logistic regression analysis (125). Kim et al. found that, among other factors, the absence of AVC facilitates THV malpositioning, thus leading to THV migration (110).

The above publications show that DLZ calcification can cause several adverse events post-TAVI. This is also reflected in an increased mortality rate post-TAVI when specific DLZ calcium volumes are surpassed. In their studies, Pollari et al. found that higher total LVOT calcium volume significantly correlated with 30-day mortality (OR=1.2, 95 % CI 1.02 to 1.43, p=0.029) (60), and Jochheim et al. showed that a total LVOT calcification volume above ≥609 mm^3 independently predicted death at 2 years post-TAVI (hazard ratio = 1.86, 95 % CI 1.17 to 2.93) (122). However, other studies have concluded that the degree of AVC does not influence in-hospital and 30-day mortality after TAVI (127).

Even though many studies on the role of severe DLZ calcification have been published and its impact on adverse events has generally been acknowledged, a standardized methodology to quantify calcium load has yet to be established. Many different concepts of AVC quantification in CTA data are being discussed in current literature (see section 4.3), with no larger-scale study to back the precision and efficacy of a specific method. This poses a problem, because each study uses a somewhat different method to score the amount of AVC present. This ultimately hinders the comparability of trials, which in turn slows the translation and adoption of new research in everyday clinical routine. Furthermore, this lack of standardization has hampered the agreement on an AVC volume cut-off above which post-TAVI complications are more likely. This study's research question was devised on the basis of this predicament.

The primary aim of this study is to evaluate how different concepts for quantifying AVC using CTA data, either at a fixed threshold of 850 HU or an individual threshold depending on the

mean LA value of the ascending aorta (based on the study of Jochheim et al. (122)), correlate with relevant postoperative outcomes. The postoperative outcomes deemed relevant in this study were merged to form a combined clinical endpoint consisting of both procedural outcomes (PVL ≥mild, annulus rupture, device migration) and subacute adverse events (PPI, 30-day mortality, and stroke post-TAVI). The specific endpoints were chosen due to their high clinical relevance, resulting either from their high incidence rate or their severity.

5 Methodology

5.1 Patient population and general procedural data

This clinical study used retrospective, monocentric data acquired from clinical patient records, pre- and postoperative echocardiography and ECG examination data, surgical reports, as well as pre- and postoperative laboratory analyses. Furthermore, discharge letters from subsequent hospital stays were used to follow up patients.

A total of 965 patients were prospectively included in this study. All patients had undergone TAVI at the German Heart Center Berlin (DHZB) between November 2012 and December 2019. All patients underwent the routine preoperative diagnostic workup including, among others, TTE, TEE, MDCT and coronary angiography, to assess relevant risk factors and ensure appropriate procedural planning. All relevant patient characteristics were discussed by a multidisciplinary heart team, guaranteeing a correct treatment indication for TAVI. The data were entered into the database by two operators between July 2019 and March 2020. The following criteria were used to define the study collective:

Inclusion criteria:
- Severe native AS (AVA ≤1.0 cm^2, indexed AVA ≤0.6 cm^2/m^2, MPG >40 mmHg, V_{max} >4 m/s)
- TAVI procedure at DHZB between November 2012 and December 2019

Exclusion criteria:
- Patients with a BAV
- Patients receiving a second THV in terms of TAV-in-TAV
- Patients receiving a THV after SAVR in terms of a THV being placed into a bioprosthetic surgical valve
- Bioprosthetic valves placed during concomitant surgical procedures like simultaneous mitral valve replacement or other cardiac surgeries
- Low-quality CT data

General procedural data
Table 2 shows which THVs were implanted in our study population. THVs were allocated to patients individually by the DHZB Heart Team according to current guidelines. THVs from four different manufacturers were used: Edwards Lifesciences (Irvine, CA, USA), Medtronic Inc. (Minneapolis, MN, USA), Boston Scientific (Marlborough, MA, USA), and Abbott (Abbott Park, IL, USA).

In descending order, the most used THVs were from Edwards Lifesciences (n=514, 53.3 %) followed by Medtronic (n=254, 26.3 %), Boston Scientific (n=165, 17.1 %) and Abbott (n=32, 3.3 %).

Table 2. Transcatheter heart valves deployed in the study population.		
	n	% of total
Total	965	
Edwards Lifesciences (Irvine, CA, USA)	514	53.3
SAPIEN XT	102	10.6
SAPIEN 3	399	41.3
SAPIEN 3 Ultra	3	0.3
CENTERA	10	1
Medtronic (Minneapolis, MN, USA)	254	26.3
CoreValve	21	2.2
Evolut R	121	12.5
Evolut PRO	112	11.6
Boston Scientific (Marlborough, MA, USA)	165	17.1
LOTUS	21	2.2
LOTUS Edge	2	0.2
ACURATE	34	3.5
ACURATE neo	108	11.2
Abbott (Abbott Park, IL, USA)	32	3.3
Portico	32	3.3
CA = California; **IL** = Illinois; **MA** = Massachusetts; **MN** = Minnesota; **USA** = United States of America		

This study was approved by the responsible local ethics commission (ethics approval number: EA1/062/19) and was performed in accordance with the Declaration of Helsinki.

5.2 Primary clinical endpoints

To test the hypothesis of this study, selected VARC-2 criteria developed by Kappetein et al. (2), which evaluate 30-day postprocedural outcomes, were merged to form a non-hierarchical combined clinical endpoint. In 2021 the updated VARC-3 criteria were published; however, since this study was carried out in 2019 and 2020 –when the VARC-2 criteria were the current standard– this study is based solely on the VARC-2 criteria (2, 44).

Study design

Primary clinical endpoints:

All primary clinical endpoints listed below were pooled to form a non-hierarchical combined clinical endpoint, which was used for statistical analysis (see section 5.6)

- In-hospital PVL ≥mild, evaluated as total aortic regurgitation measured in both qualitative and quantitative terms as outlined in section 5.3.5
- Implant-related conduction disturbances leading to in-hospital PPI after the procedure
- Mortality within 30 days after TAVR implantation
- Occurrence of in-hospital post-procedural stroke
- Annulus rupture during THV placement
- Intraprocedural device migration, defined as movement of the THV after initial correct positioning in the aortic annulus

5.3 Definition of clinical endpoints and incorporation of VARC-2 criteria in this study

Due to the large number of definitions provided by the VARC-2 consensus document, only a short overview of the VARC-2 criteria included in the combined clinical endpoint and those deemed relevant (see section 5.6) for the working hypothesis of this study will be stated. However, regarding information entered into the database, all applicable definitions included in the VARC-2 document were adhered to in this study. A more detailed explication of the VARC-2 criteria can be found in the original publication by Kappetein et al. (2).

5.3.1 Definition of mortality according to VARC-2

The immediate procedural mortality (intra-procedural to ≤72h post-procedure), as well as 30-day and follow-up mortality were recorded. If a patient died more than 30 days post-procedure or after the follow-up, the information was obtained from national death registries and added to the dataset. Whenever possible, correct identification of the cause of death (cardiovascular vs. non-cardiovascular) was sought and recorded (2).

5.3.2 Definition of stroke according to VARC-2

In-hospital post-procedural occurrence of stroke was recorded. All stroke events were classified as stroke or transient ischemic attack (TIA) events. The VARC-2 consensus document offered an updated definition of stroke, in which 'disabling' stroke was distinguished from 'non-disabling' stroke. Whenever possible, this new definition was applied in this study and carefully recorded (2).

To allow future research into the interplay of factors causing post-procedural stroke, antithrombotic and antiplatelet treatment, as well as patient baseline features (i.e., carotid stenosis) and other post-procedural adverse events were recorded in the dataset according to the VARC-2 criteria (2).

5.3.3 Definition of vascular complications according to VARC-2

Vascular complications include major and minor vascular complications, as well as percutaneous closure device failure. All applicable (post-)procedural vascular complications defined by the VARC-2 criteria were recorded in the dataset. Annulus rupture, included in the combined clinical endpoint of this study due to its dramatic clinical consequences, is regarded as a major vascular complication by the VARC-2 criteria (2).

5.3.4 Definition of conduction disturbances and pacemaker implantation according to VARC-2

The collection of all data concerning conduction disturbances, indications for PPI, medical interventions and any clinical consequences is highly recommended by the VARC-2 document and was performed systematically in this study (2). The need for and execution of in-hospital PPI was also recorded in this study.

5.3.5 Definition of paravalvular leak according to VARC-2

According to the guidelines, hemodynamic assessment of PVL severity should be performed using Doppler echocardiography. The VARC-2 consensus document aids clinical decision-making by suggesting criteria to assess the degree of regurgitation (Figure 6). These criteria were used as guidelines in this study. However, in its consensus document, the VARC-2 stated that there were not enough data available regarding PVL grading, limiting the evidence that supports the numerical benchmarks used in Figure 6 (2).

	Prosthetic aortic valve regurgitation		
	Mild	Moderate	Severe
Semi-quantitative parameters			
Diastolic flow reversal in the descending aorta—PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)	<10%	10–29%	≥30%
Quantitative parameters			
Regurgitant volume (ml/beat)	<30 ml	30–59 ml	≥60 ml
Regurgitant fraction (%)	<30%	30–49%	≥50%
EROA (cm^2)	0.10 cm^2	0.10–0.29 cm^2	≥0.30 cm^2

Figure 6. Assessment and grading of PVL severity according to the VARC-2 consensus document (2). ***EROA*** *= effective regurgitation orifice area;* ***PW*** *= puls-wave. Reprinted from Kappetein AP et al., Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2), Eur J Cardiothorac Surg. 2012;42(5):S45-60. Licensed under CC-BY-NC-ND.*

5.3.6 Definition of other complications according to VARC-2

Device migration was defined as an upward or downward movement of the THV after an initially correct prosthesis position in the aortic annulus, with or without adverse effects (2).

5.3.7 Definition of composite endpoints according to VARC-2

Analogous to the VARC-2 criteria, device success was defined as a composite endpoint consisting of three variables, all of which had to be fulfilled to meet the composite endpoint. These variables included: absence of procedural mortality *plus* correct anatomical THV positioning using only one prosthesis, *plus* achievement of anticipated THV performance (2).

5.4 Clinical data recorded for the DHZB TAVI database

Different software was needed to extract all relevant clinical data for this study from existing patient files. A clinical information software called NEXUS.MedFolio® (NEXUS AG, Villingen, DE) enabled access to patient reports, surgery reports, as well as internal and external discharge letters. Another tool was m.life® (Medisite, Hanover, DE), which permitted access to memos about patients written by doctors and nurses, as well as laboratory results. Finally, IntelliSpace Cardiovascular® (Philips, Amsterdam, NL) was used to access echocardiography images and reports, as well as CT images and other medical imaging data.

The data collected using the above software were entered into RedCap (Vanderbilt University, Nashville, USA), which served as a database for this clinical study. This database was the first TAVI database to be created at the DHZB and included all clinical data points necessary for this study. Data collection was performed by two independent operators in equal parts.

5.4.1 Pre-intervention clinical data

5.4.1.1 Basic data

- First name and surname, date of birth, sex
- Admission and patient identifier, surgery number

5.4.1.2 Pre-intervention general patient data

- Height, weight, BMI, body surface area (BSA)
- Surgical urgency
- Cardiac symptoms, pre-interventional New York Heart Association (NYHA) score, prior myocardial infarction
- Pre-intervention heart rhythm, PPI prior to the procedure
- Relevant preconditions of the patient: coronary artery disease, arterial hypertension, diabetes mellitus, PAD, carotid vascular disease, previous stroke or TIA, chronic obstructive pulmonary disease (COPD) (including the need for pre-interventional home oxygenation), pulmonary hypertension
- Chronic kidney disease (defined according to Kidney Disease Improving Global Outcomes), preoperative dialysis, AKI 48 hours prior to the procedure (defined according to Kidney Disease Improving Global Outcomes)
- Spirometry results (if available)
- Pre-interventional therapeutic anticoagulants and/or antiplatelet medication
- Previous (open or transcatheter) cardiac surgery and/or thoracic aorta surgery
- Existing chest radiation damage or porcelain aorta

5.4.1.3 Pre-interventional risk stratification

The STS score, logistic EuroSCORE I and EuroSCORE II were used in most publications investigating TAVI-related aspects, and were therefore also calculated in this study, thus improving comparability. In most cases the scores had already been calculated prospectively for pre-procedural risk stratification and were entered into the database manually. However, pre-procedural risk stratification was missing in some patient files, in which case the scores were calculated retrospectively.

The logistic EuroSCORE I was calculated using the website:
http://www.euroscore.org/calcold.html (accessed: 03.01.2022, 12:30)

The EuroSCORE II was calculated using the website: http://www.euroscore.org/calc.html (accessed: 03.01.2022, 12:45)

The STS score was calculated using the website: http://riskcalc.sts.org/stswebriskcalc/calculate (accessed: 03.01.2022, 13:00)

The STS score additionally provided risk predictions for many other outcomes, which were also calculated for this study and entered into the database (51). These included:

- STS Predicted Risk of Mortality (STS-PROM)

- STS Risk of Renal Failure
- STS Risk of Permanent Stroke
- STS Risk of Prolonged Ventilation
- STS Risk of Morbidity or Mortality
- STS Risk of Short Length of Stay
- STS Risk of Long Length of Stay
- STS/ACC TAVR Risk of in-hospital Mortality

5.4.1.4 Pre-interventional echocardiography

- Type of echocardiography
- AV morphology, disease etiology, degree/area/peak gradient/mean gradient/peak velocity of stenosis, degree of insufficiency
- Degree of mitral valve insufficiency / -stenosis
- Degree of tricuspid insufficiency
- Systolic pulmonary artery pressure
- Degree and, if available, percentage of LVEF, LV end-diastolic diameter, LV stroke volume, LV stroke volume index
- Degree and, if available, percentage of right ventricular EF
- Tricuspid annular plane systolic excursion
- If available, dobutamine stress echocardiography results

5.4.1.5 Pre-interventional laboratory results

- Complete blood count including white blood cells, red blood cells, hemoglobin, hematocrit, platelets
- Comprehensive metabolic panel including albumin, sodium, potassium, blood urea nitrogen creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin
- Coagulation tests including partial thromboplastin time, prothrombin time, international normalized ratio
- Further relevant results: creatine kinase, lipase, C-reactive protein, thyroid stimulating hormone

5.4.2 Interventional data

- Intervention date, surgeon, first assistant, duration of surgery, type of anesthesia and anesthesia monitoring time, fluoroscopy time, contrast media volume, concomitant procedures
- Procedure, access site, performance of AV balloon pre-dilatation, number of prostheses used, prosthesis type and size, performance of prosthesis repositioning, AV post-dilatation, type of VCD used
- Further interventional features: use of stent parking, use of a neuroprotection device
- Interventional complications: bioprosthetic valve fracture, intraoperative death, procedure aborted, conversion to open surgery, peripheral access site complications, unplanned

endovascular stenting or surgical vascular repair, distal embolization (non-cerebral), percutaneous VCD failure, procedural bleeding (including number of peri-interventionally transfused red blood cell units, fresh frozen plasma units, transfused platelet units), new arrhythmia during procedure, new ipsilateral lower extremity ischemia
- Intervention outcomes immediately after the procedure: fluoroscopic aortic regurgitation, post-implant transvalvular gradient measured with catheter, device success according to VARC-2 criteria, THV migration

5.4.3 Post-interventional clinical data and procedural outcomes

- Date of discharge, time in ICU, total length of hospital stay
- Post-interventional complications: peri-procedural myocardial infarction according to VARC-2, coronary obstruction requiring reintervention, postoperatively transfused red blood cell units, fresh frozen plasma units and platelet units, revision due to bleeding, postoperative stroke, postoperative TIA, postoperative delirium, new arrhythmia, new postoperative dialysis, or hemofiltration, surgical or transcatheter AV reintervention required
- Heart rhythm at discharge, post-interventional need for PPI
- Post-interventional laboratory results: maximum postoperative creatine kinase, peak postoperative creatinine

5.4.4 Follow-up data

- Date of follow-up
- Mortality, 30-day mortality, 1-year mortality, survival time
- If a detailed follow-up was available, all available information was registered

5.5 Computed tomography-based assessment of the aorta, aortic valve, and LVOT

5.5.1 Data collection and processing

The CT protocol used in this study is described in detail in the publication by Kofler et al. (128). It can be summarized as follows: ECG-triggered contrast-enhanced cardiac imaging was carried out with a second-generation dual source (2x128 slice) Siemens Somatom Definition Flash CT scanner (Siemens AG, Erlangen, Germany). A specific study protocol was implemented for all CT datasets used: tube voltage 100-120 kV, tube current 320 ref. mAs/rotation, rotation time 280 ms, flash mode with a high pitch of 3.2, slice collimation of 128 x 0.6 mm, slice width 0.75 mm, reconstruction increment 0.4 mm, reconstruction kernel B30f, and temporal resolution 75 ms. To obtain the best possible image quality collectively 80 mL non-ionic contrast medium (Imeron 400, Bracco, Altana Pharma, Constance, Germany) was introduced at 4-5 mL/s via the antecubital or jugular vein. Automated peak enhancement detection in the descending aorta was employed for contrast bolus timing with data acquisition beginning at a threshold of 200 HU. Imaging was carried out during an inspiration breath-hold of 3-4 s. Simultaneous ECG recording allowed prospective gating and reconstruction of the data at desired points in the cardiac cycle (128).

THVs are predominantly sized using systolic dimensions due to the risk of undersizing when THV sizing is based on diastolic data. Furthermore, due do the dynamic changes of the aortic root during the cardiac cycle, only end-systolic CT data were employed (14). Regarding the quality of CT images only a slice thickness of no more than 0.8 mm was included.

The CT datasets obtained using IntelliSpace Cardiovascular® contained all pre-TAVI CT scans from the clinical context. The CT data were further processed using 3mensio® (Version 8.1, Pie Medical Imaging, Maastricht, NL) to perform all measurements required for this study. At the end of each measurement the data were transferred to an Excel® (Microsoft, Redmond, USA) spreadsheet and screenshots were made. All CT measurements needed for this study were performed by two independent operators in equal parts.

5.5.2 Identification of the nadir and measurement of the aortic annular plane

At the start of every measurement, the aortic root was segmented automatically using 3mensio® and the nadir of each valve had to be identified. The nadir is defined as 'the most basal attachment points of the three AV cusps' (14). The location of each nadir is fundamental to positioning the annular plane. A location for the nadir was suggested by the software used; however, the real nadir often had to be corrected manually by changing the placement of marker points. Figure 7 shows the placement of the nadir points after manual correction to the precise position.

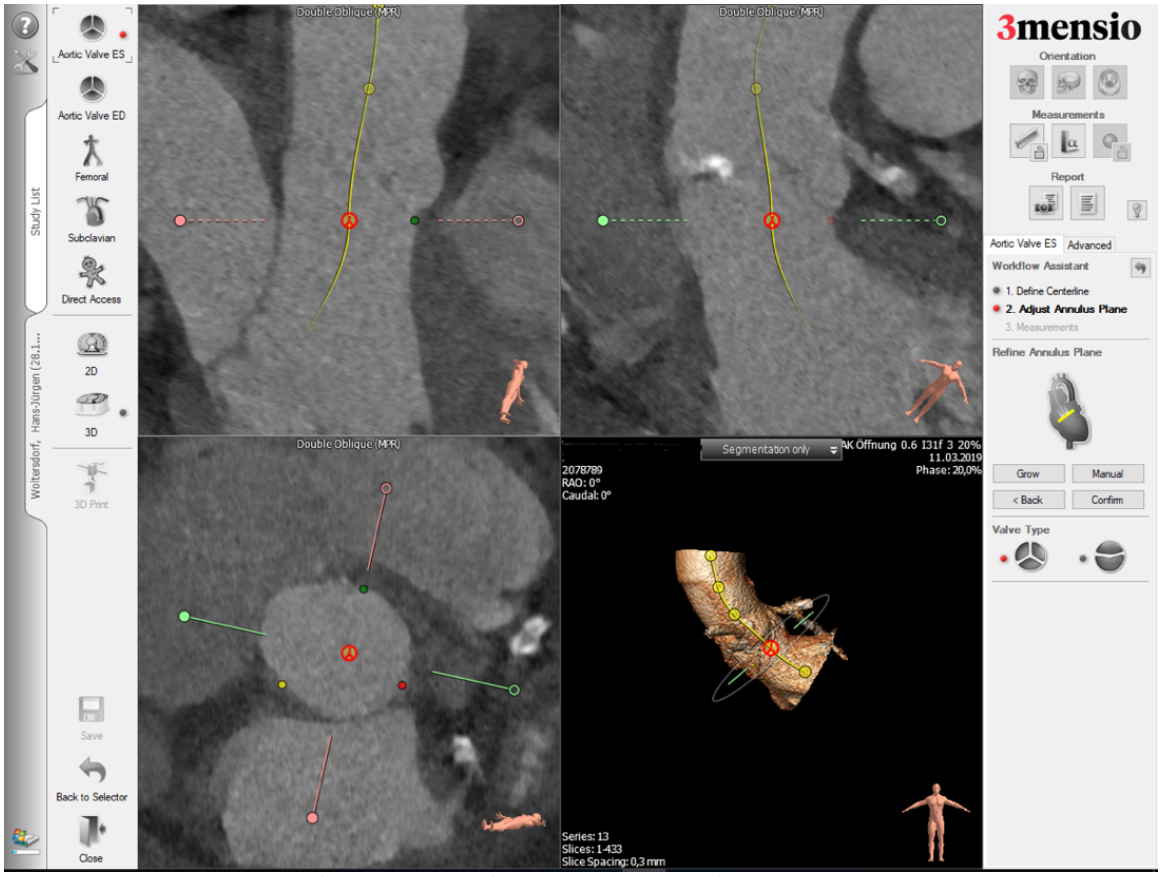


Figure 7. Manual adjustment of the nadir points for correct placement of the annular plane in 3mensio® (Version 8.1, Pie Medical Imaging, Maastricht, NL).

For CT measurements the aortic annulus is described as the luminal outline within a virtual plane aligned with and transecting the nadir of each AV cusp (14). The annular plane, also called the basal plane, was generated automatically by the software by connecting the three nadir points.

The annulus dimensions were then measured on the basis of the defined annular plane using the polygon tool, which includes diameter (minimum, maximum, and average), eccentricity, average derived area, average derived perimeter, area, perimeter, and average pixel value. The polygon measurement was also used in the following steps and will therefore not be mentioned again each time. Furthermore, in case of a calcified plaque protruding into the annular plane its depth was measured at a 90° angle, whereby only the biggest plaque was considered. Figure 8 shows an example of a measurement of the annulus dimensions and of the depth of the largest calcified plaque.

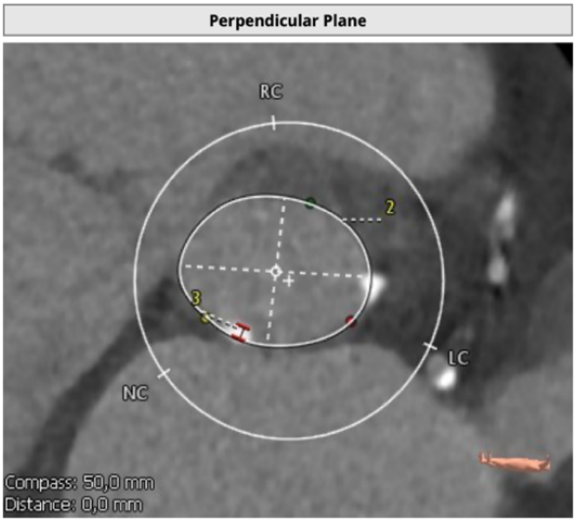


Figure 8. Measurement of annulus dimensions using the polygon tool [2] and measurement of plaque depth [3] in 3mensio® (ibid.).

5.5.3 Left ventricular outflow tract assessment

In this study the position for upper LVOT measurement was determined to be 5 mm below the annular basal plane. The polygon tool was used to measure the plane dissecting the LVOT, whereby attention was paid to reconstructing its natural shape. In case of a calcified plaque protruding into the LVOT plane its depth was measured at a 90° angle, and again only the largest plaque was considered. Figure 9 shows an example of a measurement of the LVOT dimensions and of the calcified plaque protruding into the LVOT plane.

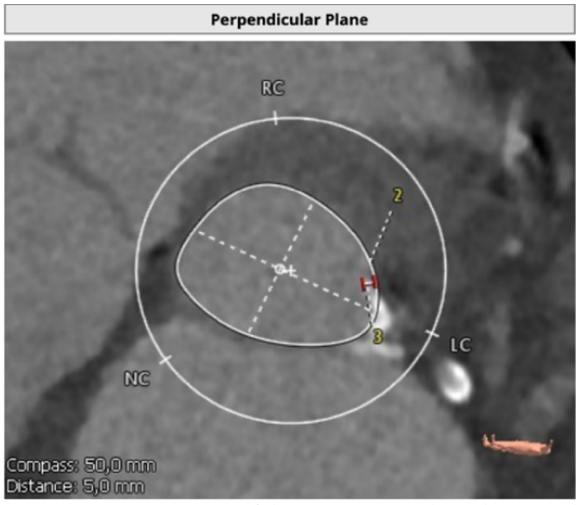


Figure 9. Measurement of the LVOT using the polygon tool [2] and measurement of plaque depth [3] in 3mensio® (ibid.).

5.5.4 Measurements of the coronary arteries, sinotubular junction, and aortic angle

5.5.4.1 Left coronary artery

The LCA location was found using 3mensio® , which automatically assigns a specific color to each of the three cusps. To locate the LCA a red dot had to be visible below a coronary artery in the stretched vessel view. The height was measured at the lower edge of the LCA using the measurement tool. Furthermore, the polygon tool was used for further measurements of the plane dissecting the lower edge of the LCA (Figure 10).

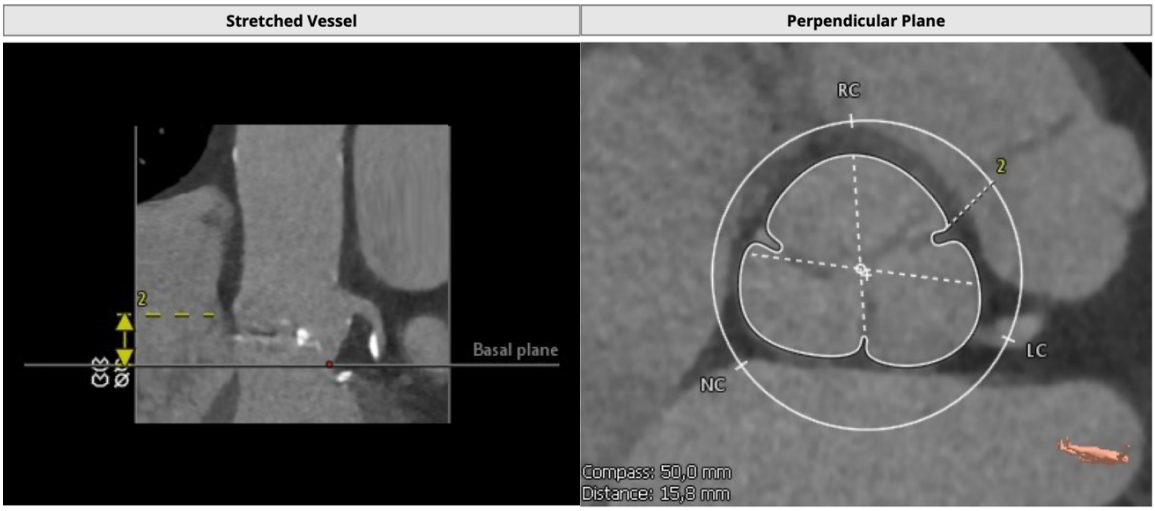


Figure 10. Measurement of LCA height (left) and use of the polygon tool (right) in 3mensio® (ibid.).

5.5.4.2 Right coronary artery

To locate the right coronary artery (RCA) a green dot had to be visible below a coronary artery in the stretched vessel view. The same measurements were obtained as for the LCA (Figure 11).

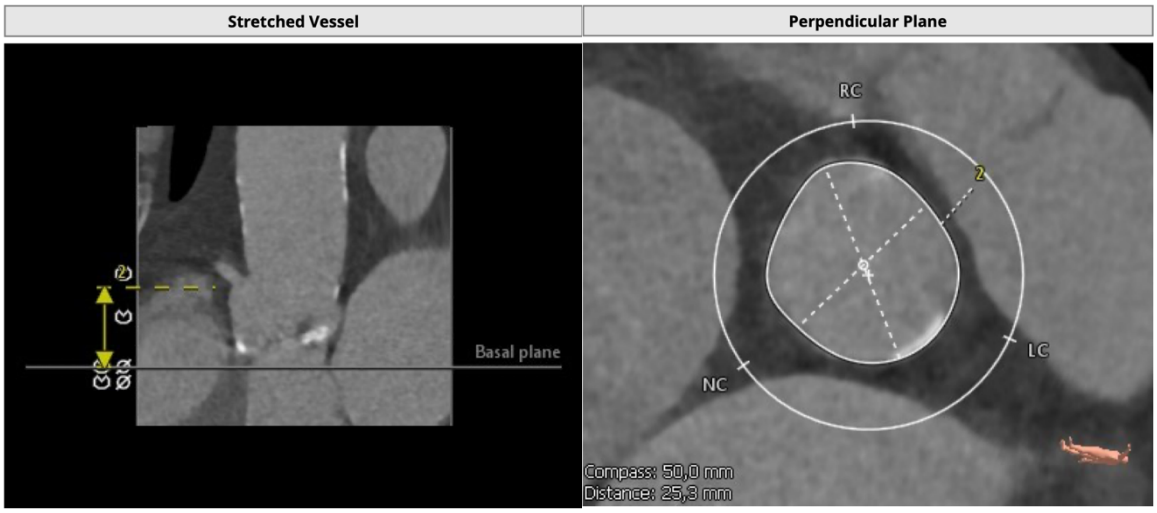


Figure 11. Measurement of RCA height (left) and use of the polygon tool (right) in 3mensio® (ibid.).

5.5.4.3 Sinotubular junction

The sinotubular junction is formed by the distal part of the sinuses toward the ascending aorta and the commissures. The sinotubular junction separates the aortic root from the ascending aorta (129). This point was found using the upper edge of the higher coronary artery in the stretched vessel view. Again, the same measurements were obtained as for the LCA and RCA (Figure 12).

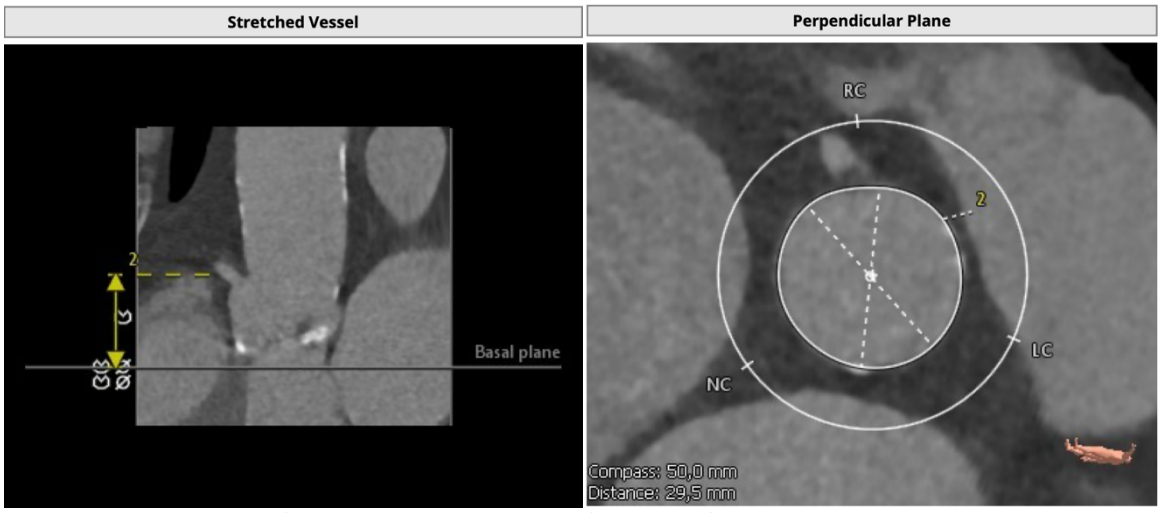


Figure 12. Measurement of sinotubular junction height (left) and use of the polygon tool (right) in 3mensio® (ibid.).

5.5.4.4 Aortic angle

To measure the aortic angle the measurement line had to be set back to the basal plane. The aorta was displayed using the 'Angio' feature of 3mensio®. The aortic angle was measured by using the automatically generated plane perpendicular to the center line of the aorta and manually drawing a horizontal line connecting to this plane. The angle of intersection of these two lines equaled the aortic angle (Figure 13).

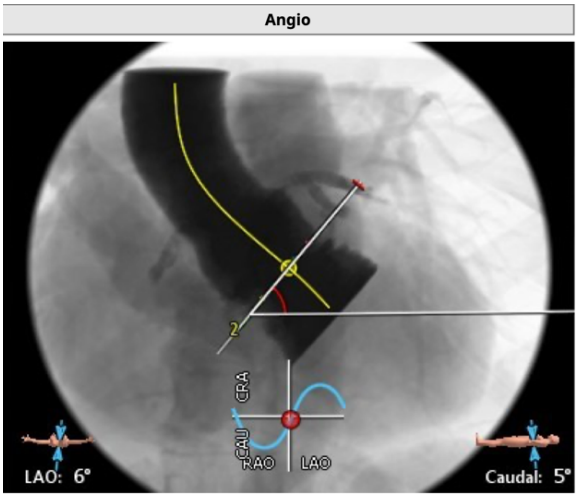


Figure 13. Measurement of the aortic angle [2] in 3mensio® (ibid.).

5.5.5 Calcium scoring

Two approaches were used to score the quantity of calcium present in the AV, annulus, and LVOT. In both approaches, calcification of the coronary arterial ostia, the aortic wall or the anterior mitral valve cusp was excluded from calcium scoring.

One approach was to measure calcification at a fixed threshold of 850 HU. This threshold was shown by several studies to have the greatest discriminatory value regarding PVL ≥mild in CTA scans (Jilaihawi et al. (120): cut-off ≥235 mm^3). It was considered to be just as good or even slightly better at predicting PVL ≥mild than the well-established Agatston score which uses NECT scans at a cut-off of 130 HU (120, 121).

The other approach was to measure calcification depending on the mean attenuation value of the ascending aorta (HU_{Aorta}) (see 5.5.5.1). Using this value, the threshold HU was set individually for each patient.

5.5.5.1 Determining the ascending aorta's mean luminal attenuation to set an individual HU threshold level

At the beginning of calcium scoring, the mean attenuation (HU_{Aorta}) of the ascending aorta above the sinotubular junction was measured using the elliptical region of interest tool (Figure 14) (130). This value was then used to calculate individual HU thresholds in accordance with a recent study published by Jochheim et al., which proposed a novel optimal HU threshold for CTA scans. The formula used to set the individual threshold was: HU_{Aorta} + 100 % of HU_{Aorta} (abbreviated '+100 % HU_{Aorta}' in the following) (122).

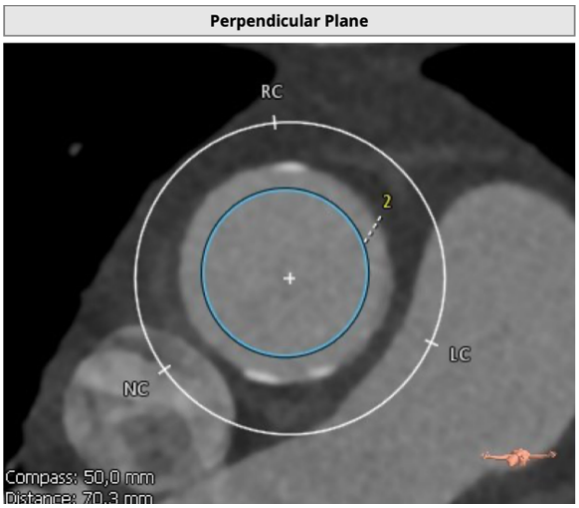


Figure 14. Measuring the HU of the ascending aorta using the elliptical Region of Interest tool in 3mensio® (ibid.).

The resulting amount of calcium quantified using this method had to be adjusted using a calibration factor (CF). The formula to calculate the CF was adopted in line with the paper of Jochheim et al. mentioned above. Their calculation was based on a linear regression between the individual HU_{Aorta} + 100 % threshold and the relation of measured calcium volumes in CTA versus NECT scans (122). The formula suggested by Jochheim et al. to calculate the CF was:

$$\text{Calibration factor} = \frac{1}{(individual\ HU\ threshold\ x\ slope) + Y\text{–}axis\ intercept}$$

The regression line calculated by Jochheim et al. had a slope of -0.0003 and a Y-axis intercept at 0.4056 (122). Therefore, the final formula used in this study was:

$$\text{Calibration factor} = \frac{1}{(individual\ HU\ threshold\ x - 0.0003) + 0.4065}$$

For a final approximation of the CTA AVC volume, the sum of multiplying the AVC volume measured with the +100 % HU_{Aorta} threshold and the CF was determined (122).

5.5.5.2 Separate leaflet scoring

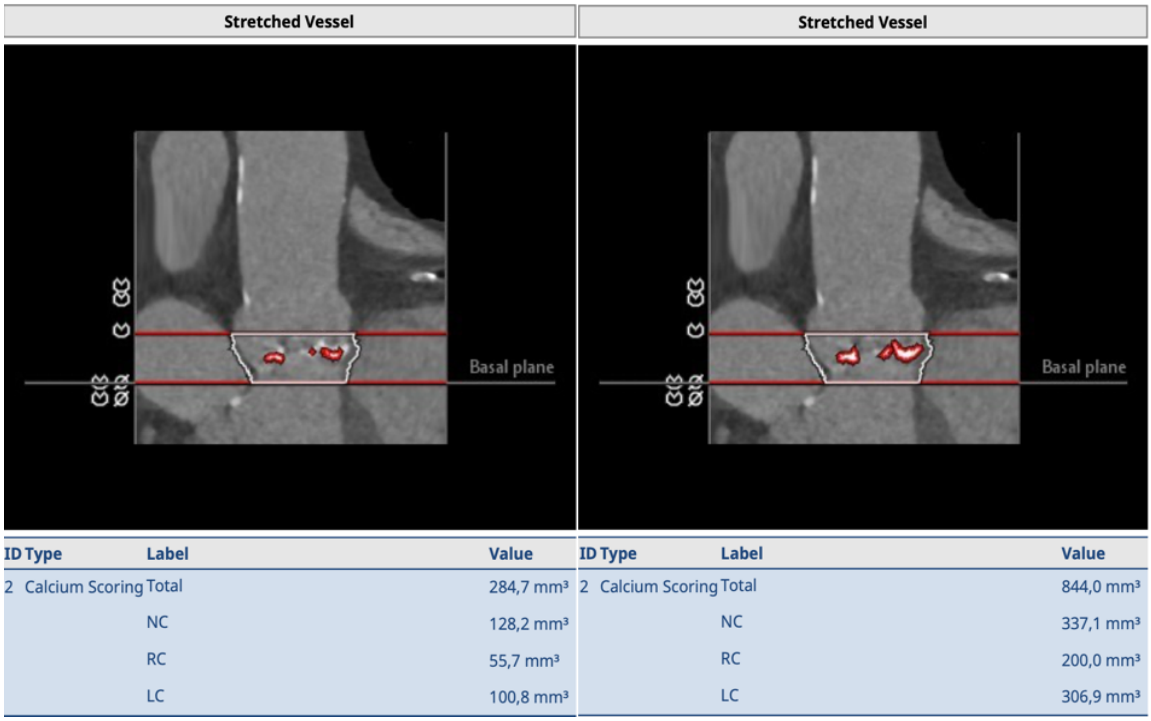
The next step was to separate the leaflets using the 'Mercedes Benz tool' of 3mensio® at the point where the three leaflets were best visible. This allowed the leaflets to be scored separately in measurements made from this point onward.

5.5.5.3 Aortic valve calcification

In this study AVC was measured using an area between the basal plane and 15 mm above the basal plane into the aorta (Figure 15). In doing so it was important to manually exclude excessive calcification of the coronary arteries and the aortic wall. Not doing so would have

confounded the results obtained, as this type of calcification does not interfere directly with THV placement and the TAVI procedure.

Calcification was measured using both the HU 850 approach and the +100 % HU_{Aorta} approach. The total amount of calcium as well as the amount of calcium in each leaflet was measured using both approaches (Figure 15).



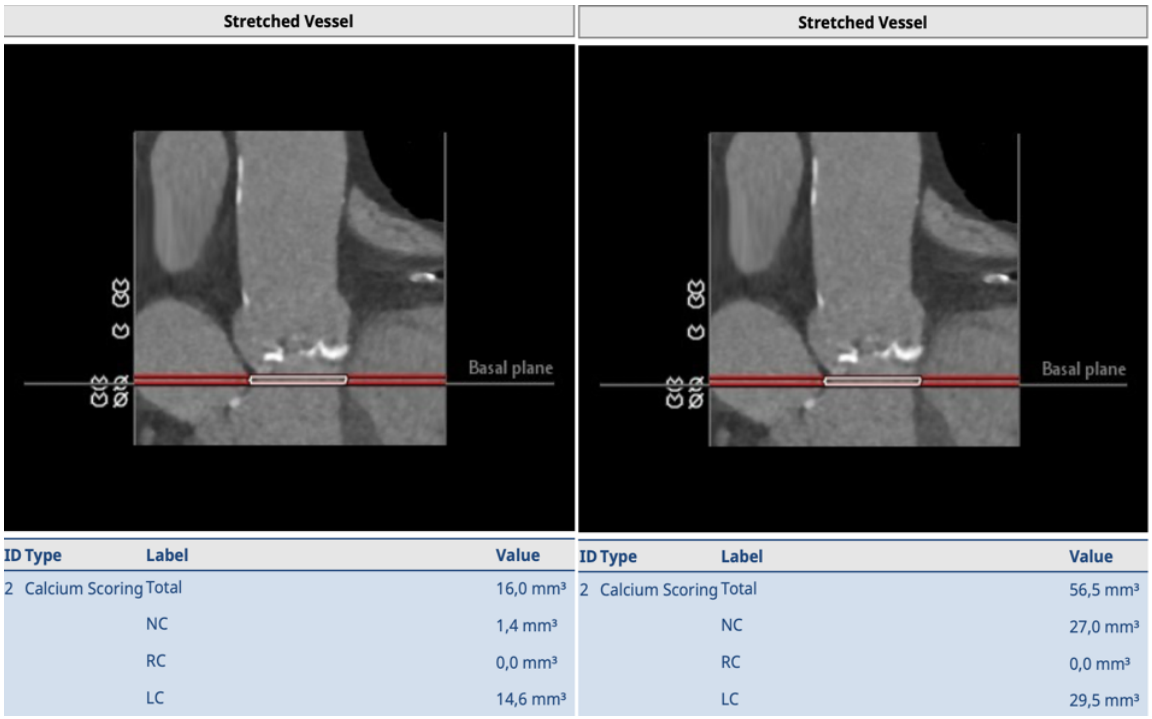
ID	Type	Label	Value
2	Calcium Scoring	Total	284,7 mm³
		NC	128,2 mm³
		RC	55,7 mm³
		LC	100,8 mm³

ID	Type	Label	Value
2	Calcium Scoring	Total	844,0 mm³
		NC	337,1 mm³
		RC	200,0 mm³
		LC	306,9 mm³

Figure 15. Determination of aortic valve calcification using the HU 850 (left) and the +100 % HU_{Aorta} method (right) in 3mensio® (ibid.). ***LC*** *= left coronary cusp;* ***NC*** *= non-coronary cusp;* ***RC*** *= right coronary cusp.*

5.5.5.4 Annulus calcification

The annulus was measured using the area between the basal plane and 2 mm above the basal plane into the aorta. The total amount of calcium as well as the amount of calcium in each leaflet was measured using the HU 850 approach and the +100 % HU_{Aorta} approach (Figure 16).



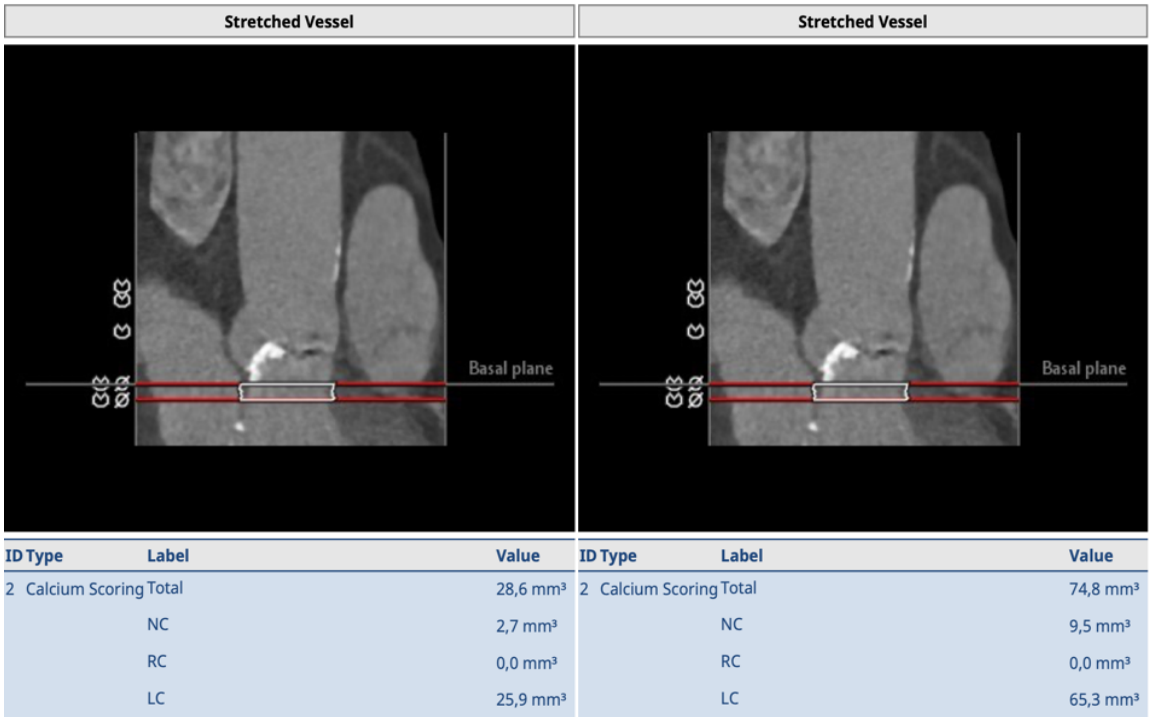
ID	Type	Label	Value
2	Calcium Scoring	Total	16,0 mm³
		NC	1,4 mm³
		RC	0,0 mm³
		LC	14,6 mm³

ID	Type	Label	Value
2	Calcium Scoring	Total	56,5 mm³
		NC	27,0 mm³
		RC	0,0 mm³
		LC	29,5 mm³

Figure 16. Determination of annulus calcification using the HU 850 (left) and the +100 % HU_{Aorta} method (right) in 3mensio® (ibid.). ***LC*** *= left coronary cusp;* ***NC*** *= non-coronary cusp;* ***RC*** *= right coronary cusp.*

5.5.5.5 Left ventricular outflow tract calcification

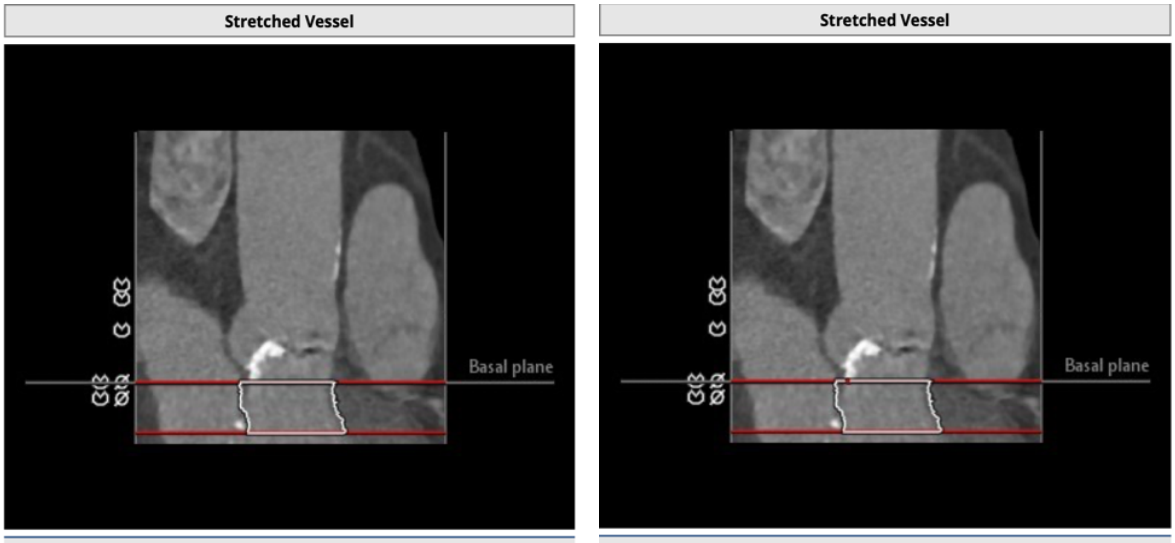
The LVOT was divided into upper LVOT and total LVOT. The upper LVOT was measured using the area between the basal plane and 5 mm below the basal plane into the left ventricle. The total LVOT was measured using the aortic area between the basal plane and 15 mm below the basal plane into the left ventricle. The total amount of calcium as well as the amount of calcium in each leaflet was measured using the HU 850 approach and the +100 % HU_{Aorta} approach (Figure 17, Figure 18).



ID	Type	Label	Value
2	Calcium Scoring	Total	28,6 mm³
		NC	2,7 mm³
		RC	0,0 mm³
		LC	25,9 mm³

ID	Type	Label	Value
2	Calcium Scoring	Total	74,8 mm³
		NC	9,5 mm³
		RC	0,0 mm³
		LC	65,3 mm³

Figure 17. Determination of upper left ventricular outflow tract calcification using the HU 850 (left) and the +100 % HU_{Aorta} method (right) in 3mensio® (ibid.). ***LC*** *= left coronary cusp;* ***NC*** *= non-coronary cusp;* ***RC*** *= right coronary cusp.*



ID	Type	Label	Value
2	Calcium Scoring	Total	64,8 mm³
		NC	37,7 mm³
		RC	0,0 mm³
		LC	27,2 mm³

ID	Type	Label	Value
2	Calcium Scoring	Total	174,7 mm³
		NC	88,0 mm³
		RC	0,0 mm³
		LC	86,7 mm³

Figure 18. Determination of total left ventricular outflow tract calcification measured using HU 850 (left) and the +100 % HU_{Aorta} method (right) in 3mensio® (ibid.). ***LC*** *= left coronary cusp;* ***NC*** *= non-coronary cusp;* ***RC*** *= right coronary cusp.*

5.6 Statistical methodology

For statistical analysis the relevant clinical data were entered in RedCap and then extracted as an Excel spreadsheet. The measurements from the CT imaging data were entered directly into an Excel spreadsheet. Both datasets were combined and statistically analyzed using R (Version 3.6.0, The R Foundation, Austria) and SPSS Statistics (Version 25, IBM, Armonk, NY, USA).

Continuous data are shown as mean with the corresponding standard deviation (mean (±SD)) or as median with the corresponding interquartile range (median [interquartile range]), whereas categorical data are shown as absolute numbers and corresponding percentages (n (%)).

A total of 198 variables were collected from each patient for the database and evaluated in relation to the occurrence of the composite clinical endpoint using univariate and multivariate regression analyses. All relevant variables were then included in a set of 35 independent variables (see Table 3). For univariate statistical testing, the Student's t-test was used to compare the mean value of each independent variable to the combined clinical endpoint being met (see Table 3). The next step was to extract all variables that were assumed to significantly influence the occurrence of adverse events post-TAVI using the Akaike information criterion (131). The 9 resulting variables were then analyzed using multivariate regression analyses to determine their individual effect on the emergence of relevant adverse events post-TAVI, summarized in this study in the form of a non-hierarchical composite clinical endpoint. Effect sizes of multivariate regression analyses are shown as odds ratios, 95 % confidence intervals, and p-values.

A schematic diagram of the variable selection method can be seen in Figure 19.

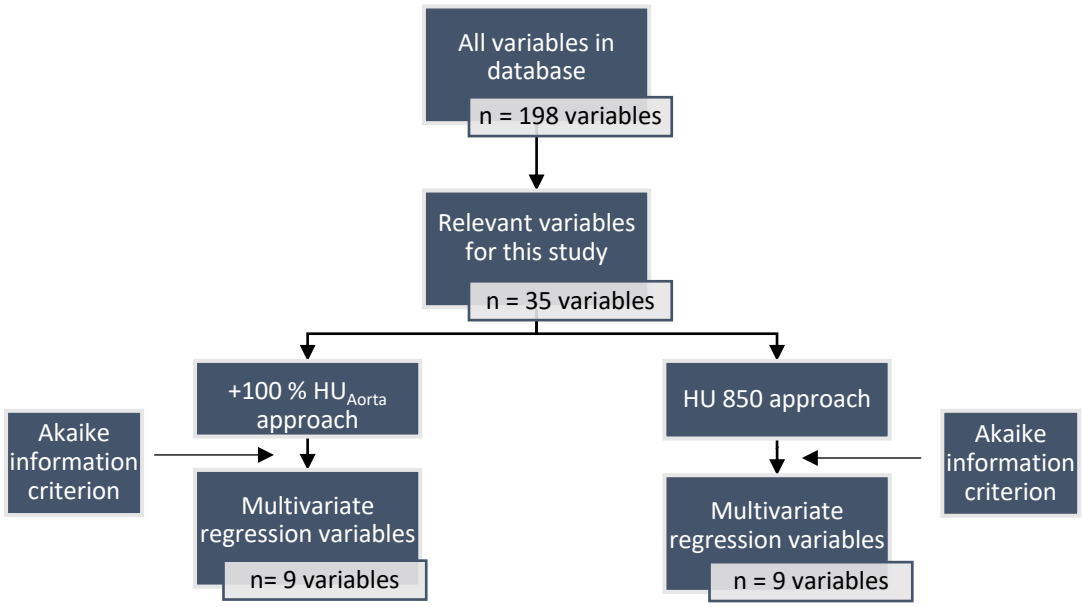


Figure 19 Schematic diagram showing the selection of variables for statistical analysis.

As described above, the CT measurement of AVC was performed in two ways: at a standard threshold of HU 850 and at an individual threshold depending on the HU_{Aorta}. To maximize the

prognostic value of AVC, the metric variable of each approach was dichotomized. Using this information, a calcium volume cut-off for each approach was devised. For the HU 850 approach, the optimal calcium volume cut-off was a cubic volume of 146 mm^3, whereas for the +100 % HU_{Aorta} approach it was 1421 mm^3.

After using the Akaike information criterion, the variables selected for multivariate regression analyses were:

- BSA in m^2
- Age in years
- Status post PPI
- Status post stroke or TIA
- Existing carotid artery stenosis
- Existing chronic kidney disease
- STS-PROM score calculated prior to TAVI
- Balloon post-dilatation necessary following THV implantation
- The ninth variable chosen using the Akaike information criterion depended on the approach used:
  - In the HU 850 approach the ninth variable was presence of AVC >146 mm^3 in all coronary cusps
  - In the +100 % HU_{Aorta} approach the ninth variable was presence of AVC >1421 mm^3 in all coronary cusps

The association between the final variables –selected with the Akaike information criterion– and the composite clinical endpoint was analyzed using a multivariate logistic regression model. This was performed for both the HU 850 and the +100 % HU_{Aorta} approach. As mentioned in section 5.2, the combined clinical endpoint consisted of six variables: PVL ≥mild, implant-related conduction disturbances, mortality within 30 days, post-procedural stroke, annulus rupture, and device migration.

In previous literature an association between severe AVC and reduced long-term survival after TAVI has been described (60, 132). Therefore, a survival analysis for both approaches was performed using the Kaplan-Meier estimator and a Kaplan-Meier curve was created.

The interclass and intraclass correlation coefficient estimates (ICC) and their 95 % confidence intervals, which assess interobserver and intraobserver variability, were calculated with SPSS Statistics. The calculation relied on 50 arbitrarily chosen MDCT datasets examined by two different operators and was based on a single rater, absolute agreement, two-way random effects model (133). Further interobserver and intraobserver variability analyses were performed and graphically demonstrated using scatter plots and Bland-Altman plots.

In this study a significant difference was assumed starting from a two-sided p-value <0.05 (*); further levels of significance were segmented into $p<0.01$ (**) and $p<0.001$ (***).

6 Results

6.1 Descriptive data analysis

6.1.1 Baseline characteristics

The baseline characteristics (n=61) of our study population include all relevant independent variables (n=35) that were chosen before using the Akaike information criterion and which are highlighted in gray in the descriptive Table 3 below. The baseline characteristics were analyzed using a bivariate analysis in respect to the occurrence of adverse events post-TAVI, in this study summarized as the combined clinical endpoint (PVL ≥mild, implant-related conduction disturbances, 30-day mortality, post-procedural stroke, annulus rupture, and device migration).

Table 3. Baseline characteristics of the study population and their bivariate correlation to the combined clinical endpoint.

	Total	**Combined clinical endpoint not met**	**Combined clinical endpoint met**	**p-value**
Total	n=965	n=589	n=376	
Demographic data				
Sex, female	492 (51)	295 (50.1)	197 (52.4)	0.526
Age, years	80.32 (±7.1)	79.83 (±7.05)	81.09 (±7.12)	0.007**
Height, meters	167.16 (±9.41)	167.38 (±9.38)	166.81 (±9.47)	0.363
Weight, kg	77.18 (±16.89)	78.12 (±16.89)	75.71 (±16.80)	0.031*
BSA, m^2	1.88 (±0.23)	1.90 (±0.23)	1.86 (±0.23)	0.030*
BMI, kg/m^2	27.6 (±5.65)	27.87 (±5.63)	27.17 (±5.66)	0.060
Clinical data & comorbidities				
NYHA III-IV	779 (80.7)	475 (80.6)	304 (80.9)	1.000
Severely reduced EF in echocardiography	77 (8)	48 (8.1)	29 (7.7)	0.903
Coronary artery disease	660 (68.4)	400 (67.9)	260 (69.1)	0.740
Atrial fibrillation	317 (32.9)	187 (31.8)	130 (34.6)	0.400
S/P myocardial infarction	158 (16.4)	95 (16.1)	63 (16.8)	0.867
S/P PPI	121 (12.5)	84 (14.3)	37 (9.8)	0.055
S/P cardiac surgery	149 (15.4)	96 (16.3)	53 (14.1)	0.405
S/P aortic surgery	4 (0.4)	1 (0.2)	3 (0.8)	0.333
COPD	231 (23.9)	140 (23.8)	91 (24.2)	0.939
Peripheral artery disease	269 (27.9)	168 (28.5)	101 (26.9)	0.626
Carotid artery stenosis	87 (9)	46 (7.8)	41 (10.9)	0.128
S/P stroke or TIA	133 (13.8)	95 (16.1)	38 (10.1)	0.011*
Hypertension	886 (91.8)	545 (92.5)	341 (90.7)	0.371
Diabetes mellitus	374 (38.8)	235 (39.9)	139 (37.0)	0.399
Chronic kidney disease	381 (39.5)	249 (42.3)	132 (35.1)	0.031*
Dialysis	34 (3.5)	23 (3.9)	11 (2.9)	0.531
Creatinine, mg/dL	1.36 (±1.7)	1.42 (±2.04)	1.27 (±0.92)	0.184
STS-PROM score	6.25 (±5.85)	6.07 (±5.67)	6.54 (±6.11)	0.223
Procedural data and outcomes				
Elective procedure	854 (88.5)	529 (89.8)	325 (86.4)	0.134
Transfemoral access route	670 (69.4)	409 (69.4)	261 (69.4)	1.000
Balloon-expandable valve implanted	504 (52.2)	311 (52.8)	193 (51.3)	0.704
Balloon dilatation pre-THV implantation	420 (43.5)	239 (40.6)	181 (48.1)	0.025*
Balloon dilatation post-THV implantation	228 (23.6)	114 (19.4)	114 (30.3)	<0.001***
Periprocedural aortic annulus rupture	3 (0.3)	0 (0.0)	3 (0.8)	0.114
PPI	73 (7.6)	0 (0.0)	73 (19.4)	<0.001***

PVL ≥mild	299 (31)	0 (0.0)	299 (79.5)	<0.001***
PVL ≥moderate	49 (5.1)	0 (0.0)	49 (13)	<0.001***
Device migration	14 (1.5)	0 (0.0)	14 (3.7)	<0.001***
Disabling stroke	14 (1.5)	0 (0.0)	14 (3.7)	<0.001***
Thirty-day mortality	19 (2)	0 (0.0)	19 (5.1)	<0.001***
Combined clinical endpoint met	376 (39)	0 (0.0)	376 (100.0)	<0.001***
VARC device success	915 (94.8)	583 (99.0)	332 (88.3)	<0.001***
One-year mortality	166 (17.2)	87 (14.8)	79 (21.0)	0.016*
Follow-up mortality	309 (32)	162 (27.5)	147 (39.1)	<0.001***
Survival time, days	683.22 (±631.14)	692.50 (±620.82)	668.68 (±647.55)	0.568
MDCT data				
Aortic angle >48 degrees	488 (50.6)	303 (51.4)	185 (49.2)	0.540
Annulus eccentricity >0. 25	390 (40.4)	231 (39.2)	159 (42.3)	0.379
LVOT eccentricity >0.4	312 (32.3)	184 (31.2)	128 (34.0)	0.402
AVC in NCC at +100 % HU_{Aorta}, mm^3	819.87 (±828.13)	716.50 (±711.91)	981.80 (±961.87)	<0.001***
AVC in RCC at +100 % HU_{Aorta}, mm^3	475.35 (±560.52)	408.43 (±491.74)	580.20 (±640.66)	<0.001***
AVC in LCC at +100 % HU_{Aorta}, mm^3	467.66 (±530.44)	400.48 (±475.93)	572.89 (±591.55)	<0.001***
AVC all coronary cusps combined at +100 % HU_{Aorta}, mm^3	1762.88 (±1553.01)	1525.41 (±1375.38)	2134.88 (±1733.94)	<0.001***
Presence of AVC >1421 mm^3 in NCC at +100 % HU_{Aorta}	425 (44)	227 (38.5)	198 (52.7)	<0.001***
Presence of AVC >1421 mm^3 in RCC at +100 % HU_{Aorta}	493 (51.1)	260 (44.1)	233 (62.0)	<0.001***
Presence of AVC >1421 mm^3 in LCC at +100 % HU_{Aorta}	471 (48.8)	247 (41.9)	224 (59.6)	<0.001***
Presence of AVC >1421 mm^3 in all coronary cusps, at +100 % HU_{Aorta}	472 (48.9)	252 (42.8)	220 (58.5)	<0.001***
AVC in NCC at HU 850, mm^3	103.51 (±106.94)	103.12 (±109.06)	104.11 (±103.66)	0.888
AVC in RCC at HU 850, mm^3	58.07 (±73.78)	56.75 (±73.52)	60.14 (±74.23)	0.486
AVC in LCC at HU 850, mm^3	57.42 (±70.69)	56.01 (±71.54)	59.62 (±69.38)	0.439
AVC in all coronary cusps combined at HU 850, mm^3	218.99 (±206.18)	215.87 (±205.03)	223.87 (±208.16)	0.557
Presence of AVC >146 mm^3 in all coronary cusps at HU 850	502 (52)	301 (51.1)	201 (53.5)	0.517
Presence of total LVOT calcification >146 mm^3 below NCC at HU 850	350 (36.3)	217 (36.8)	133 (35.4)	0.693
Presence of total LVOT calcification >146 mm^3 below RCC at HU 850	121 (12.5)	76 (12.9)	45 (12.0)	0.743
Presence of total LVOT calcification >146 mm^3 below LCC at HU 850	345 (35.8)	213 (36.2)	132 (35.1)	0.791
Presence of total LVOT calcification >146 mm^3 below all cusps at HU 850	509 (52.7)	319 (54.2)	190 (50.5)	0.301

Values are shown as n (%) and mean (± standard deviation).
Variables highlighted in gray represent the relevant independent variables (n=35) used for the Akaike information criterion.
Combined clinical endpoint consisted of PVL ≥mild, implant-related conduction disturbances, mortality within 30 days, post-procedural stroke, annulus rupture, and device migration.
AVC = aortic valve calcification; **BMI** = body mass index; **BSA** = body surface area; **COPD** = chronic obstructive pulmonary disease; **EF** = ejection fraction; **HU** = Hounsfield unit; **LCC** = left coronary cusp; **LVOT** = left ventricular outflow tract; **NCC** = non-coronary cusp; **NYHA** = New York Heart Association; **PPI** = permanent pacemaker implantation; **PVL** = paravalvular leak; **RCC** = right coronary cusp; **STS-PROM** = Society of Thoracic Surgeons Predicted Risk of Mortality; **S/P** = status post; **THV** = transcatheter heart valve; **TIA** = transitory ischemic attack; **VARC** = Valve Academic Research Consortium

The regression of baseline characteristics showed that several factors significantly correlated with the occurrence of adverse events post-TAVI and thus the combined clinical endpoint. These will be separately discussed in the following subchapters.

6.1.2 Demographic data

Table 4. Demographic data of the study population and their bivariate correlation to the combined clinical endpoint.

	Total	**Combined clinical endpoint not met**	**Combined clinical endpoint met**	**p-value**
Total	n=965	n=589	n=376	
Demographic data				
Sex, female	492 (51)	295 (50.1)	197 (52.4)	0.526
Age, years	80.32 (±7.1)	79.83 (±7.05)	81.09 (±7.12)	0.007**
Height, meters	167.16 (±9.41)	167.38 (±9.38)	166.81 (±9.47)	0.363
Weight, kg	77.18 (±16.89)	78.12 (±16.89)	75.71 (±16.80)	0.031*
BSA, m^2	1.88 (±0.23)	1.90 (±0.23)	1.86 (±0.23)	0.030*
BMI, kg/m^2	27.6 (±5.65)	27.87 (±5.63)	27.17 (±5.66)	0.060

Values are shown as n (%) or mean (± standard deviation).
Combined clinical endpoint consisted of PVL ≥mild, implant-related conduction disturbances, mortality within 30 days, post-procedural stroke, annulus rupture, and device migration.
BMI = body mass index; **BSA** = body surface area

Of the 965 patients who were included in this study and underwent TAVI between November 2012 and December 2019 at the DHZB, a total of 492 patients (51%) were female. The mean age of the study population was 80.32 years (SD=±7.1), with a mean height of 167.16 cm (SD=±9.41) and a mean weight of 77.18 kg (SD=±16,89). The mean BMI of this group was 27.6 kg/m^2 (SD=±5.65) and the mean BSA was 1.88 m^2 (SD=±0.23) (Table 4).

Regarding the demographic distribution, older age correlated most strongly with the combined clinical endpoint ($p<0.01$) being met. Lower BSA and lower weight also correlated positively with the combined clinical endpoint, however at a lower level of significance ($p=<0.05$), whereas the difference in BMI was not significant between the two groups.

6.1.3 Clinical data and comorbidities

The patients in this study population had many relevant comorbidities prior to the TAVI procedure, most of which are included in Table 5.

Table 5. Clinical data and comorbidities of the study population and their bivariate correlation to the combined clinical endpoint.

	Total	**Combined clinical endpoint not met**	**Combined clinical endpoint met**	**p-value**
Total	n=965	n=589	n=376	
Clinical data & comorbidities				
NYHA III-IV	779 (80.7)	475 (80.6)	304 (80.9)	1.000
Severely reduced EF in echocardiography	77 (8)	48 (8.1)	29 (7.7)	0.903
Coronary artery disease	660 (68.4)	400 (67.9)	260 (69.1)	0.740
Atrial fibrillation	317 (32.9)	187 (31.7)	130 (34.6)	0.400
S/P myocardial infarction	158 (16.4)	95 (16.1)	63 (16.8)	0.867

S/P PPI	121 (12.5)	84 (14.3)	37 (9.8)	0.055
S/P cardiac surgery	149 (15.4)	96 (16.3)	53 (14.1)	0.405
S/P aortic surgery	4 (0.4)	1 (0.2)	3 (0.8)	0.333
COPD	231 (23.9)	140 (23.8)	91 (24.2)	0.939
Peripheral artery disease	269 (27.9)	168 (28.5)	101 (26.9)	0.626
Carotid artery stenosis	87 (9)	46 (7.8)	41 (10.9)	0.128
S/P stroke or TIA	133 (13.8)	95 (16.1)	38 (10.1)	0.011*
Hypertension	886 (91.8)	545 (92.5)	341 (90.7)	0.371
Diabetes mellitus	374 (38.8)	235 (39.9)	139 (37.0)	0.399
Chronic kidney disease	381 (39.5)	249 (42.3)	132 (35.1)	0.031*
Dialysis	34 (3.5)	23 (3.9)	11 (2.9)	0.531
Creatinine, mg/dL	1.36 (±1.7)	1.42 (±2.04)	1.27 (±0.92)	0.184
STS-PROM score	6.25 (±5.85)	6.07 (±5.67)	6.54 (±6.11)	0.223

Values are shown as n (%) or mean (± standard deviation).
Combined clinical endpoint consisted of PVL ≥mild, implant-related conduction disturbances, mortality within 30 days, post-procedural stroke, annulus rupture, and device migration.
COPD = chronic obstructive pulmonary disease; **EF** = ejection fraction; **NYHA** = New York Heart Association; **PPI** = permanent pacemaker implantation; **STS-PROM** = Society of Thoracic Surgeons Predicted Risk of Mortality; **S/P** = status post; **TIA** = transitory ischemic attack

Cardiopulmonary comorbidities and interventions

Cardiac insufficiency graded as NYHA class III (moderate) and IV (severe) was present in 779 cases (80.7 %). A further 77 patients (8 %) showed a severely reduced LVEF (<30 %) in echocardiography. A total of 660 cases (68.4 %) of coronary artery disease, 317 cases (32.9 %) of AF, and 158 cases (16.4 %) of at least one myocardial infarction in the past were included in this study. Regarding pre-TAVI procedures, 121 patients (12.5 %) had pre-TAVI PPI, 149 (15.4 %) had undergone cardiac surgery, and only 4 (0.4 %) had undergone aortic surgery. Regarding pulmonary diseases, 231 patients (23.9 %) suffered from COPD.

Vascular comorbidities

PAD was present in 269 cases (27.9 %) and carotid artery stenosis in 87 cases (9 %).
133 patients (13.8 %) had suffered at least one stroke or transitory ischemic attack in the past.

Nephrological conditions

Hypertension was the most prevalent comorbidity in this study, affecting 886 patients (91.8 %). A total of 374 patients (38.8 %) suffered from diabetes mellitus. 381 patients (39.5 %) presented with chronic kidney disease, and 34 (3.5 %) needed dialysis. The average creatinine level in patients' serum was 1.36 mg/dL (SD=±1.7).

Regarding relevant risk stratification the average STS-PROM score was 6.25 (SD=±5.85).

Interestingly, a significant negative correlation between prior stroke or transitory ischemic attack, as well as chronic kidney disease prior to the procedure and the combined clinical endpoint was shown, however at a lower level of significance (p=<0.05).

6.1.4 Procedural data

Table 6. Procedural data of the study population and their bivariate correlation to the combined clinical endpoint.

	Total	Combined clinical endpoint not met	Combined clinical endpoint met	p-value
Total	n=965	n=589	n=376	
Procedural data and outcomes				
Elective procedure	854 (88.5)	529 (89.8)	325 (86.4)	0.134
Transfemoral access route	670 (69.4)	409 (69.4)	261 (69.4)	1.000
Balloon-expandable valve implanted	504 (52.2)	311 (52.8)	193 (51.3)	0.704
Balloon dilatation pre-THV implantation	420 (43.5)	239 (40.6)	181 (48.1)	0.025*
Balloon dilatation post-THV implantation	228 (23.6)	114 (19.4)	114 (30.3)	<0.001***
Aortic annulus rupture	3 (0.3)	0 (0.0)	3 (0.8)	0.114
PPI	73 (7.6)	0 (0.0)	73 (19.4)	<0.001***
PVL ≥mild	299 (31)	0 (0.0)	299 (79.5)	<0.001***
PVL ≥moderate	49 (5.1)	0 (0.0)	49 (13)	<0.001***
Device migration	14 (1.5)	0 (0.0)	14 (3.7)	<0.001***
Thirty-day mortality	19 (2)	0 (0.0)	19 (5.1)	<0.001***
Combined clinical endpoint met	376 (39)	0 (0.0)	376 (100.0)	<0.001***
Disabling stroke	14 (1.5)	0 (0.0)	14 (3.7)	<0.001***
VARC device success	915 (94.8)	583 (99.0)	332 (88.3)	<0.001***
One-year mortality	166 (17.2)	87 (14.8)	79 (21.0)	0.016*
Follow-up mortality	309 (32)	162 (27.5)	147 (39.1)	<0.001***
Survival time, days	683.22 (±631.14)	692.50 (±620.82)	668.68 (±647.55)	0.568

Values are shown as n (%) or mean (± standard deviation).
Combined clinical endpoint consisted of PVL ≥mild, implant-related conduction disturbances, mortality within 30 days, post-procedural stroke, annulus rupture, and device migration.
PPI = permanent pacemaker implantation; **PVL** = paravalvular leak; **THV** = transcatheter heart valve; **VARC** = Valve Academic Research Consortium

Most of the procedures were performed electively (854, 88.5 %); the TF access route was used 670 times (69.4 %), and a balloon-expandable valve was implanted 504 times (52.2 %). During the procedures, balloon dilatation of the AV pre-THV implantation was performed 420 times (43.5 %), whereas balloon dilatation post-THV implantation was performed 228 times (23.6 %). Regarding adverse procedural events, aortic annulus rupture occurred 3 times (0.3 %), PPI was necessary 73 times (7.6 %), device migration occurred 14 times (1.5 %), in-hospital PVL ≥moderate occurred 49 times (5.1 %) whereas in-hospital PVL ≥mild occurred 299 times (31 %). 19 patients (2 %) died within 30 days due to all-cause mortality. These last six independent variables were merged to a combined clinical endpoint, which was met 376 times (39 %).

Five of the six endpoints (namely new PPI, PVL ≥mild, device migration, postoperative stroke, 30-day mortality) included in the combined clinical endpoint had a high significance level (p=<0.001). However, because the combined clinical endpoint could only be met if one of the six endpoints were fulfilled, this result did not come as a surprise. The only endpoint included in the combined clinical endpoint that did not correlate significantly with the combined clinical endpoint was annulus rupture, since not enough annulus ruptures occurred in our study population.

Postoperative stroke was observed in 14 patients (1.5 %). VARC device success (as defined in section 5.3) was achieved in 915 patients (94.8 %). 166 deaths (17.2 %) were recorded after one year, as well as 309 deaths (32 %) at follow-up due to all-cause mortality. The average survival time was 683.22 days (SD=±631.14).

Regarding all other procedural variables than those included in the combined clinical endpoint, the correlation with the highest significance level (p=<0.001) and a positive correlation was achieved by two variables. These included balloon dilatation after THV implantation and all-cause mortality at follow-up. The highest significance level (p=<0.001) with a negative correlation was the achievement of successful device implantation according to the VARC-2 criteria. A positive correlation with a lower level of significance (p=<0.05) was observed between the combined clinical endpoint being met and balloon dilatation before THV implantation, as well as between the combined clinical endpoint being met and one-year mortality post-TAVI.

6.1.5 MDCT data

Table 7. MDCT data of the study population and their bivariate correlation to the combined clinical endpoint.

	Total	**Combined clinical endpoint not met**	**Combined clinical endpoint met**	**p-value**
Total	n=965	n=589	n=376	
MDCT data				
Aortic angle >48 degrees	488 (50.6)	303 (51.4)	185 (49.2)	0.540
Annulus eccentricity >0.25	390 (40.4)	231 (39.2)	159 (42.3)	0.379
LVOT eccentricity >0.4	312 (32.3)	184 (31.2)	128 (34.0)	0.402
AVC in NCC at +100 % HU_{Aorta}, mm^3	819.87 (±828.13)	716.50 (±711.91)	981.80 (±961.87)	<0.001***
AVC in RCC at +100 % HU_{Aorta}, mm^3	475.35 (±560.52)	408.43 (±491.74)	580.20 (±640.66)	<0.001***
AVC in LCC at +100 % HU_{Aorta}, mm^3	467.66 (±530.44)	400.48 (±475.93)	572.89 (±591.55)	<0.001***
AVC in all coronary cusps combined at +100 % HU_{Aorta}, mm^3	1762.88 (±1553.01)	1525.41 (±1375.38)	2134.88 (±1733.94)	<0.001***
Presence of AVC >1421 mm^3 in NCC at +100 % HU_{Aorta}	425 (44)	227 (38.5)	198 (52.7)	<0.001***
Presence of AVC >1421 mm^3 in RCC at +100 % HU_{Aorta}	493 (51.1)	260 (44.1)	233 (62.0)	<0.001***
Presence of AVC >1421 mm^3 in LCC at +100 % HU_{Aorta}	471 (48.8)	247 (41.9)	224 (59.6)	<0.001***
Presence of AVC >1421 mm^3 in all coronary cusps, at +100 % HU_{Aorta}	472 (48.9)	252 (42.8)	220 (58.5)	<0.001***
AVC in NCC at HU 850, mm^3	103.51 (±106.94)	103.12 (±109.06)	104.11 (±103.66)	0.888
AVC in RCC at HU 850, mm^3	58.07 (±73.78)	56.75 (±73.52)	60.14 (±74.23)	0.486
AVC in LCC at HU 850, mm^3	57.42 (±70.69)	56.01 (±71.54)	59.62 (±69.38)	0.439
AVC in all coronary cusps combined at HU 850, mm^3	218.99 (±206.18)	215.87 (±205.03)	223.87 (±208.16)	0.557
Presence of AVC >146 mm^3 in all coronary cusps at HU 850	502 (52)	301 (51.1)	201 (53.5)	0.517
Presence of total LVOT calcification >146 mm^3 below NCC at HU 850	350 (36.3)	217 (36.8)	133 (35.4)	0.693
Presence of total LVOT calcification >146 mm^3 below RCC at HU 850	121 (12.5)	76 (12.9)	45 (12.0)	0.743

Presence of total LVOT calcification >146 mm^3 below LCC at HU 850	345 (35.8)	213 (36.2)	132 (35.1)	0.791
Presence of total LVOT calcification >146 mm^3 below all cusps at HU 850	509 (52.7)	319 (54.2)	190 (50.5)	0.301

Values are shown as n (%) or mean (± standard deviation).
Combined clinical endpoint consisted of PVL ≥mild, implant-related conduction disturbances, mortality within 30 days, post-procedural stroke, annulus rupture, and device migration.
AVC = aortic valve calcification; **HU** = Hounsfield unit**; LCC** = left coronary cusp; **LVOT** = left ventricular outflow tract; **MDCT** = multidetector computed tomography; **NCC** = non-coronary cusp; **RCC** = right coronary cusp

An aortic angle surpassing 48 degrees was found in 488 cases (50.6 %), annulus eccentricity above 0.25 was found 390 times (40.4 %), and LVOT eccentricity above 0.4 was measured 312 times (32.3 %).

Using the +100 % HU_{Aorta} approach, the average AVC measured in the NCC was 819.87 mm^3 (SD=±828.13), 475.35 mm^3 in the RCC (SD=±560.52), and 467.66 mm^3 in the LCC (SD=±530.44); in all coronary cusps combined it was 2134.88 mm^3 (SD=±1733.94). Furthermore, at a calcium volume cut-off of 1421 mm^3, AVC was present in the NCC 425 times (44 %), 493 times in the RCC (51.1 %), and 471 times in the LCC (48.8 %); when averaging all coronary cusps AVC was present 472 times (48.9 %).

With the HU 850 approach, the average AVC measured in the NCC was 103.51 mm^3 (SD=±106.94), 58.07 mm^3 in the RCC (SD=±73.78), 57.42 mm^3 in the LCC (SD=±70.69); in all coronary cusps combined it was 218.99 mm^3 (SD=±206.18). AVC above the calcium volume cut-off of 146 mm^3 was present 502 times (52 %).

Finally, total LVOT calcification using the HU 850 approach with a calcium volume cut-off of 146 mm^3 was present 350 times in the NCC (36.3 %), 121 times (12.5 %) in the RCC, 345 times (35.8 %) in the LCC, and 509 times in all coronary cusps (52.7 %).

The MDCT variables presence of AVC >1421 mm^3, as well as the quantity of AVC in either the NCC, the RCC, the LCC or a combination of all three coronary cusps measured with the +100 % HU_{Aorta} approach correlated positively with the combined clinical endpoint at a very high significance ($p<0.001$). Surprisingly, both the presence and the quantity of AVC measured with the HU 850 approach did not correlate significantly with the combined clinical endpoint.

6.2 Multivariate analysis of the combined clinical endpoint

6.2.1 Impact estimation of AVC using the +100 % HU_{Aorta} approach on the combined clinical endpoint

The multivariate regression analyses between the combined clinical endpoint and the variables selected with the Akaike information criterion (BSA, age, status post PPI, carotid artery stenosis, status post stroke or TIA, chronic kidney disease, STS-PROM score, balloon post-dilatation, and presence of AVC according to the approach used), including AVC measured using the

+100 % HU_{Aorta} approach with a calcium volume cut-off of 1421 mm^3, showed significant coefficients for five variables (Table 8).

Table 8. Multivariate regression analysis between the combined clinical endpoint and the final variables determined using the Akaike information criterion including AVC measurement with the +100 % HU_{Aorta} approach.

	p-value	**Odds ratio**	**2.5 % confidence interval**	**97.5 % confidence interval**
BSA, m^2	0.09829	0.5798588	0.30265695	1.1034236
Age, years	0.13107	1.0163879	0.99549800	1.0384680
S/P PPI	0.10537	0.7004579	0.45114311	1.0703918
Carotid artery stenosis	0.06784	1.5432507	0.96655355	2.4596393
S/P stroke or TIA	0.00487 **	0.5482469	0.35727282	0.8265918
Chronic kidney disease	0.02707 *	0.7145426	0.52949640	0.9614052
STS-PROM score	0.03545 *	1.0273230	1.00156153	1.0534967
Balloon dilatation post-THV implantation	0.00105 **	1.6844174	1.23281873	2.3021007
Presence of AVC >1421 mm^3 in all coronary cusps, at +100 % HU_{Aorta}	$9.2x10^{-7}$ ***	1.9975370	1.51719124	2.6373857

Combined clinical endpoint consisted of PVL ≥mild, implant-related conduction disturbances, mortality within 30 days, post-procedural stroke, annulus rupture, and device migration.
AVC = aortic valve calcification; **BSA** = body surface area; **HU** = Hounsfield unit; **PPI** = permanent pacemaker implantation; **S/P** = status post; **STS-PROM** = Society of Thoracic Surgeons Predicted Risk of Mortality; **THV** = transcatheter heart valve; **TIA** = transitory ischemic attack

No significant coefficient was observed for the independent variables BSA (OR=0.58, 95 % CI 0.3 to 1.1, p=0.1), age at the time of the procedure (OR=1.02, 95 % CI 1.0 to 1.04, p=0.13), PPI prior to TAVI (OR=0.7, 95 % CI 0.45 to 1.07, p=0.11), and stenosis of the carotid artery (OR=1.54, 95 % CI 0.97 to 2.46, p=0.07). For BSA, the odds ratio showed that a lower BSA correlated with increased odds of the combined clinical endpoint being met, which was also observed in the descriptive data analysis above. Regarding age at the time of the procedure, the odds ratio showed that there was barely a difference between the two groups.

Stroke or transitory ischemic attack prior to the procedure showed a highly significant (OR=0.55, 95 % CI 0.36 to 0.83, p=0.005) and prior chronic kidney disease a significant association (OR=0.71, 95 % CI 0.53 to 0.96, p=0.03) with the combined clinical endpoint. The odds ratio suggests that both independent variables decreased the odds of the combined clinical endpoint being met.

The difference in the STS-PROM score was found to be significant (OR=1.03, 95 % CI 1 to 1.05, p=0.04) between the two groups. However, the odds ratio and the confidence interval suggested only a very small difference between the groups.

Performance of balloon dilatation following THV implantation was highly significant (OR=1.68, 95 % CI 1.23 to 2.3, p=0.0011) in the multivariate regression analysis. Furthermore, the odds ratio and the confidence interval suggest an increase in the odds of the combined clinical endpoint being met when balloon post-dilatation was performed.

Finally, presence of AVC at a calcium volume cut-off of 1421 mm^3 for all coronary cusps combined using the +100 % HU_{Aorta} approach showed the most significant difference between the two groups ($p=9.2x10^{-7}$) and the highest odds ratio (OR=2, 95 % CI 1.52 to 2.64) of all variables selected by the Akaike information criterion. The odds ratio and the confidence interval suggested a strong increase in the odds for the combined clinical endpoint being met if AVC exceeding 1421 mm^3 was present in all coronary cusps using the +100 % HU_{Aorta} approach.

6.2.2 Impact estimation of AVC using the 850 HU approach on the combined clinical endpoint

The multivariate regression analysis between the combined clinical endpoint and the variables selected by the Akaike information criterion, including AVC measured using the HU 850 approach at a calcium volume cut-off of 146 mm^3, showed significant coefficients for four variables (Table 9).

Table 9. Multivariate regression analysis between the combined clinical endpoint and the final variables selected using the Akaike information criterion, including AVC measurement with the HU 850 approach.

	p-value	**Odds ratio**	**2.5 % confidence interval**	**97.5 % confidence interval**
BSA, m^2	0.375131	0.7541129	0.40317173	1.4053422
Age, years	0.081434	1.0185721	0.99801625	1.0402745
S/P PPI	0.055813	0.6599066	0.42700302	1.0031658
Carotid artery stenosis	0.038966 *	1.6257071	1.02288284	2.5803644
S/P stroke or TIA	0.005987 **	0.5600771	0.36679031	0.8401385
Chronic kidney disease	0.018700 *	0.7021200	0.52193355	0.9415186
STS-PROM score	0.083949	1.0221727	0.99677765	1.0479482
Balloon dilatation post-THV implantation	0.000727 ***	1.7001932	1.24951808	2.3139998
AVC >146 mm^3 in all coronary cusps at HU 850	0.352165	1.1347326	0.86969403	1.4816678

Combined clinical endpoint consisted of PVL ≥mild, implant-related conduction disturbances, mortality within 30 days, post-procedural stroke, annulus rupture, and device migration.
AVC = aortic valve calcification; **BSA** = body surface area; **HU** = Hounsfield unit; **PPI** = permanent pacemaker implantation; **S/P** = status post; **STS-PROM** = Society of Thoracic Surgeons Predicted Risk of Mortality; **THV** = transcatheter heart valve; **TIA** = transitory ischemic attack

Analogous to the multivariate statistical analysis performed in section 6.2.1, no significant coefficient with the combined clinical endpoint was observed for the independent variables BSA (OR=0.75, 95 % CI 0.4 to 1.4, p=0.38), age at the time of the procedure (OR=1.02, 95 % CI 1 to 1.04, p=0.08), and PPI prior to TAVI (OR=0.66, 95 % CI 0.43 to 1, p=0.056). Again, the odds ratio showed that a lower BSA correlated with increased odds of the combined clinical endpoint being met. Regarding age at the time of the procedure, the odds ratio showed that there was barely a difference between the two groups.

A similar level of significance compared to the multivariate analysis in section 6.2.1 was observed for stroke or transitory ischemic attack prior to the procedure, which again was highly significant (OR=0.56, 95 % CI 0.37 to 0.84, p=0.006), and a significant difference between the two groups (OR=0.7, 95 % CI 0.52 to 0.94, p=0.02) was found for prior chronic kidney disease.

Again, the odds ratio of both variables suggested that their presence decreased the odds of the combined clinical endpoint being met.

Interestingly, when considering the presence of AVC measured using the HU 850 approach at a calcium volume cut-off of 146 mm^3 in all coronary cusps instead of the presence of AVC measured using the +100 % HU_{Aorta} approach at a calcium volume cut-off of 1421 mm^3 in all coronary cusps in a multivariate regression analysis, most of the resulting p-values varied considerably.

In contrast to the multivariate analysis in section 6.2.1, the difference in the STS-PROM score between the two groups was not significant (OR=1.02, 95 % CI 1 to 1.05, p=0.084). Importantly, the presence of AVC measured using the HU 850 approach at a calcium volume cut-off of 146 mm^3 in all coronary cusps was also not significant (OR=1.14, 95 % CI 0.87 to 1.48, p=0.35). Furthermore, the odds ratio and confidence interval suggest that there was barely a difference between the two groups. This result contrasted sharply with the very high significance level found for the presence of AVC measured using the +100 % HU_{Aorta} approach at a calcium volume cut-off of 1421 mm^3 in all coronary cusps (OR=2, 95 % CI 1.52 to 2.64, $p=9.2x10^{-7}$).

A disparity in the significance level between both multivariate analyses was found regarding the performance of balloon dilatation following THV implantation, which now showed a highly significant difference between the two groups with a $p<0.001$ (OR=1.7, 95 % CI 1.25 to 2.3, p=0.0007). Compared to the multivariate analysis in section 6.2.1, the odds ratio and the confidence interval suggest a small increase in the odds of the combined clinical endpoint being met when balloon post-dilatation was performed. Another divergence from the multivariate analysis in section 6.2.1 was seen with regard to carotid artery stenosis. The HU 850 multivariate analysis showed a significant difference between the two groups regarding carotid artery stenosis diagnosed prior to the procedure (OR=1.63, 95 % CI 1.02 to 2.58, p=0.039). Additionally, the odds ratio and the confidence interval increased slightly, suggesting an increase in the odds of the combined clinical endpoint being met when carotid artery stenosis was present.

6.3 Survival analysis

To evaluate and compare the impact of AVC measurements using both approaches on the survival of patients following TAVI, a Kaplan-Meier survival analysis was performed for all 965 patients. However, due to the relatively short follow-up period after the procedure, there were only enough data to calculate a Kaplan-Meier survival analysis for 360 days.

6.3.1 Kaplan-Meier survival analysis of the +100 % HU_{Aorta} approach

Figure 20 shows a Kaplan-Meier survival analysis of AVC measured with the +100 % HU_{Aorta} approach including the corresponding bivariate significance testing. The impact of the amount of AVC measured using the +100 % HU_{Aorta} approach on survival time was determined using the log rank test to compare the full curves of each group. The resulting significance level was p=0.14. Therefore, no statistically significant difference was detected between the two curves.

However, even though the difference between the two groups was not significant, a small difference in survival probability was observed. Patients with an AVC of more than 1421 mm^3 showed a slightly better survival beyond 360 days compared to those with an AVC of less than 1421 mm^3.

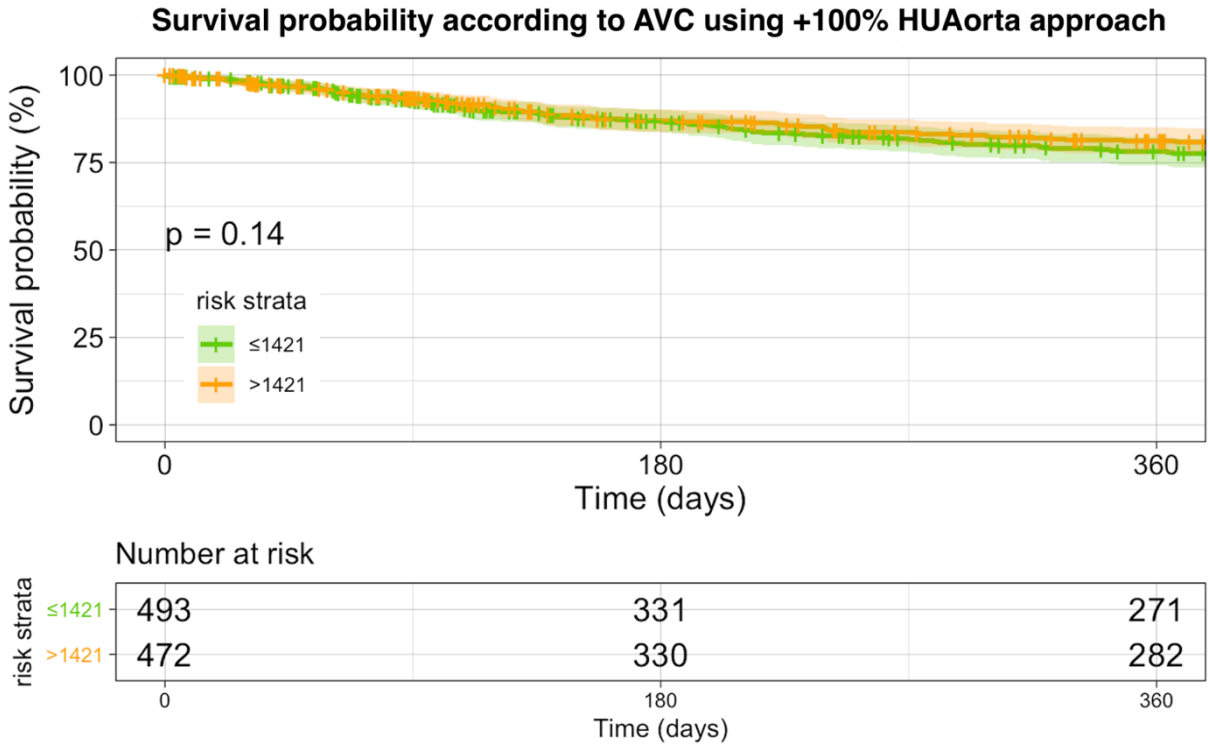


Figure 20. Kaplan-Meier curve showing the probability of survival according to the amount of aortic valve calcification using the +100 % HU_{Aorta} approach (n=965). The two groups were split using the calcium volume cut-off calculated for the +100 % HU_{Aorta} approach. Green line: total AVC calcium volume from 0 to 1421 mm^3. Orange line: total AVC calcium volume above 1421 mm^3.

6.3.2 Kaplan-Meier survival analysis of the HU 850 approach

Figure 21 shows a Kaplan-Meier survival analysis of AVC measured with the HU 850 approach including the corresponding bivariate significance testing. The impact of the amount of AVC measured using the HU 850 approach on survival time was determined using the log rank test to compare the full curves of each group. The resulting significance level was p=0.97. Consequently, no statistically significant difference was observed between the two curves. Compared to the +100 % HU_{Aorta} approach there was almost no difference between the two groups regarding survival beyond 360 days.

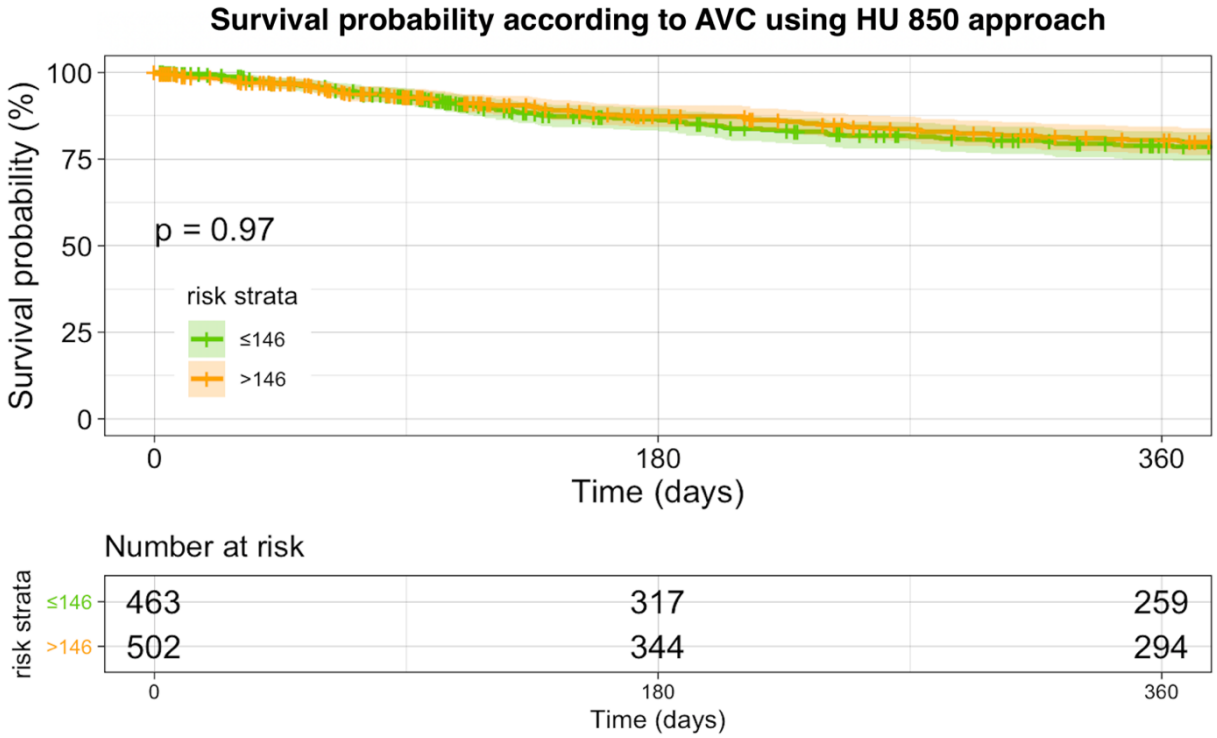


Figure 21. Kaplan-Meier curve showing the probability of survival according to the amount of aortic valve calcification using the HU 850 approach (n=965). The two groups were split using the calcium volume cut-off calculated for the HU 850 approach. Green line: total AVC calcium volume from 0 to 146 mm³. Orange line: total AVC calcium volume above 146 mm³.

6.4 Inter- and intraobserver variability in the quantification of aortic valve calcium

Quantification of AVC was performed systematically and as precisely as possible because reproducibility and reliability of the data are essential to generalize findings to routine clinical and scientific use. Based on 50 MDCT datasets assessed by the same two independent operators, data reliability was tested separately for each AV cusp using inter- and intraobserver variability analyses. After the data were shown to be normally distributed, scatter plots with associated Pearson correlation coefficients (Figure 22) and Bland-Altman plots (Figure 23) were generated to determine the correlation and agreement between operator measurements and to enable graphical illustration. Furthermore, as the MDCT data used is numeric, ICC were calculated (134).

Scatter plots and corresponding Pearson correlation coefficients can show a linear relationship and correlation between two variables. In our case it was shown that interobserver variability was low, with a very strong correlation between measurements of both operators with a Pearson's r value of 0.90 for NCC, 0.85 for RCC, and 0.94 for LCC (left column in Figure 22).Regarding intraobserver variability, the scatter plots and Pearson correlation coefficients revealed an even stronger correlation, with Pearson's r at 0.99 for NCC, 0.97 for RCC, and 0.97 for LCC (right column in Figure 22) (133, 134).

Scatter plots of inter- and intraobserver variability according to aortic valve cusp

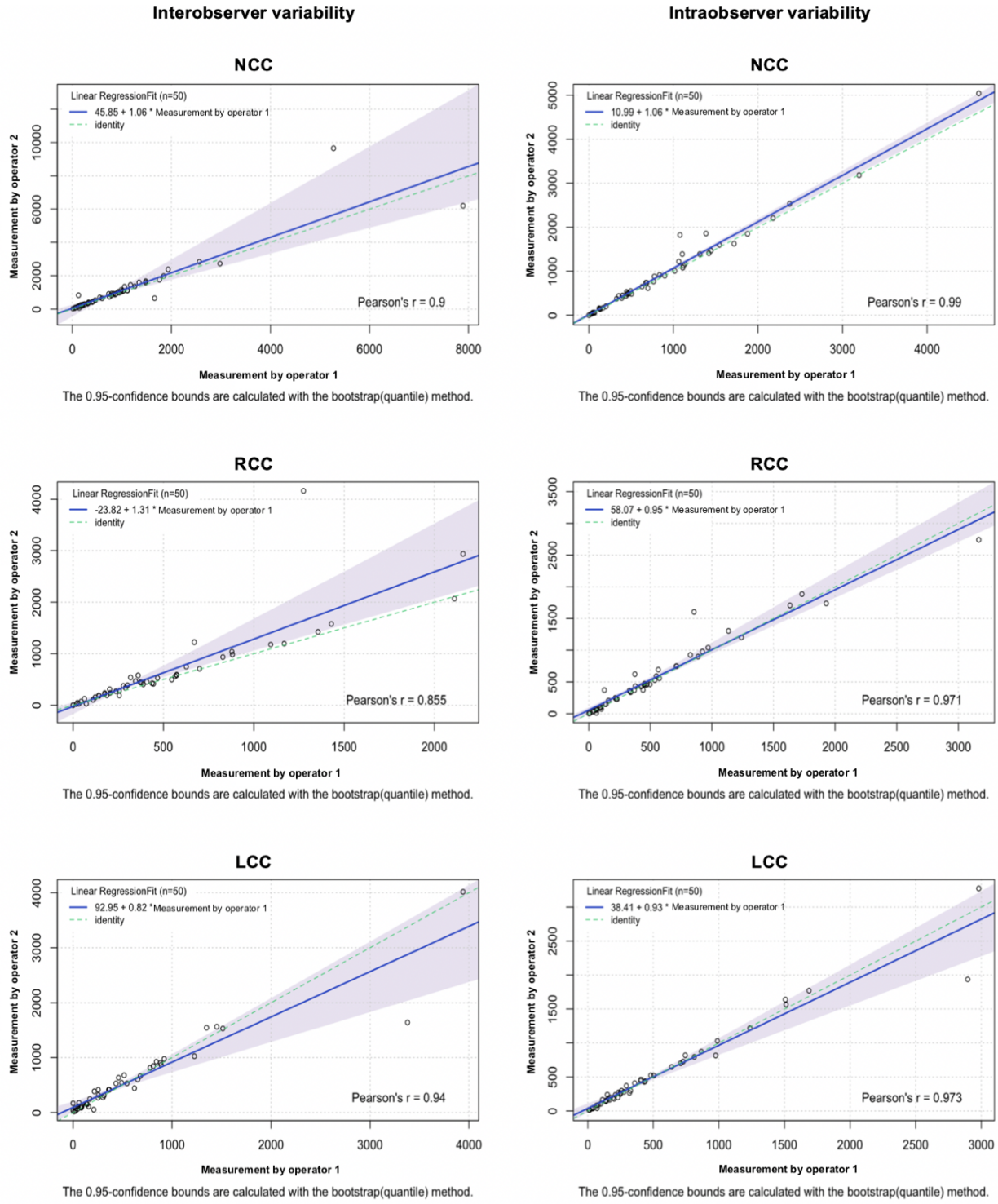


Figure 22. Units on X- and Y-axes are mm³. Scatter plots of inter- and intraobserver variability according to aortic valve cusps. Interobserver variability is displayed on the left and intraobserver variability on the right. The solid line indicates the linear regression line, the dashed line shows the line of equality (identity line), and the purple filled area shows the 95 % confidence interval of agreement. ***LCC*** *= left coronary cusp,* ***NCC*** *= non-coronary cusp,* ***RCC*** *= right coronary cusp.*

The Bland-Altman plots, which show a measure of agreement, also illustrate interobserver and intraobserver variability. They showed that measurements were mostly within the calculated upper and lower limits of agreement, indicating good agreement in general. Regarding

interobserver variability the degree of bias for NCC was high at 114.3 (level of agreement: -1275.4 to 1504), for RCC it was substantial at 127.7 (level of agreement: -715.5 to 971), whereas for LCC it was very low at -2 (level of agreement: -527.8 to 523.9) (left column in Figure 23). Regarding intraobserver variability the degree of bias was generally lower: for NCC it was 59.7 (level of agreement: -225.4 to 344.8), for RCC it was 30.5 (level of agreement: -251

Bland-Altman plots of inter- and intraobserver variability according to aortic valve cusp

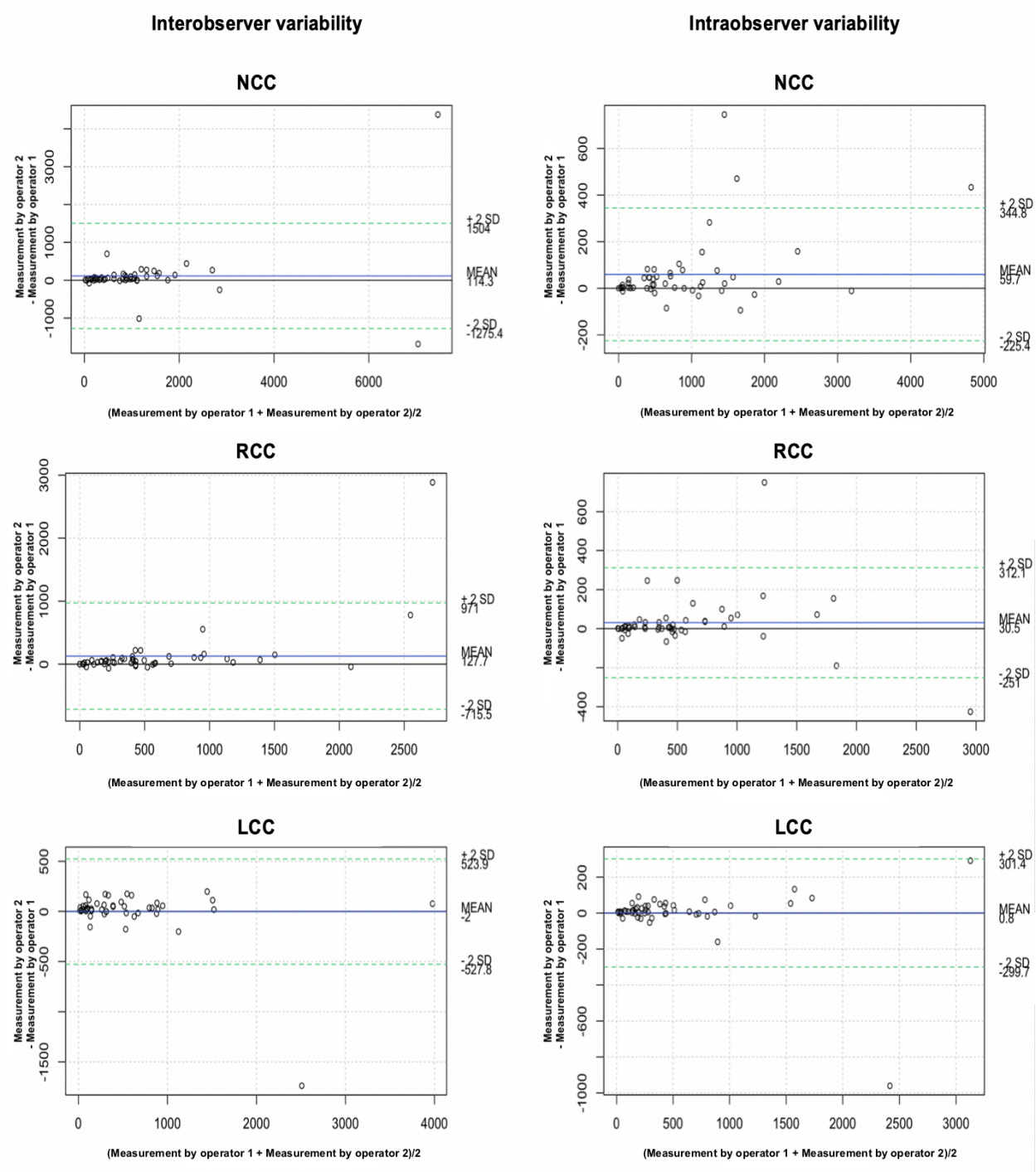


Figure 23. Units on X- and Y-axes are mm³. Bland-Altman plots of inter- and intraobserver variability according to aortic valve cusps. Interobserver variability is displayed on the left and intraobserver variability on the right. The solid black line shows the zero position, the solid blue line indicates the mean relative difference, and the dashed lines indicate the top and bottom 95 % limits of agreement. ***LCC*** *= left coronary cusp,* ***NCC*** *= non-coronary cusp,* ***RCC*** *= right coronary cusp.*

to 312.1), and for LCC it was 0.8 (level of agreement: -299.7 to 301.4) (right column in Figure 23).

It can be concluded that bias concerning interobserver variability was high and wide-ranging limits of agreement were observed, whereas for intraobserver variability bias was low with narrower limits of agreement. Interestingly, the bias was lowest in both inter- and intraobserver variability when comparing LCC measurements (133, 134).

Lastly, a variance analysis using ICC, which demonstrates both the level of correlation and agreement, was performed. Hence, it is regarded as superior to Pearson's correlation coefficient and Bland-Altman plots (133, 134). Interobserver variability determined with ICC was 0.553 for RCC ($p<0.001$, 95 % CI 0.287 to 0.720), 0.641 for LCC ($p<0.001$, 95 % CI 0.413 to 0.778) and 0.618 for NCC ($p<0.001$, 95 % CI 0.381 to 0.762). Intraobserver variability determined using ICC was 0.618 for RCC ($p<0.001$, 95 % CI 0.325 to 0.775), 0.644 for LCC ($p<0.001$, 95 % CI 0.393 to 0.785) and 0.610 for NCC ($p<0.001$, 95 % CI 0.294 to 0.774). Using this index, the reliability of our data was considered moderate (ICC: 0.5-0.6) to good (ICC: 0.6-0.74) for both inter- and intraobserver reliability (128, 133, 134).

7 Discussion

7.1 Inference of results

This study aimed to compare the +100 % HU_{Aorta} approach and the HU 850 approach in terms of their ability to quantify AVC in CTA scans and its impact on procedure-related adverse events.

The main conclusions to be drawn from this study can be summarized as follows:

- Quantifying AV calcification using an individual HU threshold for CTA data, based on the mean LA of the ascending aorta multiplied by two (+100 % HU_{Aorta} approach), permits the prediction of the most relevant adverse events post-TAVI in terms of the combined clinical endpoint being met.
- Quantifying AV calcification using a fixed threshold for CTA data, in this study at a calcium detection threshold of HU 850, does not correlate significantly with the combined clinical endpoint being met.
- The greatest discriminatory value regarding the prediction of the composite clinical endpoint of this study was achieved with the +100 % HU_{Aorta} approach and the additional use of a calcium cut-off value of >1421 mm^3 in all coronary cusps combined.
- Neither the +100 % HU_{Aorta} approach nor the HU 850 approach showed a significant correlation with survival after 360 days.
- Compared to previous single-center publications that evaluated AVC with MDCT scans, this study included a considerably larger study population.

Besides the main study outcomes listed above, a secondary finding was that lower BSA correlated with the combined clinical endpoint being met. The descriptive data analysis showed a significant correlation between BSA and the combined clinical endpoint being met. In both multivariate analyses, BSA did not correlate significantly with the combined clinical endpoint; however, a lower BSA increased the odds of the combined clinical endpoint being met. This result is noteworthy, as BSA has been used in previous publications as an important indicator for frailty, which is seen as a risk factor for the occurrence of adverse events post-TAVI (including annulus rupture, vascular complications, and PPI) (135-138).

7.2 Assessment and classification of results in the context of similar research

7.2.1 Clinical characteristics and outcomes of the study population

This subsection offers a comparison between the data considered relevant for this study and related previous publications, including a meta-analysis and two national registries. The publications were selected on the basis of the study population size, the topicality of their data and their suitability to be compared to the current study in terms of the THV systems deployed, preprocedural surgical risk evaluations, and the choice of study outcomes. An overview of the different publications is provided in Table 10. Most studies have only partly published their dataset; therefore, some fields in Table 10 were left blank. The comparison includes study characteristics, demographic data, clinical data, comorbidities, procedural data, and outcomes.

The publications chosen for the evaluation include a weighted meta-analysis by Barbanti et al. from 2017 (70), which analyzed new-generation devices in 11,882 patients, a publication from the GARY registry in 2018 (139) that evaluated 1-year outcomes of 6,469 patients with an intermediate surgical risk, and the latest data releases from the STS/ACC TVT Registry from 2017 and 2020 (76, 140), which included data from 276,316 patients who underwent a TAVI procedure in the US.

Table 10. Comparison of baseline characteristics and outcomes with other relevant contemporary research.

	Present study	**Barbanti et al. (70)**	**German Aortic Valve Registry (139)**	**STS/ACC TVT Registry 2020 (76, 140)**
Study characteristics				
Recruitment period	2012-2019	2011-2017	2012-2014	2011-2019
TAVI population, n	965	11,882	6,469	276,316
THV system	SAPIEN XT/ 3/ 3 Ultra, CENTERA; CoreValve, Evolut R/ PRO; LOTUS/ Edge, ACURATE/ neo; Portico	SAPIEN 3; LOTUS Valve; Portico; JenaValve; ACURATE; Evolut R	SAPIEN XT/ 3; CoreValve; others (<5 %)	SAPIEN/ XT/ 3; CoreValve, - Evolut R/ PRO; LOTUS/ Edge
Study design	Retrospective, monocentric	Weighted meta-analysis of 37 studies	Retrospective, multicentric	Retrospective, multicentric
Demographic data				
Sex, female	492 (51)	-	4063 (62.8)	126,627/276,284 (45.8)
Age, years	80.32 (±7.1)	Pooled estimate: 82.1 [81.4–82.9]	82.5 (±5.0)	81 [75–86]
BSA, m^2	1.88 (±0.23)	-	-	-
BMI, kg/m^2	27.6 (±5.65)	-	27.0 (±5.0)	-
Clinical data & comorbidities				
NYHA III-IV	779 (80.7)	-	5,623 (86.9)	203,373/274,130 (74,2)
Severely reduced EF in echocardiography	77 (8)	-	-	3,077 (7.3)*
Coronary artery disease	660 (68.4)	-	-	26,798 (63.1)*
Atrial fibrillation	317 (32.9)	-	2,114 (32.7)	17,634 (41.2)*
S/P myocardial infarction	158 (16.4)	-	827 (12.8)	-
S/P PPI	121 (12.5)	-	762/6,368 (12.0)	7,909 (18.4)*
History of cardiac surgery	149 (15.4)	-	1,144/6,456 (17.7)	13,283 (30.9)*
History of aortic surgery	4 (0.4)	-	-	-
COPD	231 (23.9)	-	848/6,466 (13.1)	11,754 (27.6)*
Peripheral artery disease	269 (27.9)	-	1,131/6,462 (17.5)	13,271 (31.0)*
Carotid artery stenosis	87 (9)	-	-	-
S/P stroke or TIA	133 (13.8)	-	.	5,250 (12.2)*
Hypertension	886 (91.8)	-	5,687/6,380 (89.1)	-
Diabetes mellitus	374 (38.8)	-	2,302/6,461 (35.6)	-
Chronic kidney disease	381 (39.5)	-	-	-
Dialysis	34 (3.5)	-	94 (1.5)	1,726 (4.0)*
STS-PROM score	6.25 (±5.85)	6.1 [5.6–6.9]	5.6 (±1.1)	5.2 [3.3–8.4]

Procedural data and outcomes				
Elective procedure	854 (88.5)	-	-	251,569/276,090 (91,1)
Transfemoral access route	670 (69.4)	10,184 (86.1)	5,016 (77.5)	248,985/275,357 (90,4)
Balloon-expandable valve implanted	504 (52.2)	5,423 (45.9)	3,111.6 (48.1)	33,053 (76.9)*
Aortic annulus rupture	3 (0.3)	10/7,164 (pooled estimate rate 0.1)	-	-
PPI	73 (7.6)	2,016/11,678 (pooled estimate rate 16.2)	1,014/5,606 (18.1)	22,911/229,475 (10)
PVL ≥mild	299 (31)	-	-	-
PVL ≥moderate	49 (5.1)	280/10,096 (pooled estimate rate 1.6)	236/6,172 (4.3)	7,437/242,645 (3,1)
Device migration	14 (1.5)	-	-	-
Disabling stroke	14 (1.5)	107/8,173 (pooled estimate rate 1.1)	93 (1.4)	-
Thirty-day mortality	19 (2)	280/11,598 (pooled estimate rate 2.2)	-	7,980/240,228 (3.3)
VARC device success	915 (94.8)	2,437/2,764 (pooled estimate rate 94.2)	-	-
One-year mortality	166 (17.2)	-	1,131/6,469 (17.5)	22,979/147,097 (15.6)

*Complimentary data from a 2017 STS/ACC TVT registry publication (recruitment period: 2011-2015, n=42,988), that were not included in the 2020 publication (140).
Values are shown as n (%), mean (± standard deviation) or median [interquartile range].
BMI = body mass index; **BSA** = body surface area; **COPD** = chronic obstructive pulmonary disease; **EF** = ejection fraction; **NYHA** = New York Heart Association; **PPI** = permanent pacemaker implantation; **PVL** = paravalvular leak; **STS-PROM** = Society of Thoracic Surgeons Predicted Risk of Mortality; **STS/ACC TVT** = Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy; **S/P** = status post; **TAVI** = transcatheter aortic valve implantation**; THV** = transcatheter heart valve; **TIA** = transitory ischemic attack; **VARC** = Valve Academic Research Consortium

Study characteristics

The recruitment periods of the included publications were fairly similar, except the GARY registry, which has not published data regarding patient characteristics and general outcomes since 2014. However, as the present study was performed in Germany, it was assumed that a comparison of patient characteristics to the GARY registry would provide relevant information, as the other two newer studies mostly recruited patients in the USA and Canada. The TAVI populations exceeded this study's TAVI population by far; however, all the above publications relied on data from multiple centers, whereas this study used data from a single center. In contrast to the other publications, various THV systems were assessed in this study. Still, when viewed together, the above publications facilitate an adequate juxtaposition to the results of the present study (70, 76, 139, 140).

Demographic data

The demographic data of the present study's TAVI population were similar to the other selected publications. The proportion of women included in the present study averaged the proportion of women in the GARY and STS/ACC TVT registries. Patients in the present study were slightly younger on average. Patients' average BMI was only published by the GARY registry and was similar to this study's cohort (70, 76, 139, 140).

Clinical data and comorbidities

In general, a thorough comparison of clinical data was challenging as the data published by the above studies vary considerably. To ensure adequate comparability, only studies with a similar STS-PROM score to this study's mean score of 6.25 (±5.85) were chosen. The above publications included mostly patients with a slightly lower STS-PROM score than ours, namely 6.1 [5.6–6.9] for Barbanti et al., 5.6 (±1.1) for the GARY registry, and 5.2 [3.3–8.4] for STS/ACC TVT registry. No other relevant clinical data and comorbidities were published by Barbanti et al., therefore, regarding clinical data, only the STS-PROM score from the meta-analysis was compared to the present study. The STS/ACC TVT registry data showed similarities to the current study regarding severely reduced EF measured using echocardiography, as well as status post stroke or TIA. Pre-existing hypertension was found to be similar to the GARY registry. Fewer patients with history of cardiac surgery were included in this study compared to the GARY and STS/ACC TVT registries.

Some patient characteristic data in this study ranged in certain respects between those of the STS/ACC and GARY registries. Some characteristics, including status post PPI and presence of AF were closer to the GARY registry. Other characteristics, including need for dialysis, dyspnea graded as NYHA III-IV, presence of COPD and PAD, were more similar to the STS/ACC registry. This study included more patients with status post myocardial infarction and pre-existing diabetes mellitus than the GARY registry. Also, pre-existing coronary artery disease was more frequent in this study compared to the STS/ACC TVT registry (70, 76, 139, 140).

One reason for the difference to the results of the GARY registry might have been the TAVI cohort included. At the time of data acquisition by the GARY registry, mainly patients with a high to prohibitive risk were included, which can have significant effects on the clinical data recorded. The STS/ACC TVT registry, on the other hand, has a similar recruitment period to the present study; therefore, differences might rather be due to dissimilarities between countries and health care systems.

Procedural data and outcomes

Compared to the other studies, the TF access route was used less often in this study. Compared to Barbanti et al., VARC device success was accomplished at a similar rate in this study. The proportion of electively treated patients matched that of the STS/ACC TVT registry. Aortic annulus rupture was slightly higher than the rate determined by Barbanti et al. The rate of one-year mortality post-TAVI corresponded to that found in the GARY registry but was greater than in the STS/ACC TVT registry. The number of balloon-expandable THVs implanted ranged between those of the three studies but were closer to the results of Barbanti et al. and the GARY registry. The rate of in-hospital disabling strokes was marginally higher than the rate of in-hospital disabling strokes published by Barbanti et al. and the overall rate determined by the GARY registry. Compared to all three studies, the rate of in-hospital PPI post-TAVI was considerably lower in the present study. 30-day mortality in this study was similar to the study by Barbanti et al. and lower than in the STS/ACC TVT registry (70, 76, 139, 140).

The above studies published data only for PVL ≥moderate, which were significantly lower than the in-hospital rate found in this study (the STS/ACC TVT registry only published 30-day data). This study focused on PVL ≥mild, due to the now rarer occurrence of PVL ≥moderate and the increased relevance of mild PVL, as TAVI is being performed in ever younger patients. A meta-analysis published in 2018 found that the incidence of mild PVL varied widely between studies and ranged from 5.9 % to 63.4 % (106). Data published in 2020 from the SOLVE-TAVI trial suggested a mild and moderate PVL rate of 35.8 % for balloon-expandable THVs and 43.9 % for self-expanding valves (141). This indicates that the rate of PVL ≥mild is lower in this study (31 %) compared to the SOLVE-TAVI trial and most studies included in the meta-analysis by Ando et al., whereas it is similar to the rate determined in the Low Risk Evolut Trial at 30 days (29.5 %) (41, 106, 141). The incidence of device migration was also not published in the above studies. Kim et al. published data collected from 26 international sites, showing a device migration incidence of 0.92 %, which is notably lower than the incidence in the present study (1.5 %) (70, 76, 139, 140).

Overall, this study's population and the outcomes are in agreement with data published by comparable studies. Hence, the results obtained in this study can to some extent be generalized, as they represent the typical clinical characteristics of patients undergoing TAVI in the study period.

7.2.2 MDCT data

In this subsection the results of the MDCT analysis will be compared with those of other similar peer-reviewed publications. The major methodological disparities between the existing publications, including the calcium detection thresholds utilized, the use and amount of contrast medium, the use of ECG gating to acquire MDCT data, and the examination of different endpoints significantly limited the ability to perform a thorough comparative analysis of our MDCT data. The subsequent evaluation was also complicated by the fact that, until now, no other publication has used the +100 % HU_{Aorta} approach to measure AVC, thus precluding a comparison of the detected calcium volumes. Furthermore, only a limited number of studies published other MDCT data than calcium volume detected and calcium volume cut-off values. As a result, only the HU 850 calcium detection threshold can be compared to similar publications. An overview of the MDCT data published by other research groups using the HU 850 method to quantify AVC and their respective study characteristics is given in Table 11.

Table 11. Comparison of HU 850 MDCT data with relevant contemporary research.

	Present study	**Jilaihawi et al. 2014 (120)**	**Maeno et al. 2017 (142)**	**Bettinger et al. 2017 (119)**	**Kim et al. 2018 (143)**
Total	n=965	n=198	n=240	n=104	n=141
Study characteristics					
Recruitment period	2012-2019	2007-2012	2013-2015	2014-2015	2016
THV system	SAPIEN XT/ 3/ 3 Ultra, CENTERA; CoreValve, Evolut R/ PRO; LOTUS/ Edge, ACURATE/ neo; Portico	SAPIEN/ XT	SAPIEN 3	CoreValve	SAPIEN 3; ACURATE neo
Study design	Retrospective, monocentric	Retrospective, monocentric	Retrospective, monocentric	Retrospective, monocentric	Retrospective, monocentric
Post-TAVI clinical endpoints	PVL ≥ mild, new PPI, 30-day mortality, stroke, annulus rupture, device migration	PVL ≥ moderate	New PPI	PVL ≥ moderate	PVL ≥ mild
Demographic data					
Sex, female	492 (50.9)	99 (50)	96 (40)	56 (54)	79 (56)
Age, years	80.32 (±7.1)	86 [81-90]	81.74 (±7.42)	83 (±9)	81.3 [77.5-85.1]
MDCT data					
Calcium detection thresholds tested	CTA: HU 850, HU_{Aorta} (LA x 2)	CTA: HU 450, 650, 850, 1050, 1250 NECT: HU 50, 130, 300, 450	CTA: HU 850	CTA: HU 650 and 850; LA x 1.25, LA x 1.5, LA + HU 50, LA + HU 100	CTA: HU 450, 850; LA + 2SD, LA + 4SD + 5 mm^3 volume filter NECT: HU 130
AVC in NCC at HU 850, mm^3	103.51 (±106.94)		68.1 [28.3–161.5]		
AVC in RCC at HU 850, mm^3	58.07 (±73.78)		34.7 [11.5–92.0]		
AVC in LCC at HU 850, mm^3	57.42 (±70.69)		45.9 [16.3–96.9]		
AVC in all coronary cusps combined at HU 850, mm^3	218.99 (±206.18)	146 [58–268]	184.8 [78.9–324.3]	304 [130-567]	381 [188–681]*
Calcium volume cut-off for HU 850 method in all coronary cusps, mm^3	>146	>235		>359	

*The study by Kim et al. quantified calcification of the device landing zone (includes LVOT + AV region).
Values are shown as n (%), mean (± standard deviation) or median [interquartile range].
AVC = aortic valve calcification; **CTA** = computed tomography angiography; **HU** = Hounsfield unit; **LA** = luminal attenuation; **LCC** = left coronary cusp; **MDCT** = multidetector computed tomography; **NCC** = non-coronary cusp; **NECT** = non-enhanced computed tomography; **PPI** = permanent pacemaker implantation; **PVL** = paravalvular leak; **RCC** = right coronary cusp; **TAVI** = transcatheter aortic valve implantation**;** **THV** = transcatheter heart valve.

Two of the publications detected a lower quantity of AVC at HU 850 than the present study. Maeno et al. investigated the association between AVC calcification, measured at HU 850, and the need for post-TAVI PPI in 240 patients. The patients' baseline characteristics (provided in the publication's supplement) and the CTA protocols used were, to a great extent, similar to those of this study, thus adequate agreement with this study can be assumed. Of all MDCT results published by Maeno et al., only the quantity of calcium measured in the different AV cusps was relevant for this comparative analysis. A higher mean calcium volume was measured in the present study compared to the median calcium volume of the respective anatomical locations in the study by Maeno et al., both with regard to total AVC and AVC in each cusp. The difference in calcium quantification was most pronounced in the NCC region (142). Jilaihawi et al. compared various calcium detection thresholds in respect to their ability to predict post-TAVI PVL ≥ moderate in 198 patients. Like Maeno et al., the baseline features and data acquisition protocols of the study of Jilaihawi et al. were comparable to those in the present study, therefore permitting a comparison of the results. They found that, of all calcium detection thresholds tested, a threshold of HU 850 offered the highest predictive ability. Using the HU 850 threshold, they detected a median calcium volume of 146 mm^3 [58-268] (120) which, similar to the study by Maeno et al., is significantly lower than the mean calcium volume measured in the present study. Regarding calcium volumes detected, the difference between the studies discussed above and the present study could be partly due to them having used different measurements of central tendency or due to the slight differences in CTA acquisition protocols**.**

In contrast, the two other comparable studies detected a higher quantity of AVC at HU 850 than the present study. The study by Bettinger et al., also suited for a comparison to this study due to its similar study population and data acquisition protocol, compared different calcium detection thresholds (including individual thresholds) in terms of their predictive value for post-TAVI PVL ≥ moderate occurrence. The median AVC volume detected in their study at HU 850 was 304 mm^3 [130-567] which, contrary to the studies of Jilaihawi et al. and Maeno et al., is higher than that detected in the present study (119). In another similar publication, Kim et al. evaluated the accuracy of AVC quantification using various calcium detection thresholds based on a comparison with the current gold standard, the Agatston method in NECT. Furthermore, they evaluated the ability of the various calcium detection thresholds to predict PVL occurrence post-TAVI. In their study a median calcium volume of 381 mm^3 [188-681] was detected in the DLZ at HU 850 which, like the publication of Bettinger et al., is significantly higher than the volume measured in this study. However, in their study they quantified calcification of the DLZ as a whole, which includes the LVOT and the AV region, thus the reason for the higher median calcium volume measured is self-evident. In the study by Kim et al. the 850 HU threshold allowed a good prediction of PVL occurrence; however, when compared with the other thresholds studied, case-specific calcium detection thresholds offered a better approximation. Moreover, the authors stated that, of all thresholds studied, use of the 850 HU threshold resulted in the greatest share of calcium volume being underestimated. This underestimation could be due to the inherent drawback of using fixed thresholds for calcium detection, namely that the attenuation measured varies widely between individuals as well as different contrast media volumes, and that this variability is not considered when fixed HU thresholds are used (143).

When viewed in the context of the other publications discussed above, the average AVC detected in this study lies in the middle of the four studies examined, hence an appropriate approximation of AVC volume at HU 850 in the present study can be assumed.

Two of the four studies discussed above also used a calcium volume cut-off to maximize the prognostic value of AVC. Jilaihawi et al. achieved the highest sensitivity and specificity to predict post-TAVI PVL occurrence by setting the calcium volume cut-off at >235 mm^3. This cut-off value is almost two times the cut-off value determined in this study (120). Bettinger et al. determined the ideal calcium volume cut-off in their study as 359 mm^3. Use of this cut-off facilitated a significant prediction of ≥ moderate PVL; however, use of individual calcium detection thresholds and their respective calcium volume cut-offs enabled a prediction with a considerably higher sensitivity and specificity at a higher level of significance. Similar to the study by Jilaihawi et al., the determined calcium volume cut-off is notably higher than the one used in the present study (119). The considerably higher calcium volume cut-offs used in the above studies could be due to the fact that they considered only one primary clinical endpoint (≥moderate PVL occurrence post-TAVI) instead of a combined clinical endpoint like in this study, that an older study population was included, and that only a single THV variety was exclusively investigated instead of the twelve THV types assessed in the present study.

7.3 Limitations

7.3.1 Limitations of the study

Study design

Some fundamental limitations are inherent to the patient sampling approach chosen in the present study. Above all, the results and conclusions rely on data from a retrospective study design, hence, even though risk factors and confounders were accounted for in this study, total independence from remaining or unknown confounders cannot be assumed. Additionally, due to the single-center design, selection bias can be assumed and hence the degree to which the results are generalizable to the general population could be limited. Finally, a complete list of all suitable patients who underwent TAVI between November 2012 and December 2019 at the DHZB was carried out; hence, all results apply only to this period and can therefore only be partly applied to current TAVI procedures.

The assignment of a THV type to a specific patient by the DHZB Heart Team was based, among other aspects, on AV morphological criteria, factors influencing lifetime management, (THV-specific) expected procedural complications, clinical experience, and current scientific literature. This THV allocation process could have had a significant influence on the outcomes of this study, as the different THVs were implanted in different conditions.

In this study a post-procedural follow-up was carried out, whenever possible, at 30 days and one year for mortality (based on official death records). Limitations of this approach include that information beyond mortality was limited to in-hospital data and that, in a few cases, in-hospital data were incomplete. Thus, the complication rates of post-procedural stroke, PPI and PVL

≥mild at 30 days could be significantly higher than the in-hospital data stated in the results section. A more complete and longer post-procedural follow-up could have helped to better assess adverse events and other important variables after the index hospitalization, as well as improve comparability to current research. Calculation of a mortality follow-up of more than one year would have enabled longer-term survival analyses, which might have shown that post-TAVI survival after three or five years is significantly influenced by pre-TAVI AVC levels.

Study population size

A variety of THVs were included in the present study, which means that only a relatively small number of cases for each THV were available for statistical testing. This in turn resulted in insufficient statistical power to separately test the impact of the respective THVs on the composite clinical endpoint being met. This segmentation might have altered the results of the statistical analyses and would have allowed a more specific determination of calcium volume cut-offs for each of the THVs included. On the other hand, the large variety of THVs included could be interpreted as the results being representative for a wide range of THVs. In a recent publication, Akodad et al. highlighted the significance of this issue. They compared the impact of AVC on postoperative adverse events for different THVs. They found that the amount of AVC correlated significantly with PVL ≥mild and major adverse events post-TAVI (composite endpoint consisting of all-cause mortality, stroke, myocardial infarction, heart failure, or rehospitalization due to cardiac ailments within 1 month) when first-generation THVs (CoreValve, SAPIEN XT) were implanted. However, for newer THV generations (SAPIEN 3, Evolut R) the AVC amount did not correlate with PVL ≥mild and major adverse events (except for a statically significant correlation between AVC quantity and PVL ≥mild for Evolut R) (144). This finding can be attributed to THV design improvements that led to newer-generation THVs being less influenced by the presence of AVC (143). Thus, future studies should seek to perform statistical analyses with respect to the THV model or generation used.

The limited size of the study population also meant an additional loss of information, which can be illustrated using the publications by Mauri et al. and Maier et al. They showed that the distribution of calcium on the different aortic cusps can have a significant effect on TAVI-related adverse events (e.g., need for PPI) (97, 98). Due to insufficient statistical power in the present study, the effect of AVC distribution on adverse events could not be determined using multivariate statistical analysis.

The results of these three publications highlight limitations that can generally arise from a limited study population. Hence, future research in this field should aim at including an adequately large TAVI population or, in case of a lacking segmentation of THV models, limit investigations to the newer generations of THVs to enhance the clinical applicability for future TAVI procedures.

Composite clinical endpoint

In the present study, the independent variables were pooled in a composite clinical endpoint which, compared to separate clinical endpoints, allows exposing smaller discrepancies between two groups with a higher methodological efficiency. At the same time, this approach results in a

loss of information and inherently complicates the interpretation of the study results. Also, for the results obtained by this approach to be of direct value for routine clinical use, the independent variables included need to be comparable in terms of their impact on individual patients, their incidence rates, and the biological factors influencing the different endpoints. The different endpoints included in the combined clinical endpoint of this study can be categorized into two more homogeneous groups according to the severity of the endpoints' ramifications on an individual patient's health. 30-day mortality, stroke, annulus rupture and device migration are very acute and serious adverse events post-TAVI that are associated with a high rate of mortality, whereas PVL ≥mild and conduction disturbances rather limit long-term survival and pose a lower risk to immediate survival. This difference in clinical significance is a further obstacle to the interpretability of the results and decreases the usefulness of this study's results for routine clinical care. The different endpoints also show different incidence rates post-TAVI. In section 7.2.1 the results of the present study were determined to be more or less in line with current peer-reviewed publications; therefore, the comparison of incidence rates will be based solely on the present study. Grouping with regard to the incidence rates yields the same groups as above. The acute and serious adverse events are rather rare, with incidence rates ranging from 0.3 % for annulus rupture to 2 % for 30-day mortality. In contrast, the endpoints with longer-term and less serious effects occurred significantly more frequently, with 7.6 % for conduction disturbances and 31 % for PVL ≥mild. This difference in incidence rates means that further information is lost and, more importantly, the high incidence rate of PVL ≥mild probably had, compared to its importance, an outsized impact on the level of significance of the combined clinical endpoint in the present study. Finally, several previous publications showed a statistically significant correlation between the presence and quantity of calcium in the AV and/or LVOT and the adverse events included in the combined clinical endpoint. Therefore, it can be assumed that, in the context of TAVI, the endpoints share a biological genesis similar enough to be included in the same combined clinical endpoint. In conclusion, on the one hand the way the combined clinical endpoint was applied in this study seems questionable and reduced the information relevant for clinical decision-making provided by this study (145). On the other hand, the aim of this study was not to precisely predict different post-TAVI adverse events, but rather to compare two different approaches to quantify AVC based on a clinically significant dependent variable. As the composition of the combined clinical endpoint was equivalent in both approaches, a real difference between the approaches can be supposed.

7.3.2 Limitations of the calcium scoring methodology

This study used prospective ECG gating to acquire pre-TAVI CTA data. This technique offers a similar general image quality compared to retrospective ECG gating, but at a substantially lower radiation dose. A shortcoming of prospective ECG gating is that, compared to retrospective ECG gating, it offers less consistent AVC measurements. It remains questionable whether the benefits gained from more consistent AVC quantification outweigh the significantly increased radiation dose. Thus, before retrospective ECG gating is routinely performed in future research, benefits of this approach for individual patients' health should be better understood so that an ethical risk/benefit analysis can be carried out (143).

For the HU 850 approach, it was shown in section 7.2.2 that this study's methodology and the results of AVC quantification were consistent with similar publications. No comparable studies are currently available to evaluate the results of the +100 % HU_{Aorta} approach, therefore the question arises whether the approach was appropriate for our CT protocol and suitable to quantify AVC, as performed in this study, instead of solely quantifying LVOT calcification, as performed by Jochheim et al., who first described this specific approach. Regarding the suitability of our CT protocol, good agreement with Jochheim et al. can be confirmed, as the published pre-procedural image acquisition was similar in most aspects, except for a slightly higher reference pitch volume (Jochheim et al.: 3.4; present study: 3.2) and the use of less iodinated contrast agents (Jochheim et al.: 60 mL; present study: 80 mL) in the study of Jochheim et al. Furthermore, compared to the HU 850 approach, the +100 % HU_{Aorta} approach provided a significantly better prediction of the combined clinical endpoint of this study being met, thus it can be anticipated that the +100 % HU_{Aorta} approach is also valuable for approximating AVC and not just LVOT calcification. Even if the +100 % HU_{Aorta} approach appears to be a valid methodology for quantifying AVC, further external validation of the study results is warranted.

The present study did not consider the influence of sex on the relationship between AVC quantity and adverse events. Using NECT scans and the Agatston score, Pawade et al. carried out a multicenter international study in which they were able to show that the optimal calcium detection threshold for calcium quantification varies between the sexes (women: 1377 AU; men: 2062 AU) regarding both the grading of AS severity and its predictive value for the occurrence of postoperative adverse events. Even though this distinction was not a part of the present study's research question and would have slightly complicated the statistical analysis, implementing it could have increased the accuracy, reproducibility, and real-world applicability of the present study's results. Future research should take this aspect into consideration to enhance the ability of AVC-based pre-TAVI risk stratification to predict postprocedural adverse events (146).

As mentioned in section 4.3, recent research into the effects of AVC on postoperative adverse events has suggested that not just the densest calcium deposits affect postoperative outcomes, but that the volume of calcification also has a pronounced influence. This paradigm shift is supported by the present study, as the use of a patient-specific calcium detection threshold with a relatively high calcium volume cut-off, which is mostly influenced by the volume of calcification, enabled a significantly better prediction of the combined clinical endpoint of this study than the fixed calcium threshold of HU 850, which is largely influenced by the density of calcification (119, 120).

Finally, it is very important that any future research aiming to replicate the present study's findings pays careful attention to the CTA acquisition protocols used in this study. Inconsistencies between such protocols can have a pronounced impact on the reproducibility of calcium quantification and the subsequent statistical analysis (143). Furthermore, future research into this field should pay closer attention to minimizing inter- and intraobserver variability by defining more precise standards for CT calcium quantification. This could result in more

objective, reproducible and operator-independent data than is implied by the moderate to good inter- and intraobserver reliability of the calcium quantification data in the present study.

7.3.3 Summary of limitations

The previous sections highlighted numerous possible limitations which should be seen in the context of the scientific advances provided by the present study. In contrast to other comparable publications, the present study included a considerably larger number of patients and cardiac CTs, thus reducing the level of uncertainty of the study results. Furthermore, it was carried out in a single center, thereby reducing possible inconsistencies that can arise from differing operational sequences in a multiple center design, however at the cost of limiting the generalizability of the results.

In summary, this study should be regarded as important complementary research on the role of a new patient-specific calcium quantification method in predicting different important adverse events post-TAVI. With a significantly larger study population and more extensive CT dataset than similar published studies, the present study was able to show that the individual calcium quantification approach developed by Jochheim et al. is applicable to the AV region and is significantly better at predicting adverse events than previous quantification methods that use a fixed calcium detection threshold. Further research is undoubtedly required in this field, on the one hand to validate the present study's results and on the other hand to allow a distinction between the different clinical endpoints and THVs used in it. The prerequisite for future studies in this field is a considerably larger study population or a more focused assessment of specific THVs to allow sufficient power to evaluate more specific endpoints. In conclusion, the optimal study to validate the present study's findings should include a larger patient cohort in a multicenter RCT.

7.4 Clinical impact

The key role of AVC in the emergence of calcific AS and its major impact on TAVI-related adverse events is increasingly accepted. However, to further clarify its role in these processes, quantification of calcification should be carried out correctly and in a standardized fashion. Standardization of AVC quantification would allow a higher degree of comparability and reproducibility between all relevant research published, which in turn would allow an improved estimation of the actual impact of AVC on post-TAVI outcomes. This holds true not only in terms of enhancing procedural planning (including THV model and size selection) but also regarding the further refinement of preprocedural risk stratification to avoid adverse events post-TAVI. Currently the TAVI-related adverse events that are thought to be most influenced by the presence of AVC are annulus rupture, cardiac arrhythmias, cerebrovascular events, PVL occurrence, and decreased long-term survival (60, 93, 97, 98, 100). Further elucidation of the exact role of AVC in the occurrence of TAVI-related adverse events will be of increasing importance in the near future, as TAVI is being performed in ever younger and lower-risk patients in whom the long-term effects of TAVI-related adverse events will be of even greater significance.

Recently, patient-specific calcium detection thresholds were shown to enhance AVC quantification and improve the prediction of post-TAVI adverse events compared to the traditional Agatston score and fixed calcium detection thresholds (16, 119, 122). These findings are supported by the present study, which showed that AVC detection in CTA scans using a patient-specific HU threshold was superior to using a fixed HU threshold in CTA scans. Use of an individual threshold is a recent refinement of AVC quantification, and its standardized use could represent a significant advance regarding MDCT-based calcium analysis and quantification. A desirable application of this enhanced calcium quantification method in everyday clinical routine would be its addition to preprocedural risk stratification, including pre-TAVI risk scores, based on which patients with substantial calcification could be assigned to more favorable procedures like TAVI with balloon-expandable THVs or SAVR (119). Calculating the correct individual calcium detection threshold remains time-consuming, but once this approach is more widely accepted the individual calcium threshold could be calculated automatically by software, which would enable its routine clinical use. However, before this method can be widely implemented in scientific research and routine clinical care, further comparative studies of additional calcium detection methods are warranted to establish superiority of a single approach.

8 Conclusion

The present study demonstrated that approximating AVC using a patient-specific calcium detection threshold for CTA imaging is feasible and relevant. The first ever TAVI database was created at the DHZB specifically for the present study. The complete collection of data from 965 prospectively included patients who underwent TAVI between November 2012 and December 2019 at the DHZB represents an extensive and valid dataset. Furthermore, it can be assumed that the data is generalizable to a certain degree as the most relevant confounders (BSA, age, S/P PPI, carotid artery stenosis, S/P stroke or TIA, chronic kidney disease, STS-PROM score, and balloon post-dilatation) were taken into consideration in the statistical analyses. The careful review and thorough comparison with other data showed that the results of this study are in line with the outcomes of relevant peer-reviewed publications, thus implying good external validity.

Regarding the dependent variables of this study, a consistent picture emerges in terms of superiority of the patient-specific approach over a fixed calcium detection threshold for the prediction of post-TAVI adverse events. Moreover, the patient-specific calcium detection threshold enables an adequate prediction of the combined clinical endpoint being met. However, in contrast to previous publications, neither approach to calcium scoring offers accurate predictions of one year survival.

The findings of this study present a substantial contribution to the field of pre-TAVI risk stratification, as correct quantification of AVC enables a more thorough and substantiated understanding of how AVC influences and triggers the occurrence of TAVI-related adverse events. This could help avoid or reduce the occurrence of adverse events in future, for example, by allocating patients to the most favorable AVR procedure based on their individual risk

profile. Once pre-TAVI AVC quantification has been standardized, it could be included in future risk scores to enhance their respective predictive ability. These applications could help further decrease the incidence of post-TAVI adverse events and thus prolong patients' lives. However, this study should only be regarded as a starting point for future studies, as more trials are warranted before a widely accepted and standardized AVC quantification is employed. In addition, the therapeutic relevance of AVC quantification needs to be improved by identifying adequate measures that prevent further AVC accumulation or reduce AVC load or by modifying the TAVI procedure to prevent adverse events caused by AVC.

9 Outlook

The high prevalence of calcific AS has attracted immense scientific and industrial interest in therapeutic options, which in recent decades has led to a vast improvement of its prognosis. As ever younger patients are undergoing TAVI, researchers have increasingly focused on long-term adverse events post-TAVI. Current research addresses a wide range of AS- and TAVI-related fields, from the pharmacological prevention of AVC accumulation to pre-TAVI computational models aimed at predicting and thereby avoiding post-TAVI complications.

Research on pharmacological approaches to calcific AS has focused more on preventing the occurrence or hindering the progression of calcific AS. Contemporary studies have shown that inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) results in a significant reduction in low-density lipoprotein cholesterol concentrations and, in populations with an increased cardiovascular risk, decreases cardiovascular adverse events. The study by Perrot et al. advocates that PCSK9 and low-density lipoprotein cholesterol play a key role in the accumulation of AVC and the progression of calcific AS. Furthermore, they were able to show that PCSK9 inhibition reduces the calcium content in valvular interstitial cells (which play a key role in the development of calcific AS) by half (147). A similar research field concerns the role of the omega-3 polyunsaturated fatty acid's biochemical axis in the development and progression of calcific AS. The study by Artiach et al. showed that this axis could act as a barrier against calcific AS formation, as it inhibits calcium accumulation in valvular interstitial cells, and is dysregulated in calcified areas. Therefore, it could be a key axis to influence the progression of calcific AS and could thus be used as a novel therapeutic target. However, even if these results are promising, the biochemical axes have not been targeted in a human in-vivo environment. Further trials are needed to determine whether calcific AS can be prevented, or its prognosis enhanced, by targeting these biochemical axes in humans (147, 148).

Another focus of recent research is the optimization of THVs to improve the moderate long-term durability of current xenografts. An obstacle that most contemporary THVs face is the process of recalcification and subsequent restenosis after implantation. Premature calcification can be caused by an animal antigen, called galactose- α -1,3 galactose β -1,4- N-acetylglucosamine (α-Gal), which is a common surface component of current cardiac xenografts. This antigen triggers a local immune response which leads to more rapid calcification. Lim et al. evaluated the feasibility of a biocompatible α-Gal-free xenograft substitute in preclinical large animal models using the TAVI procedure. In contrast to the control group who received a 'standard' THV, no subclinical thrombosis and no calcification occurred in the α-Gal-free THV group after

eight months. However, further examination of valve performance and long-term valve durability in in-human trials is warranted (149).

A possible alternative material for THVs is flexible polymeric fiber. It has many potential benefits: cost-effectiveness, higher resilience than bioprosthetic THVs with better hemocompatibility than mechanical valves (lifelong anticoagulation is thus not required); also, THVs made of this material can be crimped to a smaller diameter than contemporary THVs, and the crimping does not negatively affect leaflet mechanics, and the flexibility of these THVs allows a better fit to different DLZ anatomies or calcification configurations, which would make repeated TAV-in-TAV procedures feasible. In future these advantages could be complemented by the recently discovered self-healing polymers, which could make polymeric materials even more attractive. Recent publications investigating a flexible polymeric valve show encouraging results. However, only a limited number of cases of in-human use have been published. Furthermore, additional refinements of THV design and production as well as further innovations in the field of material sciences are required before they can replace current THVs in routine clinical use (113, 150).

The most significant drawbacks of current THV models are their inability to regenerate and to adapt to functional alterations of the cardiovascular system, as well as their lack of resistance to infections and lack of complete nonthrombogenicity. All these drawbacks could be resolved by tissue-engineered heart valves. After implantation, this kind of THV would offer a lifelong regenerative capacity while at the same time being less constrained by the limitations of current THVs. Different approaches to manufacturing tissue-engineered valve have been developed, of which the most promising is the tissue-engineered heart valve manufactured using in-vitro cultivated decellularized tissue-engineered matrices. They are cost-effective and time-efficient, and the decellularization ensures good immunocompatibility. An in-vitro cultivated decellularized tissue-engineered matrix THV has been successfully implanted in an animal model within the scope of transcatheter pulmonary and AVR. In the short term this tissue-engineered heart valve showed a good performance without developing stenosis or regurgitation. After two months, full endothelialization of the tissue-engineered heart valve was determined (73). Going forward, further refinements of this approach are conceivable. A tissue-engineered THV can be designed using pre-interventional three-dimensional models of a patient's anatomy and subsequent manufacturing through three-dimensional bioprinting using individualized cardiovascular tissue. Preclinical experiments in animal models have shown that this approach reduces the strain on the prosthetic valve, decreases PVL occurrence, and enhances durability (73). However, before any of the conceivable tissue-engineered heart valves receive regulatory approval, the fundamental principles of the tissue processes have to be understood, in-human deployment has to be tested, and long-term outcomes need to be investigated (113).

Another rapidly evolving research field concerning the prevention of post-TAVI adverse events is the use of case-specific computer simulations. Current computer simulations mostly use mathematical models based on computational fluid dynamics and finite element analysis. These methods allow an enhanced quantification of myocardial strain and characterization of cardiac hemodynamics (151). These data can be used to analyze the interplay of various materials and

geometries, which can thereafter be used to simulate THV deployment and forecast device-patient interactions post-TAVI (152). The usefulness of such models was shown by Sivakumar et al., who found that pre-TAVI computational modeling offers good predictive abilities regarding the risk of cardiac conduction disturbances post-TAVI and coronary obstruction after a TAV-in-TAV procedure (153). However, current computational simulations are expensive and only a limited number of commercially available computational simulations exist for clinical use today (151). One currently available computational model is the HEART-guide™ platform (FEops nv, Ghent, Belgium). It uses conventional pre-TAVI MSCT data and offers a simulation of various pre-, peri- and post-procedural scenarios within two weekdays. These scenarios include suggestions for suitable THV sizes and THV positioning, as well as post-TAVI adverse events like conduction disturbances, PVL, and other possible complications. However, further research into the actual impact of computational predictions on post-TAVI outcomes is warranted before these models can be used in everyday clinical care. In future, the field of case-specific computer simulation could benefit immensely from further advances in artificial intelligence, which could decrease costs while offering more accurate predictive models (113).

The current developments in the field of calcific AS and TAVI outlined above demonstrate that more factors are relevant to successful TAVI than just the mere presence of AVC. However, it was also shown that calcification plays a role in most of the discussed developments. The accumulation of calcification is either prevented or its breakdown promoted, THVs are modified to allow more flexibility, permitting a satisfactory seal in a highly calcified annulus, THV materials are being continuously improved to prevent THV calcification, and use of computational TAVI simulations post-TAVI can facilitate the prevention, rapid detection, and early treatment of adverse events caused by AVC. Due to its high incidence rate, calcific AS, the role of AVC in its pathogenesis, and the prevention of AVC-triggered adverse events will most likely continue to be a central research field in the future.

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11 Statutory declaration

„Ich, Philipp Leibfried, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Computertomographie-basierte Bestimmung von Aortenklappenkalk und seine Assoziation mit Komplikationen nach interventioneller Aortenklappenimplantation (TAVI) / Computed tomography aortic valve calcium scoring and its association with adverse events following transcatheter aortic valve implantation (TAVI) selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe. Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum	Unterschrift

12 Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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14 Statistics certificate

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Bescheinigung

Hiermit bescheinige ich, dass Herr Philipp Leibfried innerhalb der Service Unit Biometrie des Instituts für Biometrie und klinische Epidemiologie (iBikE) bei mir eine statistische Beratung zu einem Promotionsvorhaben wahrgenommen hat. Folgende Beratungstermine wurden wahrgenommen:

- Termin 1: 15.06.2021

Folgende wesentliche Ratschläge hinsichtlich einer sinnvollen Auswertung und Interpretation der Daten wurden während der Beratung erteilt:

- P-Werte sollten immer mit Effektstärken, z.B. Odds Ratios und deren Konfidenzintervalle, berichtet werden.
- Für multiples Testen muss aufgrund des explorativen Charakters der Studie nicht adjustiert werden.

Diese Bescheinigung garantiert nicht die richtige Umsetzung der in der Beratung gemachten Vorschläge, die korrekte Durchführung der empfohlenen statistischen Verfahren und die richtige Darstellung und Interpretation der Ergebnisse. Die Verantwortung hierfür obliegt allein dem Promovierenden. Das Institut für Biometrie und klinische Epidemiologie übernimmt hierfür keine Haftung.

Datum: 15.06.2021 [redacted] Name des Beraters/ der Beraterin: Kerstin Rubarth

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Unterschrift BeraterIn, Institutsstempel