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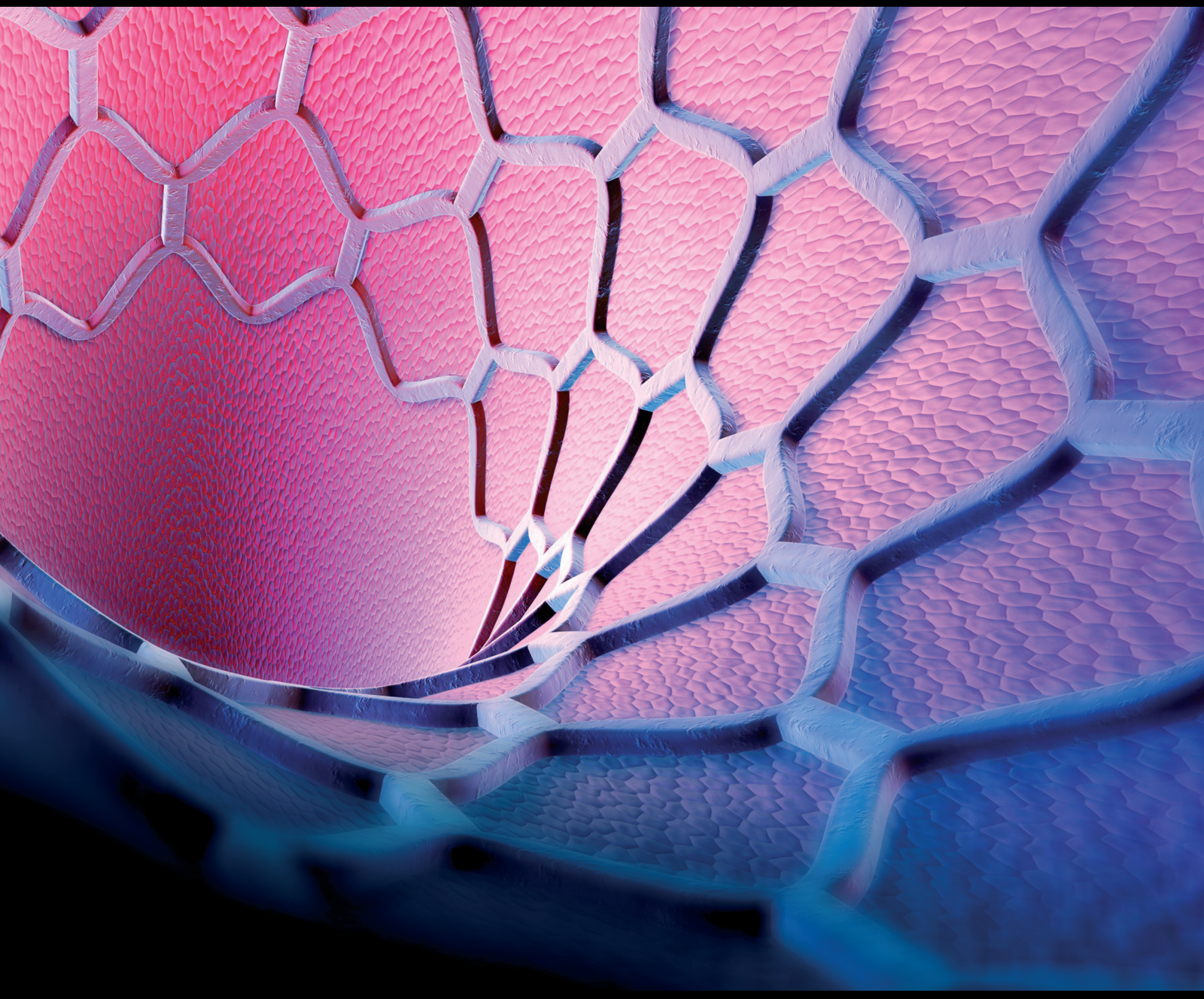

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Contents

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Review Article

TAVR: A Review of Current Practices and Considerations in Low-Risk Patients

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Transcatheter aortic valve replacement (TAVR) is an established treatment for severe, symptomatic, aortic stenosis (AS) in patients of all risk categories and now comprises 12.5% of all aortic valve replacements. TAVR is a less invasive alternative to traditional surgical aortic valve replacement (SAVR), with equivalent or superior outcomes. The use of TAVR has increased rapidly. The success and increase in use of TAVR are a result of advances in technology, greater operator experience, and improved outcomes. Indications have recently expanded to include patients considered to be at low risk for SAVR. While TAVR outcomes have improved, remaining challenges include the management of coexistent coronary artery disease, prevention of periprocedural stroke, and issue of durability. These issues are even more relevant for low-risk, younger patients.

1. Introduction

Transcatheter aortic valve replacement (TAVR) has been a rapidly evolving field since the first valve was implanted in an inoperable patient with severe aortic stenosis in 2002, amidst strong early criticism [1]. TAVR has now been performed in over 400,000 patients worldwide [1]. Randomized controlled trials (RCT) have demonstrated the safety and efficacy of TAVR, first in inoperable, and then in high-risk, intermediate, and most recently low-risk patients. The success and rapid evolution of TAVR have grown as a result of advances in technology and operator experience. TAVR faces many challenges, especially surrounding durability in low-risk patients. We review the current status of TAVR with emphasis on patient selection, preprocedural workup, and limitations and challenges which are especially relevant in low-risk patients [2].

2. Epidemiology of Aortic Stenosis

Aortic stenosis (AS) is a common valvular disease in developed countries [3]. It is most frequently caused by age-related valvular calcification and less likely rheumatic heart disease [3, 4]. As the population ages, aortic stenosis will become an increasingly significant health burden [5]. The prevalence of aortic stenosis increases with age and affects 2.8% of patients aged 60–74 years and 13.1% in patients 75 years and older, which corresponds to approximately 16.1 million people [5]. The estimated number of patients with severe aortic stenosis is 3.2 million, and approximately one million of them are eligible for TAVR [5]. Of these patients eligible for TAVR, approximately 378,890 are considered to be low risk [5]. If left untreated, severe aortic stenosis is associated with a mortality rate of up to 50%, within 3–5 years after symptom onset [5].

3. Evolution of TAVR, and Where We Are Now

Transaortic valve replacement (TAVR) has been studied in patients with severe, symptomatic (NYHA Class II or worse) aortic stenosis of varying perioperative risks. The first TAVR trials were conducted in patients considered to be inoperable [6, 7]. TAVR was superior to standard therapy, which included balloon valvuloplasty in inoperable patients [6, 7]. In high-risk patients, TAVR was noninferior to surgical aortic valve replacement (SAVR) for all-cause mortality [8–10].

However, TAVR was associated with significantly higher rates of major vascular complications and neurological events [8, 9]. TAVR was subsequently studied in intermediate-risk patients and found to be noninferior to SAVR for all-cause mortality and disabling stroke but continued to be associated with more periprocedural major vascular complications and higher rates of significant paravalvular regurgitation [11–14]. Based on these findings, the 2017 AHA/ACC guidelines for the management of severe, symptomatic aortic stenosis were changed [15]. TAVR received an I (*A*) recommendation for both inoperable (with predicted survival of over 1 year) and high-risk patients, and a IIa (B) recommendation for intermediate-risk patients [15].

TAVR in low-risk patients has been studied in recent randomized controlled trials (RCTs) including NOTION, Evolut R Low Risk, and PARTNER III. None of the aforementioned trials studied TAVR for patients with bicuspid aortic stenosis, congenital AS, rheumatic valve disease, or isolated aortic regurgitation [16, 17] [Table 1].

The PARTNER III trial showed that TAVR was superior to SAVR for the primary endpoints of all-cause mortality, stroke, rehospitalization, and new-onset atrial fibrillation at one year [16]. There were no significant differences between SAVR and TAVR for major vascular complications or moderate to severe paravalvular regurgitation [16]. Compared with SAVR, TAVR was associated with a 50% reduction in length of hospital stay, as these patients less frequently required general anesthesia and intensive care unit level care [16]. Given these results, the United States Food and Drug Administration expanded the indications for TAVR to low-risk severe AS patients [20]. Two-year follow-up data in low-risk TAVR patients showed persistent superiority for the combined primary endpoint (death, stroke, or cardiovascular rehospitalization) and rehospitalization alone [2]. Initially, at 1 year, the outcomes of death and stroke strongly favored TAVR; however, this benefit was diminished at two years [2].

A meta-analysis of four RCTs (NOTION, PARTNER III, SURTAVI, and Evolut Low-Risk) comparing TAVR and SAVR outcomes in low-risk patients found that TAVR was associated with a significantly lower risk of all-cause and cardiovascular mortality at one year [21]. The results of this meta-analysis differed significantly from PARTNER III. In the meta-analysis, there was no significant difference in the stroke rate between TAVR and SAVR; TAVR was associated with significantly higher rates of permanent pacemaker implantation and moderate to severe paravalvular leak [21]. This study also showed no significant difference between SAVR and TAVR in the rate of major vascular complications [21]. In this meta-analysis of low-risk patients, the improved all-cause mortality in TAVR compared with SAVR was also reflected in a meta-analysis of patients of all surgical risk categories [22]. However, in the meta-analysis of patients of all risk categories, TAVR was associated with a significantly lower risk of stroke, [22] but significantly increased risk of major vascular complications and permanent pacemaker implantation, compared with SAVR [22]. Follow-up data will be needed to assess long-term results of TAVR compared with SAVR, especially in low-risk patients.

4. Patient Selection

Patient selection begins with a careful history and physical exam. Valve anatomy and hemodynamics are then established with transthoracic echocardiography (TTE) [17]. The severity of aortic stenosis is commonly assessed by noninvasive methods such as Doppler TTE but may also be diagnosed during cardiac catheterization [4]. Invasive evaluation is indicated when there is a discrepancy between noninvasive testing and clinical evaluation and the suspicion for significant AS remains high [4].

Severe aortic stenosis is classified by a valve area $<1.0\,cm^2$ and a peak aortic velocity ≥ 4.0 m/s with a mean valve gradient ≥ 40 mm Hg [4]. Variants of classic severe AS, such as low-flow and low-gradient (LFLG) AS are important to consider when evaluating for TAVR. These patients may have concomitant reduced LVEF, with lower peak velocity and gradient than would be anticipated with the severely reduced valve area [4]. The mechanisms of LFLG AS include reduced flow due to LV systolic dysfunction or diminished ventricular volume from a stiff, hypertrophied left ventricle [4]. LFLG AS patients have a higher associated mortality postintervention, as compared with patients with high gradient severe symptomatic AS [4, 17].

5. Risk Stratification

The AHA/ACC recommends assessing TAVR perioperative risk with the Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) score and an assessment of frailty, comorbidities, and procedural impediments [17].

The STS PROM score predicts the 30-day mortality risk of SAVR and categorizes patients as low to high risk. Patients with <4% predicted mortality are considered low risk, those with 4–8% are intermediate risk, and those with >8% are high risk [17]. Patients with a >50% preoperative risk of mortality and morbidity at 1 year are considered inoperable [17]. Although the STS score was derived from a surgical patient database, it has continued to be applied to TAVR patients, given its use in the original TAVR trials [11, 23].

The STS score has been updated with the 2018 version being the most current [23]. This updated version differs significantly from the previous 2008 version, which was used in the early TAVR trials to assess patient risk [23]. Notably, based on the updated score, 19% of patients from the original TAVR trials would now be reclassified to a lower risk category [23]. This complicates risk stratification and should be considered when evaluating patients for TAVR. [23].

The STS score is also limited in its ability to predict 30-day and 1-year TAVR mortality [24–27]. The STS score overestimates the 30-day mortality in TAVR and does not accurately reflect the impact of comorbidities on TAVR [23, 24]. The STS score overpredicts diabetics' mortality risk in TAVR, while the opposite is true for patients with atrial fibrillation [23]. TAVR-specific prognostic scores are not routinely used in preoperative evaluation but may have a role in future practice [26]. Two examples of these are the $TAVI_2SCORe$ and the STS Transcatheter Valve Therapy Registry, which have been shown to be better predictors of mortality compared with the STS score

Table 1: Low-risk TAVR trials [16, 18, 19].

	Notion	Evolut Low-Risk Trial	PARTNER III
Valve type	Self-expanding	Self-expanding	Balloon-expandable
Number of patients	280	1200	1328
Average age	79.1 years	74 years	73 years
Inclusion STS PROM score	N/A (81.8% of patients were at low-risk, with a STS<4)	<3	<4
Mean STS PROM score	3.0%	1.9%	1.9%
Inclusion Criteria	(i) Patients ≥70 years of age with severe degenerative AS referred for SAVR and also candidates for TAVR were eligible for inclusion regardless of their predicted risk of death after surgery. (ii) Severe AS was defined as an effective orifice area <1 cm^2 or indexed for body surface area <0.6 cm^2/m^2 and a mean AV gradient >40 mm Hg or peak systolic velocity >4 m/s. (iii) Symptomatic patients had to have dyspnea, NYHA class II or higher, angina pectoris, or cardiac syncope to qualify for the trial. (iv) Asymptomatic patients could be included if they had left ventricular posterior wall thickness ≥17 mm, decreasing LVEF, or new-onset AF. (v) Eligible patients were expected to survive for more than 1 year.	(A) Severe aortic stenosis: (a) for symptomatic patients, AVA ≤1.0 cm^2 (or AVA index of ≤0.6 cm^2/m^2) or mean gradient ≥40 mmHg or maximal AV velocity ≥4.0 m/sec by TTE at rest. (b) For asymptomatic patients, (i) very severe AS with an AVA of ≤1.0 cm^2 (or AVA index of ≤0.6 cm^2/m^2) and maximal aortic velocity ≥5.0 m/sec, or mean gradient ≥60 mmHg by TTE at rest or (ii) AVA of ≤1.0 cm^2 (or AVA index of ≤0.6 cm^2/m^2) and a mean gradient ≥40 mmHg or maximal AV velocity ≥4.0 m/sec by TTE at rest and an exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response or arrhythmia or (iii) AVA of ≤1.0 cm^2 (or AVA index of ≤0.6 cm2/m2) and mean gradient ≥40 mmHg or maximal AV velocity ≥4.0 m/sec by TTE at rest and LVEF <50%. (B) The patient is considered low risk for surgery, with a predicted risk of mortality for surgery <3% at 30 days per multidisciplinary local heart team assessment. C) Agreement that the patient will return for all required postprocedure follow-up visits.	(A) Severe calcific AS with AVA ≤1.0 cm^2 or AVA index ≤0.6 cm^2/m^2 and Jet velocity ≥4.0 m/s or mean gradient ≥40 mmHg. (B) NYHA functional class ≥2 or exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response or arrhythmia or asymptomatic with LVEF <50% (echo must be within the 90 days prior to randomization). (C) Heart team agrees the patient has a low risk of operative mortality and an STS < 4. D) The patient has provided written informed consent.

Table 1: Continued.

	Notion	Evolut Low-Risk Trial	PARTNER III
Selected exclusion criteria	(i) Other severe valvular disease or CAD requiring intervention. (ii) Previous cardiac surgery. (iii) Stroke or MI within 30 days. (iv) Renal failure requiring dialysis. (v) Pulmonary failure with forced expiratory volume within 1 second (FEV_1) <40% of expected.	(i) Bicuspid AV. (ii) Preexisting prosthetic heart valve (iii) Candidates for mechanical valves. (iv) Valvular disease (severe MR, severe TR, ≥moderate MS) that is amenable to surgery or repair. (v) Unprotected left main coronary artery and/or multivessel coronary disease with SYNTAX score >22. (vi) Stroke or TIA within 2 months, MI within 30 days. (vii) Estimated life expectancy under 2 years.	(i) AV that is bicuspid, unicuspid, or noncalcified. (ii) Severe MR, severe AR, or ≥ moderate MS. (iii) Preexisting mechanical or bioprosthetic valve (not including mitral ring). (iv) LVEF < 30%. (v) unprotected left main coronary artery, SYNTAX score >32 (in absence of prior revascularization), no ability for optimal coronary revascularization. (vi) Stroke or TIA within 90 days. (vii) MI within 30 days. (viii) Renal insufficiency (eGFR< 30 mL/min) or requiring renal replacement therapy. (ix) Severe lung disease with FEV_1 < 50% of predicted or currently on home oxygen. (x) Significant frailty. (xi) History of cirrhosis or active liver disease. (xii) Estimated life expectancy under 2 years.
Endpoint	All-cause mortality, stroke and MI at one year.	All-cause mortality or disabling stroke at 2 years.	All-cause mortality, stroke, and rehospitalization at 1 year
Result	No significant difference between TAVR and SAVR.	TAVR noninferior to SAVR.	TAVR superior to SAVR, with significantly lower rate of death, stroke, or rehospitalizations.

AS = aortic stenosis; AV = aortic valve; AVA = aortic valve area; AR = aortic regurgitation; CAD= coronary artery disease; eGFR = estimated glomerular filtration rate; FEV_1 = forced expiratory volume within 1 second; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; MS = mitral stenosis; STS PROM Score = Society of Thoracic Surgeons Predicted Risk of Mortality Score; SYNTAX score = synergy between percutaneous coronary intervention with taxus and cardiac surgery; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve; TIA = transient ischemic attack; TTE = transthoracic echocardiogram; TR = tricuspid regurgitation.

[28, 29]. Preoperative TAVR risk assessment should be done by a multidisciplinary heart team. This assessment may include traditional risk scores; however, their limitations should be recognized [26] [Table 2].

6. Preprocedural Workup

Preprocedural workup is essential to reduce procedural complications and to risk-stratify patients. Patients should be assessed for major cardiovascular and noncardiovascular comorbidities prior to TAVR [17].

The initial assessment of aortic stenosis is completed with TTE which evaluates the severity of stenosis, leaflet motion, annular size, and degree of calcification [17]. The severity of AS is classified based on the calculated aortic valve area (AVA) and the mean transaortic gradient [31] [Table 3]. The role of transesophageal echocardiography (TEE) for TAVR preoperative assessment has been diminished by the advent of CT [17]. TTE can be supplemented with ECG-gated multidetector computed tomography (MDCT) during preprocedural TAVR planning, to provide a three-dimensional anatomical assessment [17].

Coronary angiography is currently the standard practice to evaluate for CAD, prior to TAVR [32]. However, coronary computed tomography angiography (CCTA) has been increasingly utilized [32]. CCTA allows patients to avoid invasive angiography and has an excellent negative predictive value (NPV) [32]. Conversely, the presence of calcified vessels or prior stents leads to false-positive results and limits CCTA's ability to assess the severity of coronary lesions [32]. Coronary angiography is performed to confirm the presence and severity of CAD, after a positive CCTA scan [32]. Although CCTA is a convenient alternative for coronary angiography, ensuring proper patient selection with low pretest probability for coronary disease is important [32]. Preoperative CCTA may decrease the number of invasive coronary angiograms in low-risk patients [32].

A CTA of the chest, abdomen, and pelvis is done to identify peripheral vascular disease. Although transfemoral access is preferred for TAVR, alternatives such as transapical, transaortic, or subclavian approaches are occasionally pursued based on peripheral vascular suitability [33]. Transfemoral access has an associated mortality benefit over other approaches and allows for a shorter hospital stay [34].

7. Procedural Sedation and Minimalist Approach

TAVR was historically primarily done under general anesthesia (GA) with endotracheal intubation and periprocedural TEE [17]. TAVR centers are increasingly using a minimalist approach with conscious sedation (CS) instead of GA, although there is still significant variation in CS use between hospitals [35]. A recent study of 120,000 patients from the Transcatheter Valve Therapy Registry showed an increase in the proportion of transfemoral TAVR cases done under CS, from 33% in 2016 to 64% in 2019 [35]. The use of conscious sedation was associated with lower in-hospital and 30-day mortality compared with GA [35]. Avoiding GA with intubation is associated with shorter procedure time, fluoroscopy time, ICU length of stay, and hospital length of stay and decreases the need for inotropic support [36, 37]. TAVR with CS has comparable rates of periprocedural complications such as PPM implantation, MI, stroke, vascular complications, and residual PVL as GA [37].

There are individual patient factors that favor the use of GA, such as morbid obesity, obstructive sleep apnea, an inability to lay flat during the procedure, or the need for an alternate, nontransfemoral access site [35, 38]. Minimally invasive approaches may play a larger role for higher-risk patients with multiple comorbidities, chronic obstructive lung disease, or difficult airways, as GA is associated with more complications in this patient group [39, 40]. The use of CS may further improve the short-term mortality of TAVR, which is of special importance in low-risk patients. Low-risk patients are more likely to be candidates for minimalist TAVR with CS. The convenience, short-term mortality benefit, and less invasive nature of minimalist TAVR will likely be additional factors that influence a low-risk patient's decision between TAVR and SAVR.

8. Challenges Facing TAVR in Low-Risk Patients

Many challenges remain surrounding TAVR in low-risk patients. Comparative TAVR and SAVR outcomes in the low-risk TAVR trials are listed in Table 4.

8.1. Vascular Complications. The rate of major vascular complications in TAVR has decreased but still occur in >4% of procedures [6–8, 11, 41, 42]. This is the result of improved operator technique, reduced delivery system sheath size, and vascular access closure devices [41]. Early TAVR required large (20 to 24 Fr) sheaths, which more often necessitated transapical or transaortic access [42, 43]. Current generation TAVR devices feature lower profile (14-Fr to 16-Fr) delivery systems [42]. The smaller size allows for transfemoral approach access, more precise valve positioning, and delivery while reducing the risks of major vascular complications [42, 44]. The increased use of direct ultrasound guidance and micropuncture technique has substantially reduced femoral vascular complications [45]. Transfemoral access is preferable to other access methods, as it is associated with mortality benefit, shorter hospital stays, and faster recovery [13].

8.2. Coronary Artery Disease. Almost half of TAVR candidates have coexisting coronary artery disease (CAD), with many having multivessel CAD [32]. Prosthetic valve struts can obstruct coronary ostia and therefore complicate accessing the coronaries during percutaneous coronary intervention (PCI) [32]. Therefore, a TAVR patient's future ability to successfully undergo PCI may be affected by the presence of a prosthetic valve.

Ongoing trials are evaluating PCI in patients with stable CAD undergoing TAVR [32]. Common practice is to revascularize proximal-mid coronary lesions pre-TAVR. [32]. Pre-TAVR staged PCI is more commonly done than a combined procedure [32]. Overall mortality has not been

Table 2: Comparison of factors used in SAVR and TAVR risk scores [28, 30].

	STS score	EuroSCORE II	$TAVI_2SCORe$
Peripheral vascular disease	Yes	Yes	No
Renal failure	Yes	Yes	Yes
Dialysis	Yes	No	No
Neurological dysfunction	Yes	Yes	No
Diabetes	Yes	No	No
Atrial fibrillation	Yes	No	No
COPD	Yes	Yes	No
NYHA class	Yes	Yes	No
LVEF	Yes	Yes	Yes
CAD	Yes	No	No
Pulmonary hypertension	No	Yes	No
Others			Porcelain thoracic aorta, recent myocardial infarction (within 90 days), anemia (<10 g/dl), male sex, critical aortic valve stenosis (mean gradient ≥70 mmHg), age (>85 years)

SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association Class; LVEF = left ventricular ejection fraction; CAD = coronary artery disease.

Table 3: Aortic stenosis severity [4, 31].

	Aortic valve area (cm^2)	Mean transaortic pressure gradient (mmHg)	Maximum aortic velocity (m/s)
Normal	3.0–4.0	—	—
Mild	1.6–2.0	<25	2.5–3.0
Moderate	1.1–1.5	25–40	3.1–4.0
Severe	≤1.0	>40	>4.0

shown to be affected by the timing of PCI [32]. However, patients who underwent PCI within 30 days before TAVR had more bleeding and minor vascular complications after TAVR compared with patients who underwent PCI >30 days prior to TAVR [32].

Aggressive management of modifiable cardiac risk factors, through smoking cessation, weight loss, regular physical activity, and use of a moderate or high-intensity statin, can decrease the incidence and progression of CAD and is especially important in TAVR patients [46, 47].

8.3. Paravalvular Regurgitation. Paravalvular regurgitation (PVR) is a complication that occurs due to incomplete apposition between the aortic annulus and the device [48]. Echocardiography can identify PVR after TAVR, although invasive hemodynamics and cine-angiography can also be utilized [49]. Risk factors for PVR include valve calcification, leaflet asymmetry, prosthesis malposition, or undersizing and the use of self-expanding valves [50]. Self-expanding valves exert less radial force than their balloon-expandable counterparts [50]. Annular calcification has a larger effect on the final figuration of self-expanding valves, and therefore they are more often underexpanded or eccentrically shaped. [50]. Although balloon-expandable devices can generate higher forces to overcome severe calcification, this can lead to annular rupture [50].

The severity and acuity of valvular regurgitation play a role in patient outcomes after TAVR [51]. Moderate and severe PVR are independent predictors of early and late mortality, while the significance of mild PVR is unclear [51]. Moderate to severe PVR occurs in 3.7–5.3% of intermediate-risk patients and in 0.6–3.5% of low-risk patients [11, 12, 16, 18]. Mild PVR occurs in 23–36% of intermediate-risk patients and 30–36% of low-risk patients [11, 12, 16, 18]. After TAVR, the acute onset of moderate to severe aortic regurgitation (AR) is associated with higher mortality and should be promptly managed to decrease the regurgitant volume. [51]. Therapeutic strategies include balloon post-dilatation, leak closure with vascular plugs, implantation of a second valve, or even surgical removal of the prosthetic valve [51]. After TAVR, chronic AR refers to the presence of moderate to severe regurgitation, which is not worse compared with the degree of AR pre-TAVR [51]. Chronic AR does not have the same high mortality as acute AR but should be closely monitored [51].

Although SAVR has historically had a lower rate of moderate or severe PVR than TAVR, PARTNER III TAVR patients had comparable rates to SAVR patients at 30 days [Table 2] [16]. Decreasing the rate of significant PVR in low-risk patients is especially important as it directly impacts early and long-term mortality. The findings from PARTNER III will likely influence preprocedural planning, as the SAPIEN 3 valve may improve TAVR outcomes for low-risk patients who are at high-risk of PVR based on anatomic factors.

The Evolut Low-Risk Trial PVR outcomes were less promising, as TAVR patients had a significantly greater incidence of moderate to severe PVR (3.5%) than SAVR (0.5%)

Table 4: Comparison of outcomes between TAVR and SAVR patients in Low-Risk TAVR Trials.

	PARTNER III	Evolut Low-Risk	NOTION*
All-cause and CV-mortality at 1 year	TAVR: 1.0 % SAVR: 2.5%	TAVR: 2.4% SAVR: 3.0%	TAVR: 4.9% SAVR: 7.5%
Disabling stroke at 1 year	TAVR: 0.2% SAVR: 0.9%	TAVR: 0.8% SAVR: 2.4%	TAVR: 2.9% SAVR: 4.6%
Nondisabling stroke at 1 year	TAVR: 1.0% SAVR: 2.2%	TAVR: 3.4% SAVR: 2.2%	
TIA at 1 year	TAVR: 1.0% SAVR: 1.1%	TAVR: 1.7% SAVR: 1.8%	TAVR: 2.1% SAVR: 1.6%
Major vascular complications at 30 days	TAVR: 2.2% SAVR: 1.5%	TAVR: 3.8% SAVR: 3.2%	TAVR: 5.6% SAVR: 1.5%
AKI (stage II or III) (in 30 days)	TAVR: 0.4% SAVR: 1.8%	TAVR: 0.9% SAVR: 2.8%	TAVR: 0.7% SAVR: 6.7%
New-onset AF (at 1 year)	TAVR: 7.0% SAVR: 40.9%	TAVR: 9.8% SAVR: 38.3%	TAVR: 21.2% SAVR: 59.4%
New PPM implantation at 1 year	TAVR: 7.5% SAVR: 5.5%	TAVR: 19.4% SAVR: 6.7%	TAVR: 38.0% SAVR: 2.4%
Coronary artery obstruction requiring intervention at 1 year	TAVR: 0.2% SAVR: 0.7%	TAVR: 0.9% SAVR: 0.4%	No TAVR-treated patient required PCI during the procedure; 1 SAVR patient required concomitant coronary artery bypass resulting from a right coronary ostium lesion
MI at 1 year	TAVR: 1.2% SAVR: 2.2%	TAVR: 1.7% SAVR: 1.6%	TAVR: 3.5% SAVR: 6.0%
Valve thrombosis at 1 year	TAVR: 1.0% SAVR: 0.2%	TAVR: 0.2% SAVR: 0.3%	Not reported
PVL (≥moderate) at 1 year	TAVR: 0.6% SAVR: 0.5%	TAVR: 3.5% SAVR: 0.5%	TAVR: 15.7% SAVR: 17.7%
Patient-prosthesis mismatch (30 days)	TAVR moderate: 29.8% SAVR moderate: 23.3% TAVR severe: 4.3% SAVR severe: 6.3%	TAVR moderate: 5.0% SAVR moderate: 15.7% TAVR severe: 1.8% SAVR severe: 8.2%	Not reported
Rehospitalization at 1 year (valve or procedure related, including CHF)	TAVR: 7.3% SAVR: 11.0%	TAVR: 3.2% SAVR: 6.5% (CHF rehospitalization only)	Not reported

AF = atrial fibrillation; AKI = acute kidney injury; CHF = congestive heart failure; CV = cardiovascular; MI = myocardial infarction; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; PVL = paravalvular leak; TIA = transient ischemic attack. *Although NOTION studied patients of all surgical risks; 81.8% of patients were considered low-risk (STS<4%).

[18]. These findings are likely related to the fact that PARTNER III features a balloon-expandable valve (SAPIEN 3), while Evolut featured a self-expanding valve (CoreValve, Evolut R, and Evolut PRO).

Current generation TAVR has decreased the incidence of significant valvular regurgitation at 30 days, due to improved prosthesis design [44]. New-generation valves have design features which minimize PVR, including the external fabric skirt of SAPIEN 3 valve or the external sealing system of the Evolut PRO valve [51]. Although self-expanding Evolut valves were associated with increased PVR, they also had less patient-prosthesis mismatch [18]. Patient-prosthesis mismatch is associated with higher incidences of perioperative stroke, renal failure, and lack of ventricular regression after TAVR [52]. Severe patient-prosthesis mismatch is also felt to have an impact on mortality, although this is controversial in studies [52]. Only 1.8% of TAVR patients in the Evolut Low-Risk Trial had severe mismatch, compared with 8.2% of SAVR patients [18]. The patients in the Evolut Trial also had less mismatch than the patients in the PARTNER III, where 4.3% of TAVR patients developed severe mismatch [16, 18]. Risk factors for mismatch include older age, female sex, diabetes, renal failure, and higher surgical risk scores [52]. These risk factors occurred at similar rates in the Evolut and PARTNER III patient groups, which may suggest that the difference in outcomes is due to valve characteristics. Design features that minimize PVR may worsen conduction system complications and patient-prosthesis mismatch.

8.4. Permanent Pacemaker Implantation. During TAVR implantation, trauma to the conduction system, namely, the bundle of His and the left bundle branch, can occur and result

in complete heart block or left bundle branch block (LBBB). Implantation of a permanent pacemaker (PPM) is most often necessitated as a result of new high-degree AV block and in a minority of patients for sick sinus syndrome [53].

TAVR is associated with significantly more PPM implantation than SAVR, in patients of all-risk categories. [21, 22]. Complications of new PPM implantation were similar in recent low-risk TAVR trials to the those in the previous studies in higher-risk patients [54]. The Evolut Low-Risk TAVR Trial with self-expanding valves also showed that significantly more low-risk TAVR patients underwent postoperative permanent pacemaker (PPM) implantation than SAVR patients (17.4% vs. 6.1%, respectively) [18]. The PARTNER III Trial had 6.6% of TAVR patients requiring PPM, which was found to not be significantly different compared with SAVR (at 4.1%) [16]. However, significantly more patients in the TAVR cohort developed new LBBB than SAVR patients (22% compared to 8%, respectively) [16].

Factors that impact the need for PPM in TAVR are preexisting conduction abnormalities, calcification of the LVOT, balloon valvuloplasty, and depth of THV implantation [53, 55]. Balloon-expandable THV are associated with a lower risk of PPM implantation than self-expanding valves [37, 53, 55, 56]. This is felt to be due to the increased radial force on the LVOT by self-expanding valves [54]. For example, an average of 25.8% of TAVR cases with the self-expanding CoreValve is associated with new PPM, while the average rates in TAVR with balloon-expanding SAPIEN valve are much lower at 6.5% [53]. The type of THV also plays a role, as seen with the higher rates of PPM with newer generation SAPIEN 3 THV, compared with the previous generation SAPIEN XT [56, 57]. The higher complication rate in SAPIEN 3 valves are attributed to the increased length, implantation height, and radial force exerted by its fabric skirt [54, 57]. Preoperative TAVR evaluation should include assessment for patient risk factors such as baseline conduction disturbances and LVOT calcification to assist procedural planning and to minimize the risk of PPM implantation [55].

Despite improvements in many of the complications of TAVR, the incidence of new conduction system disease and PPM implantation have remained steady or increased [56]. Although PPM implantation is more often required in higher-risk patients, the implications of a PPM are especially significant in low-risk TAVR patients [58]. Understanding the patient and procedural factors that predict postoperative PPM insertion are important when counseling low-risk patients about the possible need for PPM [55]. Conduction abnormalities that occur as a complication of TAVR are transient in a considerable number of patients [54]. Cohort studies that included a variety of TAVR prostheses have shown that long-term pacemaker dependency ranged from 27% to 68% of patients with PPM [54]. Therefore, the optimal timing of PPM implantation and long-term benefit of PPM are unclear [55]. To avoid unnecessary PPM, it may be reasonable to have patients undergo a period of rhythm monitoring after TAVR before PPM implantation. Many patients with severe aortic stenosis also have left ventricular hypertrophy and underlying heart failure. Conduction system disease and the need for pacing in these patients can lead to new heart failure or worsen existing cardiac function. On average, most PPMs typically last 10–15 years [59, 60]. The lifetime of a pacemaker is important to be considered, especially in low-risk patients. Patients should be counseled that they may require PPM exchange in the future, which is another procedure that carries risks of complications.

Studies of the prognostic consequences of PPM implantation in TAVR have had conflicting findings. Some studies have shown that PPM has no negative impact on 1-year mortality, while results from the TVT registry have shown that PPM implantation is associated with increased mortality [53, 54, 58]. A recent study in intermediate-risk patients evaluated the incidence of new LBBB after TAVR and found that 15.2% of TAVR patients developed new LBBB. This did significantly increase the all-cause and cardiovascular mortality, rehospitalization, PPM implantation and decreased LV function at 2 years [56]. This would suggest that PPM is associated with at least cardiovascular morbidity, which likely puts patients at risk of long-term increased mortality. Further studies are needed to define the impact that PPM has on cardiovascular morbidity and mortality and to establish the optimal timing of PPM implantation to avoid placement in patients with transient conduction abnormalities.

8.5. Stroke and the Role of Cerebral Protection. Stroke is an important cause of morbidity and mortality in TAVR [61]. The incidence of stroke after TAVR varies considerably [61]. Stroke complicates 2.7 to 5.5% of cases at 30 days but is underestimated in many trials [61, 62]. In PARTNER III, only 1.2% of low-risk TAVR patients had a major stroke at 1 year, compared with 3.1% of SAVR patients [16]. This was significantly lower than in the previous trials in higher-risk patients [8, 11, 12, 16]. However, at 2 years, TAVR was no longer statistically superior to SAVR [2]. Many studies report only major clinical strokes and do not include sensitive assessments of stroke such as evaluation by neurologists or imaging [61, 62]. Several studies have shown that, with routine MRI screening, the incidence of stroke after TAVR is 9–28% at 30 days [61, 63]. The Neurological Research Consortium has made recommendations to make evaluation of neurological endpoints more uniform [64]. In CEP studies, the recommended early efficacy endpoints are overt CNS injury, CNS infarction and hemorrhage, neurological dysfunction (TIA), MRI total lesion volume, and cognitive change [64]. They recommend that all eligible patients receive a baseline MRI for subtraction against the post-procedure MRI [65].

Approximately half of the strokes that occur after TAVR are periprocedural (within 48 hours of TAVR) and are embolic in nature [62, 66, 67]. Periprocedural stroke increases the 30-day mortality by 4- to 6-fold [62, 68, 69]. Cerebral embolic protection devices (CEPD) prevent embolization of debris to the brain during TAVR and may play a role in

preventing periprocedural stroke [61, 67]. The routine use of CEPD for stroke prevention in TAVR has been controversial. The utility of CEPD in TAVR was highlighted in the SENTINEL Trial, where embolic debris was captured in 99% of patients [67, 70]. When the debris was analyzed, it not only consisted of the anticipated thrombus and calcium, but also included foreign material (35% of patients), arterial wall, valve tissue, and myocardium [67, 70]. This study showed no clinically significant reduction in stroke; however, there was a 42% reduction in new lesion volume on diffusion-weighted MRI (DW MRI) in the CEPD group compared with that in the unprotected group [67]. Silent infarcts are evident only on imaging and have no associated focal neurological dysfunction attributed to them [61]. However, silent infarcts are associated with an increased risk of dementia and independently increase the risk of cognitive decline and future clinical strokes by 2- to 4-fold [62, 65]. CEP devices may play a role in preventing silent infarcts, which the majority of patients develop after TAVR [61, 67].

Despite the high frequency of embolization of debris in TAVR, CEPDs are not commonly used. Current RCTs have significant limitations in study size and have failed to show any significant reduction in stroke or mortality with CEPD [61]. Meta-analysis has also shown reductions in death and stroke with CEPD; however, these results were not statistically significant [61]. Given the lack of statistically significant results, the routine use of CEPDs in TAVR is not supported in the guidelines [61]. Despite the lack of widespread use, CEPDs have rapidly evolved with TAVR. New CEPDs cover all three aortic cerebral branches, as seen with TriGUARD 3, and offer more vascular protection than the previous devices [61, 62].

Registries have shown that operator experience and increasing site volume were associated with better outcomes in regards to mortality, vascular complication, and bleeding but not for stroke [66]. The role of CEPD in TAVR is yet to be determined by further RCTs that are adequately powered and include sensitive assessments of stroke [61]. The argument for the use of CEPD is even stronger in younger, low-risk patients who have more time to develop long-term cognitive effects of silent infarcts.

8.6. Durability. A major challenge facing TAVR in low-risk patients is a limited valve lifespan, as these patients are usually younger with less comorbidities and are more likely to require repeat procedures. The mean age of patients in the recent low-risk TAVR trial was 73 years versus 82 years in the intermediate-risk TAVR trials [11, 16]. There are no explicit guidelines advising which age of patients derives lasting benefit from TAVR implantation.

While the longevity of surgical bioprosthetic valves is well studied, there is a lack of similar data for TAVR valves. Transcatheter bioprosthetic valves can degenerate similar to surgical bioprosthetic valves; however, the longevity of TAVR valves may be further limited by the trauma and mechanical stress to the valve during the preparation, dilatation, or positioning of the valve. Data from early TAVR studies cannot be applied to current low-risk patients. This is primarily due to the rapid turnover of prosthetic valves and the differences in the patient population. In studies of surgical bioprosthetic valves, younger age at implantation has been shown to be associated with increased structural valve degeneration (SVD), especially in patients under the age of 60 [71, 72].

SVD is an irreversible intrinsic change, such as leaflet tear or calcification, that leads to deterioration and/or dysfunction of the valve [73]. SVD is an important etiology of bioprosthetic valve failure (BVF) as it can result in eventual stenosis or regurgitation [73]. Meta-analyses in surgical bioprosthetic valves have shown SVD begins 8 years after implantation, with further substantial increased SVD after 10 years [74]. The incidence of SVD after TAVR varies in the literature, from <5% to 10% at 1 year, 12–20% at 5 years, and approximately 13–23% at 8 years [74–76]. Other sources of BVF include nonstructural valve dysfunction, valve thrombosis, and endocarditis. It is important to differentiate the source of valve failure as these other sources may be reversible [73].

When approaching TAVR in low-risk patients, the limited evidence of valve durability has to be taken into account. Patients must be counseled on the potential need for repeat procedures.

9. Conclusion and Future Directions

TAVR has rapidly evolved since its inception and is now indicated for severe, symptomatic aortic stenosis in patients of all risk categories. There are clear advantages to TAVR, as the focus is placed on minimally invasive procedures to reduce complications and length of stay. TAVR now accounts for 12.5% of all aortic valve replacements [77]. There is still uncertainty regarding the optimal management of coexisting CAD, the prevention of periprocedural stroke, and the durability of TAVR. Further studies are needed to develop and assess the efficacy of TAVR-specific risk scores, to better characterize patient risk preoperatively. Other areas of interest will include defining the durability, long-term morbidity, and mortality associated with transaortic bioprosthetic valves in low-risk patients. The effects of permanent pacemaker implantation and patient-prosthesis mismatch on long-term morbidity and mortality are still being studied and are of particular importance to low-risk patients. Certain trade-offs exist, and individualized preoperative evaluation is needed to determine the best choice of prosthesis. Patient preference may be for TAVR; however, in select low-risk patients, a surgical mechanical valve may be a better option. Understanding the long-term risks of TAVR is essential to counseling low-risk patients about their choice of procedure.

Lastly, certain aortic valve disease states were excluded from TAVR trials, including moderate aortic stenosis, aortic insufficiency, and bicuspid aortic valves. Therefore, TAVR is not indicated in these patients. The management of these patients is a continued challenge and requires further investigation. Future trials in these patients may further expand the indications of TAVR.

Abbreviations

ACC:	American College of Cardiology
AHA:	American Heart Association
AR:	Aortic regurgitation
AS:	Aortic stenosis
AVA:	Aortic valve area
BVF:	Bioprosthetic valve failure
CAD:	Coronary artery disease
CEPD:	Cerebral embolic protection device
CABG:	Coronary artery bypass graft
CT Scan:	Computed tomography scan
CCTA:	Coronary computed tomography angiography
CTA:	Computed tomography angiography
DW MRI:	Diffusion-weighted magnetic resonance imaging
EuroSCORE II:	European System for Cardiac Operative Risk Evaluation
GA:	General anesthesia
LBBB:	Left bundle branch block
LFLG:	Low-flow low-gradient
LVEF:	Left ventricular ejection fraction
LVOT:	Left ventricular outflow tract
MDCT:	Multidimension computed tomography
MI:	Myocardial infarction
NPV:	Negative predictive value
NYHA:	New York Heart Association
PVR:	Paravalvular regurgitation
PCI:	Percutaneous coronary intervention
PPM:	Permanent pacemaker
RCT:	Randomized controlled trial
SAVR:	Surgical aortic valve replacement
STS PROM Score:	Society of Thoracic Surgeons Predicted Risk of Mortality Score
SVD:	Structural valve degeneration
TAVI:	Transcatheter aortic valve implantation
TAVR:	Transcatheter aortic valve replacement
THV:	Transcatheter heart valve
TEE:	Transesophageal echocardiogram
TIA:	Transient ischemic attack
TTE:	Transthoracic echocardiogram.

Data Availability

The data underlying this article are available within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Impact of Combined "CHADS-BLED" Score to Predict Short-Term Outcomes in Transfemoral and Transapical Aortic Valve Replacement

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Background. High CHA_2DS_2-VASC and HAS-BLED scores are linked to increased mortality in structural and nonstructural cardiovascular interventions irrespective of the presence of atrial fibrillation (AF) or oral anticoagulation. We aimed to use the aforementioned scores to quantify the risk of 30-day mortality, major vascular and bleeding events (MVASC/BARC), and cerebrovascular insults (CVI) in patients undergoing different access routes in transcatheter aortic valve replacement (TAVR). *Methods*. Out of 1329 patients, 980 transfemoral (TF) TAVR (73.7%) and 349 transapical (TA) TAVR (26.3%) were included. CHA_2DS_2-VASC, HAS-BLED, and combined "CHADS-BLED" scores were calculated and compared to the predictive value of the established EuroSCORE and STS score. *Results*. In all-comers TF TAVR patients, the applied risk models showed only poor association with 30-day mortality while, in patients with concomitant AF, a strong association was observed using the combined CHADS-BLED score (c-index: 0.83; 95% CI: 0.76–0.91; $p < 0.0001$). Concerning 30-day mortality, only the STS score for TF TAVR (c-index: 0.68; 95% CI: 0.59–0.76; $p = 0.001$) and EuroSCORE for TA TAVR (c-index: 0.66; 95% CI: 0.56–0.76; $p = 0.005$) could show some predictive value. High CHADS-BLED was associated with enhanced CVI (3.0% vs. 7.2%; $p = 0.0039^*$) and more frequent MVASC/BARC (3.2% vs. 6.3%; $p = 0.0362$) in the all-comers TAVR cohort. All risk models failed in the prediction of CVI and MVASC/BARC for TA TAVR patients. *Conclusion*. The combined CHADS-BLED score was a strong predictor for 30-day mortality in TF TAVR patients with AF. A high CHADS-BLED score showed a good predictive value for major vascular and bleeding events as well as CVI in TF TAVR patients. This study is registered at clinical trials (NCT01805739).

1. Introduction

Transcatheter aortic valve replacement (TAVR) is an established therapeutic option in patients with symptomatic severe aortic stenosis (AS). While the STS score and the EuroSCORE are two appropriate risk score models to ascertain patients' individual short-term mortality and morbidity after cardiac surgery [1, 2], there are no comparable tools particularly established for patients undergoing TAVR, especially in terms of different access routes. In this context, the transapical (TA) approach was shown to be associated with higher morbidity and mortality compared to transfemoral (TF) access [3, 4].

The CHA_2DS_2-VASC score has been demonstrated to predict the risk of cerebrovascular events in patients with [5] and without atrial fibrillation (AF) [6,7]. Additionally, the

HAS-BLED score can predict the risk of major bleeding and mortality in patients using oral anticoagulation [8], even in the absence of AF [9]. Although these risk scores have not been developed for the prediction of the outcome after TAVR, many components included cover the typical TAVR patient profile. Thus, both tools are considered to be associated with enhanced mortality and morbidity in several structural [10–13] and nonstructural cardiovascular interventions [6, 7, 9]. Therefore, we sought to (i) quantify the risk of 30-day mortality, major vascular and bleeding events (MVASC/BARC), and the incidence of cerebrovascular insults (CVI) in dependence from these well-established scores, (ii) to assess their combined usage (CHADS-BLED) as short-term risk stratification tool in patients undergoing TAVR with focus on differences in access routes, namely, TF and TA approach, and (iii) to compare these results with the predictive value of traditional risk scores (EuroSCORE and STS).

2. Methods

2.1. Study Population. From 2009 to 2019, out of 1329 patients with either TF ($n = 980$, 73.7%) or TA ($n = 349$, 26.3%) TAVR, CHA_2DS_2-VASC and HAS-BLED scores were calculated as well as the logistic EuroSCORE I and STS-PROM scores. The combined CHADS-BLED score was calculated by adding the values of the single CHA_2DS_2-VASC and HAS-BLED scores. All procedures were performed according to the current guidelines between 2009 and 2019, respectively, and under local anesthesia for TF access and general anesthesia for TA access. TF TAVR was performed with different generations of either the self-expandable CoreValve System (Medtronic Inc., Minneapolis, MN) or the balloon-expandable SAPIEN System (Edwards Lifesciences, Irvine, CA). TA TAVR was predominantly performed by using the SAPIEN System (Edwards Lifesciences, Irvine, CA) or in very few cases the Engager System (Medtronic Inc., Minneapolis, MN).

All patients provided written informed consent for TAVR and the use of clinical, procedural, and follow-up data for research. The study procedures were in accordance with the Declaration of Helsinki. The Institutional Ethics Committee of the Heinrich-Heine University approved the study protocol (4080). The study is registered at clinical trials (NCT01805739).

2.2. Clinical Outcomes, Definitions, and Assessment. All clinical outcomes were systematically assessed using the VARC-2 consensus statement [14] and are reported accordingly. The primary study endpoints were defined as 30-day all-cause mortality, MVASC/BARC (defined as requiring a vascular surgical input, procedure-related life-threatening, disabling, or major bleeding with need for blood transfusion), and CVI (defined as an acute episode of a focal or global neurological deficit caused by ischemic, hemorrhagic, or undetermined etiology and confirmed by neurological specialist or neuroimaging). Secondary clinical endpoints were need for cardiopulmonary resuscitation, conversion to surgery, sepsis, acute kidney injury, and new permanent pacemaker insertion within 30 days of TAVI.

2.3. Statistical Analysis. The collected data included patients' characteristics, imaging findings, periprocedural in-hospital data, laboratory results, and follow-up data. Continuous data were described by mean and standard deviation, median, or upper and lower 95% confidence interval (interquartile ranges). Categorical variables were characterized by frequencies and percentages. Continuous variables were compared using Student's t-test or Kolmogorov–Smirnov test depending on variable distribution. Categorical variables were compared using Fisher's exact test. Survival was analyzed using the Kaplan–Meier plots and logrank tests. Receiver operating characteristic (ROC) analysis and the c-index (area under the curve (AUC)) were used to identify the sensitivity and specificity of the CHA_2DS_2-VASC, HAS-BLED, and combined CHADS-BLED cutoff points for 30-day mortality, MVASC/BARC, and CVI. The optimal cutoff values were defined by Youden's index, the point at which the value of "sensitivity + specificity − 1" was maximum.

The data analysis was performed using the statistical software SPSS (version 23.0, SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 6.0, GraphPad Software, San Diego, CA, USA). All statistical tests were 2-tailed, and a value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline Characteristics: Clinical and Functional Data. Baseline patients' characteristics differed in consequence of the particular risk profile and selection bias of TF versus TA assigned approaches: TA patients were younger (TF vs. TA AVR: age 81.7 ± 5.7 vs. 78.5 ± 6.8; $p < 0.0001$) and predominantly male (TF vs. TA TAVR: female 54.5% vs. 39.3%; $p < 0.0001$). In summary, general atherosclerosis in the meaning of concomitant coronary artery disease (CAD), peripheral artery disease (PAD), cerebrovascular disease (CVD), and porcelain aorta (PAo) were more frequent in patients undergoing TA TAVR. The logistic EuroSCORE I (logES-I) was higher in TA TAVR patients according to the predescribed risk profile (TF vs. TA TAVR: logES-I 25.4 ± 15.8 vs. 27.9 ± 16.8; $p = 0.011$). No difference was observed concerning mono or dual antiplatelet therapy, usage of (new) oral anticoagulants, or triple therapy at admission. A full overview of baseline clinical and functional characteristics is displayed in Supplemental Table 1.

3.2. Outcome Analysis in Different TAVR Access Routes. Periprocedural death within the first 30 days was recorded in 59 cases (4.4%) in the overall cohort with a mortality distribution of 3.3% ($n = 32$) in the TF TAVR and 7.7% ($n = 27$) in the TA TAVR cohort ($p = 0.0012\%$). Cardiovascular death was documented in 39 cases with higher amount in patients undergoing TA approach (TF vs. TA TAVR: 2.1% vs. 5.2%; $p = 0.0003$). Further causes of overall 30-day death were cerebrovascular accidents ($n = 3$, 0.2%), infection/sepsis ($n = 15$; 1.1%), and unknown reasons ($n = 2$; 0.2%).

Cerebrovascular events were recorded in 68 cases (5.1%) in the overall cohort with a distribution of 5.3% ($n = 52$) in the TF TAVR and 4.6% ($n = 16$) in the TA TAVR cohort. There were no significant differences in both cohorts regarding the overall distribution and subclassifications. Transient ischemic attacks counted with 19 events (1.4%), ischemic strokes with 33 events (2.5%), hemorrhagic CVI with 4 events (0.3%), and undetermined CVI with 6 events (0.5%). MVASC/BARC events recorded in 146 cases (11.0%) were significantly higher in the TA TAVR cohort (TF vs. TA TAVR: 9.5% vs. 15.2%; $p < 0.0001$). Except for conversion to surgery and need for permanent pacemaker therapy, all secondary outcomes were more unfavorable in TA TAVR patients. A complete overview of primary and secondary outcomes according to VARC-2 is displayed in Supplemental Table 2.

3.3. CHA_2DS_2-VASC, HAS-BLED, and Combined CHADS-BLED Performance for Prediction of 30-Day Mortality, CVI, and MVASC/BARC (All-Comers). The risk model discrimination performance is reported in Table 1 and Supplemental Figure 1. The aforementioned risk models showed only poor association with 30-day mortality in TF TAVR (CHA_2DS_2-VASC: c-index: 0.57, 95% CI: 0.47–0.68, $p = 0.162$; HAS-BLED: c-index: 0.58, 95% CI: 0.46–0.69, $p = 0.132$; CHADS-BLED: c-index: 0.60, 95% CI: 0.49–0.71, $p = 0.058$) and TA TAVR patients (CHA_2DS_2-VASC: c-index: 0.53, 95% CI: 0.43–0.64, $p = 0.559$; HAS-BLED: c-index: 0.58, 95% CI: 0.47–0.70, $p = 0.157$; CHADS-BLED: c-index: 0.57, 95% CI: 0.46–0.68, $p = 0.217$). Concerning 30-day mortality in all-comers TF and TA TAVR patients, only the STS score for TF TAVR (c-index: 0.675; 95% CI: 0.59–0.76; $p = 0.001$) and the EuroSCORE for TA TAVR (c-index: 0.66; 95% CI: 0.56–0.76; $p = 0.005$) could show a predictive value.

HAS-BLED (c-index: 0.66; 95% CI: 0.58–0.74; $p < 0.0001$) and CHADS-BLED (c-index: 0.66; 95% CI: 0.58–0.73; $p < 0.0001$) performed best concerning prediction of CVI.

Regarding the prediction of MVASC/BARC, HAS-BLED (c-index: 0.59; 95% CI: 0.51–0.68; $p = 0.035$) and CHADS-BLED (c-index: 0.59; 95% CI: 0.50–0.67; $p = 0.048$) were superior to CHA_2DS_2-VASC (c-index: 0.54; 95% CI: 0.47–0.62; $p = 0.319$) in TF TAVR patients, while the best prediction of MVASC/BARC for TF TAVR was reached by the STS score (c-index: 0.65; 95% CI: 0.58–0.73; $p < 0.0001$). Indeed, all risk models failed in the prediction of the primary endpoints in patients undergoing TA access.

Receiver operating characteristic (ROC) analysis and the c-index (area under the curve, AUC) were used to identify the sensitivity and specificity of the CHADS-BLED cutoff points for 30-day mortality, CVI, and MVASC/BARC. The optimal cutoff values were defined by Youden's index. >7 points turned out to be the cutoff with "sensitivity + specificity − 1" becoming the maximum regarding the combined CHADS-BLED calculation (see Supplemental Figure 1) in every event (30-day mortality, CVI, and MVASC/BARC) and access class (TF vs. TA TAVR).

In the following, the Kaplan–Meier curves were plotted to clarify the impact on 30-day mortality of combined CHADS-BLED considering ≤7 points and >7 points: according to the previously established discrimination model, mortality increased in TF TAVR patients classified with more than 7 points, but was not significantly different as compared to low CHADS-BLED ≤7 points (≤7 points vs. >7 points: 2.8% vs. 4.9%; $p_{\text{logrank}} = 0.1781$, Figure 1(a)). Surprisingly, TA TAVR patients showed inverse relationship (≤7 points vs. >7 points: 12.4% vs. 6.7%; $p_{\text{logrank}} = 0.2534$, Figure 1(b)). Looking at the several event rates, high CHADS-BLED was associated with enhanced CVI (≤7 points vs. >7 points: 3.0 [1.4–4.6] vs. 7.2 [5.0–9.3]; $p_{\text{logrank}} = 0.0039$, Figure 1(c)), increased MVASC/BARC (≤7 points vs. >7 points: 3.2 [1.6–4.9] vs. 6.3 [4.2–8.3]; $p_{\text{logrank}} = 0.0362$, Figure 1(c)), and more combined events (≤7 points vs. >7 points: 6.0 [3.7–8.2] vs. 12.3 [9.5–15.1]; $p_{\text{logrank}} = 0.0007$, Figure 1(c)) in TF TAVR patients. Again, no association could be found in low vs high CHADS-BLED scoring and the incidence of the primary endpoint events in TA TAVR patients (Figure 1(d)).

3.4. Subanalysis of CVI and/or MVASC/BARC Positive Patients regarding Access Sites. To clarify which factors may have an impact on the adverse vascular and bleeding events in TF vs TA TAVR cohorts, CVI and/or MVASC/BARC positive patients were further analyzed towards differences in baseline characteristics, risk models, and the underlying antithrombotic regime.

As mentioned before, TA patients were predominantly male (TF vs. TA TAVR: female 64.5% vs. 39.6%; $p < 0.0001$) and less obese (TF vs. TA TAVR: BMI 27.0 ± 4.7 vs. 25.4 ± 4.3; $p = 0.043$). Concomitant CAD, PAD, and PAo were also more frequent in patients undergoing TA TAVR. While all other risk models were comparable in both groups, only the HAS-BLED was higher in TF TAVR patients (TF vs. TA TAVR: 3.5 ± 0.9 vs. 3.0 ± 1.1; $p = 0.005$). No difference was documented concerning mono or dual antiplatelet therapy, usage of (new) oral anticoagulants, or triple therapy following TAVR. A full overview of differing characteristics between TF and TA TAVR patients with CVI and/or MVASC/BARC positive profile is displayed in Supplemental Table 3.

3.5. Subanalysis of Patients with AF. Risk model discrimination performance is reported in Table 2 and Supplemental Figure 2. In patients with AF, the aforementioned risk models showed good association with 30-day mortality in TF TAVR. Best prediction was performed by CHADS-BLED (c-index: 0.83; 95% CI: 0.76–0.91; $p < 0.0001$), followed by CHA_2DS_2-VASC (c-index: 0.78; 95% CI: 0.70–0.87; $p = 0.001$) and HAS-BLED (c-index: 0.74; 95% CI: 0.59–0.89; $p = 0.004$), and STS score (c-index: 0.73; 95% CI: 0.60–0.87; $p = 0.006$). Again, no association at all could be found for risk models in TA TAVR patients.

HAS-BLED performed best concerning prediction of CVI (c-index: 0.66; 95% CI: 0.54–0.77; $p = 0.019$), while the STS score (c-index: 0.72; 95% CI: 0.61–0.84; $p = 0.001$) and

Table 1: Discrimination performance (ROC and AUC statistics): all-comers.

Groups/endpoints	Variables	AUC	p value	Lower 95% CI	Upper 95% CI
(A) TF TAVR					
	Log. EuroSCORE I	0.53	0.535	0.42	0.64
	STS score	0.68	**0.001**	0.59	0.76
30-day mortality	CHA_2DS_2-VASC	0.57	0.162	0.47	0.68
	HAS-BLED	0.58	0.132	0.46	0.69
	"CHADS-BLED"	0.60	0.058	0.49	0.71
	Log. EuroSCORE I	0.53	0.488	0.49	0.61
	STS score	0.59	**0.022**	0.52	0.67
CVI	CHA_2DS_2-VASC	0.60	**0.015**	0.53	0.67
	HAS-BLED	0.66	**<0.0001**	0.58	0.74
	"CHADS-BLED"	0.66	**<0.0001**	0.58	0.73
	Log. EuroSCORE I	0.55	0.246	0.46	0.64
	STS score	0.65	**<0.0001**	0.58	0.73
MVASC/BARC	CHA_2DS_2-VASC	0.54	0.319	0.47	0.62
	HAS-BLED	0.59	**0.035**	0.51	0.68
	"CHADS-BLED"	0.59	**0.048**	0.50	0.67
(B) TA TAVR					
	Log. EuroSCORE I	0.66	**0.005**	0.56	0.77
	STS score	0.64	**0.016**	0.55	0.73
30-day mortality	CHA_2DS_2-VASC	0.53	0.559	0.43	0.64
	HAS-BLED	0.58	0.157	0.47	0.70
	"CHADS-BLED"	0.57	0.217	0.46	0.68
	Log. EuroSCORE I	0.41	0.240	0.29	0.54
	STS score	0.41	0.244	0.28	0.55
CVI	CHA_2DS_2-VASC	0.64	0.054	0.52	0.76
	HAS-BLED	0.53	0.725	0.36	0.69
	"CHADS-BLED"	0.60	0.174	0.46	0.74
	Log. EuroSCORE I	0.53	0.598	0.44	0.61
	STS score	0.56	0186	0.48	0.65
MVASC/BARC	CHA_2DS_2-VASC	0.53	0.490	0.44	0.63
	HAS-BLED	0.49	0.866	0.39	0.59
	"CHADS-BLED"	0.54	0.462	0.44	0.63

EuroSCORE (c-index: 0.69; 95% CI: 0.56–0.82; $p = 0.007$) were superior to HAS-BLED (c-index: 0.64; 95% CI: 0.52–0.76; $p = 0.043$) in terms of MVASC/BARC, similar to the results for all-comers TF TAVR cohort.

Once again, all risk models failed in the prediction of the primary endpoints in patients undergoing TA access.

While the optimal cutoff values in TF patients with AF were defined by Youden's index with a CHADS-BLED >8 points for 30-day mortality and >7 points for CVI and MVASC/BARC, the Kaplan–Meier curves and cumulative statistics were plotted. Mortality was significantly different in TF patients classified with more than 8 points as compared to low CHADS-BLED ≤8 points (≤8 points vs. >8 points: 0.7% vs. 10.4%; $p_{\text{logrank}}<0.0001$, Figure 2(a)). Looking at the several event rates, high CHADS-BLED was associated with increased incidence, but not significantly different from low CHADS-BLED. For further information, see also Figure 2(b). Because all scores failed in TA TAVR patients with AF, no further discrimination was established.

4. Discussion

The present study evaluated the risk of 30-day mortality, major vascular and bleeding events, and the incidence of CVI in dependence from the aforementioned scores in patients undergoing different access routes in TAVR and revealed several findings:

(1) Only in patients with AF, the combined CHADS-BLED was superior to a single use of CHA_2DS_2-VASC or HAS-BLED and superior to the use of the traditional risk scores, STS and EuroSCORE, in prediction of 30-day mortality

(2) In all-comers TF TAVR patients, high CHADS-BLED (>7 points) was associated with enhanced CVI and more frequent MVASC/BARC, but only to the same extent as HAS-BLED

(3) The risk models failed even with higher score thresholds to predict primary endpoints in TA TAVR patients, except for EuroSCORE and STS score in terms of 30-day mortality

(4) CVI and MVASC/BARC events were not linked to different antithrombotic and/or antiplatelet regimes

4.1. Predictive Value of CHA_2DS_2-VASC, HAS-BLED, and Combined CHADS-BLED. Accurate risk assessment for TAVR patients remains challenging and simple risk scores

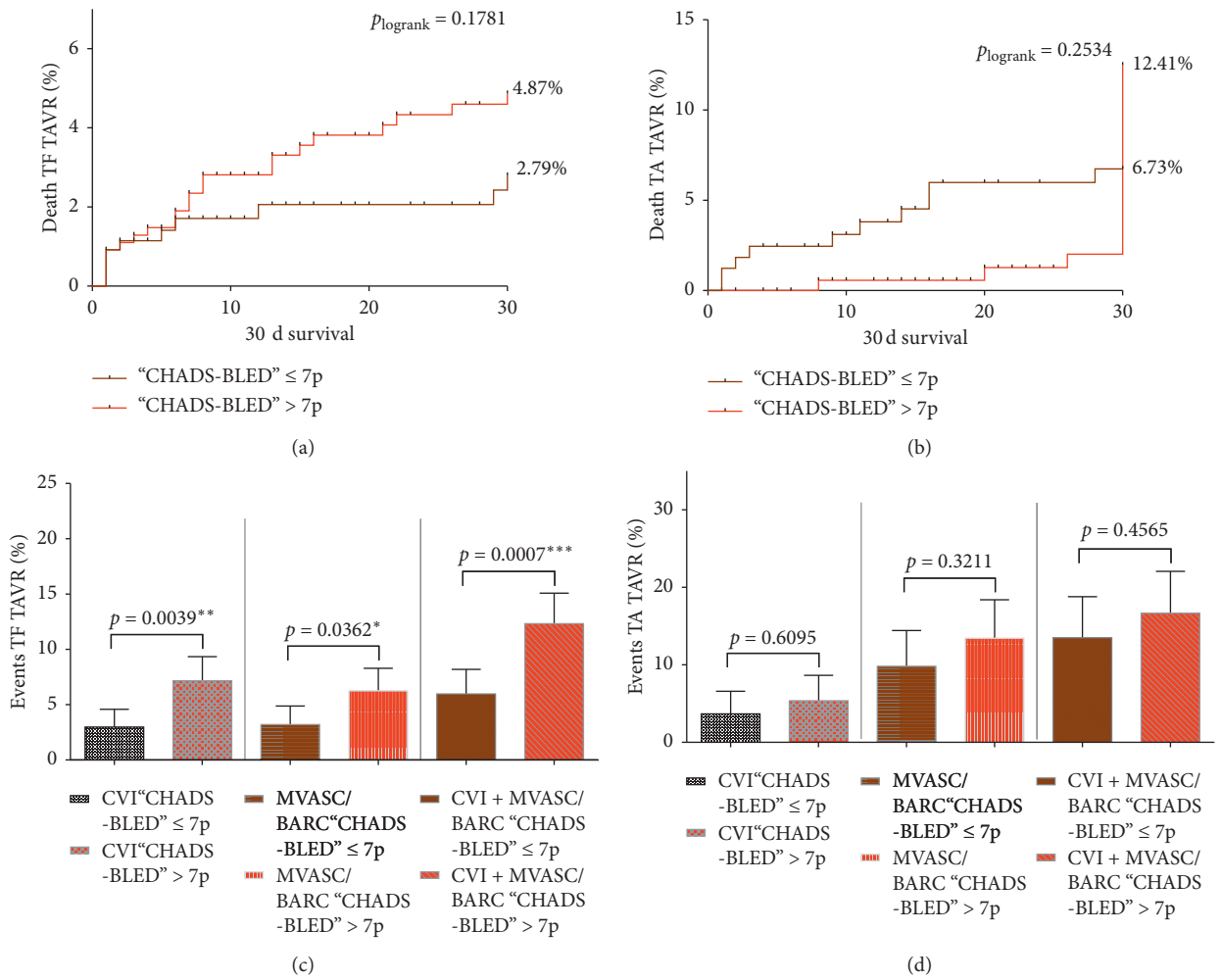

Figure 1: Kaplan–Meier survival curves for 30-day mortality and adverse event rates according to high and low combined CHADS-BLED score. (a) Kaplan–Meier survival curves according to the combined CHADS-BLED score in TF TAVR and (b) TA TAVR patients. (c) Awarding of adverse event rates according to high and low combined CHADS-BLED score in TF TAVR and (d) TA TAVR patients.

for bedside use are still lacking. Both the CHA_2DS_2-VASC (congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke, vascular disease, age 65–74 years, and female sex) and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, and drugs/alcohol concomitantly) are well-established and routinely used scores for therapeutic decision support concerning patients with AF. In the past few years, these risk models were also stratified for conditions other than AF [9–13]. Hamid et al. showed a strong association between a modified $R_2CHA_2DS_2$-VASC score and 30-day mortality. Patients with a baseline CHA_2DS_2-VASC score ≥6 or a modified score ≥7 appeared to have increased short-term mortality [10]. In comparison with our work, the population of Hamid et al. showed lower risk profile (log EuroSCORE 21.8 vs. 26.7) but higher 30-day mortality (7.7% vs. 4.4%), probably due to the older character of the study with first-generation devices and less experienced heart teams. Orvin et al. recently demonstrated in a three-category model that both stroke and mortality at 1 year were significantly more frequent with increasing CHA_2DS_2-VASC score [12]. Honda et al. showed that the HAS-BLED score could predict the risk of severe bleeding and mortality in patients who underwent TF TAVR independent of the presence of AF [13].

However, bedside score-derived prediction of mortality and adverse events in the context of different access routes comparing TF and TA TAVR has not been investigated so far. Our study is in line with former reports that TA patients show higher mortality and periprocedural adverse events than TF patients [3, 4]. Surprisingly, in our study, neither CHA_2DS_2-VASC nor HAS-BLED score was associated with 30-day mortality in all-comers TF and TA TAVR patients, and all risk models failed in the prediction of the primary endpoints in patients undergoing TA access. Hence, only in patients with AF, the CHADS-BLED was strongly associated with 30-day mortality. This is in close relation to the original use of the scores, namely, prediction of outcome only in

Table 2: Discrimination performance (ROC and AUC statistics): subanalysis of patients with AF.

Groups/endpoints	Variables	AUC	p value	Lower 95% CI	Upper 95% CI
(C) TF TAVR					
	Log. EuroSCORE I	0.64	0.105	0.49	0.79
	STS score	0.73	**0.006**	0.60	0.87
30-day mortality	CHA_2DS_2-VASC	0.78	**0.001**	0.70	0.87
	HAS-BLED	0.74	**0.004**	0.59	0.89
	"CHADS-BLED"	0.83	**<0.0001**	0.76	0.91
	Log. EuroSCORE I	0.52	0.720	0.40	0.65
	STS score	0.61	0.102	0.49	0.73
CVI	CHA_2DS_2-VASC	0.59	0.195	0.46	0.71
	HAS-BLED	0.66	**0.019**	0.54	0.77
	"CHADS-BLED"	0.64	**0.040**	0.52	0.76
	Log. EuroSCORE I	0.69	**0.007**	0.56	0.82
	STS score	0.72	**0.001**	0.61	0.84
MVASC/BARC	CHA_2DS_2-VASC	0.54	0.543	0.43	0.65
	HAS-BLED	0.64	**0.043**	0.52	0.76
	"CHADS-BLED"	0.62	0.101	0.50	0.73
(D) TA TAVR					
	Log. EuroSCORE I	0.31	0.072	0.12	0.50
	STS score	0.43	0.497	0.27	0.59
30-day mortality	CHA_2DS_2-VASC	0.31	0.070	0.17	0.45
	HAS-BLED	0.40	0.356	0.22	0.58
	"CHADS-BLED"	0.31	0.077	0.17	0.45
	Log. EuroSCORE I	0.45	0.82	0.26	0.64
	STS score	0.64	0.489	0.43	0.86
CVI	CHA_2DS_2-VASC	0.39	0.591	0.00	0.80
	HAS-BLED	0.25	0.235	0.00	0.60
	"CHADS-BLED"	0.31	0.369	0.00	0.72
	Log. EuroSCORE I	0.42	0.336	0.30	0.54
	STS score	0.47	0.756	0.33	0.62
MVASC/BARC	CHA_2DS_2-VASC	0.42	0.371	0.27	0.58
	HAS-BLED	0.56	0.485	0.39	0.73
	"CHADS-BLED"	0.49	0.865	0.31	0.66

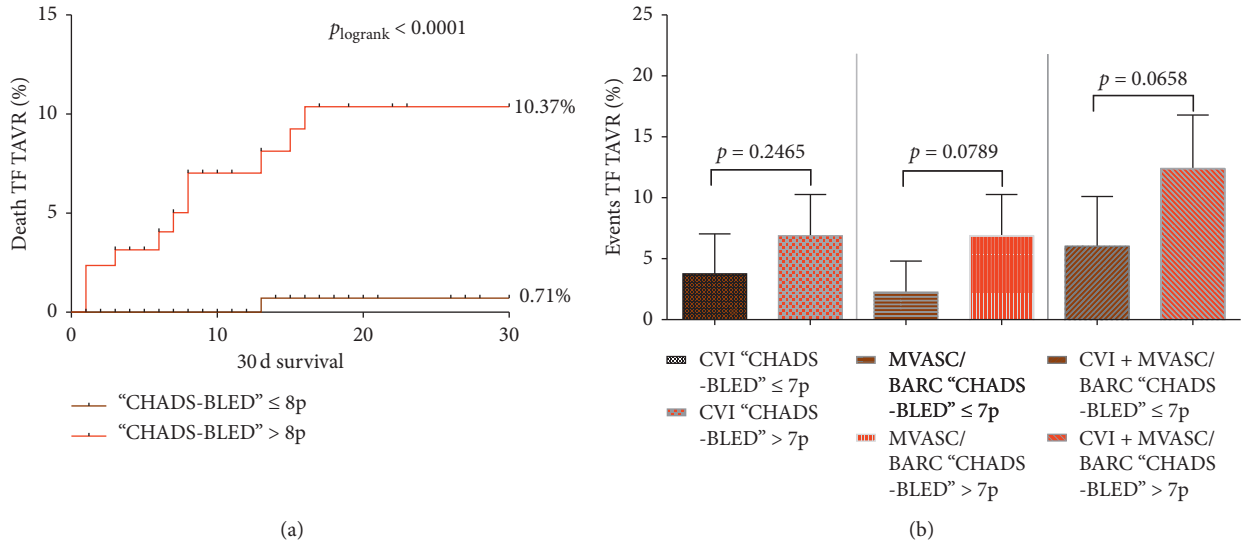

Figure 2: Kaplan–Meier survival curves for 30-day mortality and adverse event rates according to high and low combined CHADS-BLED score in patients with AF. (a) Kaplan–Meier survival curves according to the combined CHADS-BLED score in TF TAVR patients with AF. (b) Awarding of adverse event rates according to high and low combined CHADS-BLED score in TF TAVR patients with AF.

patients with AF, refusing former results about their usefulness in risk prediction regardless of the presence of AF [10, 12, 13].

Looking at the several event rates, high CHADS-BLED >7 points was associated with enhanced CVI, MVASC/BARC, and combined events in TF TAVR patients, but only in the all-comers cohort (with and without AF). No association could be found in low vs high CHADS-BLED scoring and incidence of the primary endpoint events in TA TAVR patients. Former studies could show that single use of CHA_2DS_2-VASC is able to provide strong correlations for in-hospital stroke but with low accuracy [11], comparable to our results. Interestingly, the HAS-BLED discriminated best for CVI and not for internally predetermined bleeding events. Furthermore, despite the fact that CVI was equally distributed between TF and TA patients and that MVASC/BARC events were significantly more frequent in TA TAVR patients, this discrimination applied only in TF TAVR patients, supposing more influencing variables like concomitant antiplatelet [15, 16] or antithrombotic regimes [17]. However, subanalysis of CVI + MVASC/BARC events refused any dependency from underlying antithrombotic or antiplatelet regimes, including mono and dual antiplatelet therapy, usage of single oral anticoagulants, or combination with antiplatelet therapy.

4.2. Comparison to the Established STS Score and EuroSCORE. The more traditional risk scoring systems STS score and logistic EuroSCORE I have been developed and validated for the prediction of 30-day mortality and major comorbidity rates in surgical populations. They are commonly used to assess risk in patients considered for TAVR as well due to lack of proper alternatives. As expected, the STS score and EuroSCORE turned out to be most predictive for 30-day mortality in all-comers TF and TA TAVR in the present study.

Surprisingly, the STS score was superior to HAS-BLED in the prediction of MVASC/BARC events although the STS score does not contain any bleeding-specific features as HAS-BLED does. As reported in former studies, there is an effect of post-TAVI bleeding on short-term mortality. Wang et al. showed by meta-analysis that there is an about 3-fold increase in 30-day mortality associated with bleeding events, which could explain the good predictive value of the STS score in this field [18].

However, while these operative risk scores are derived from surgical aortic valve replacement, they tend to overestimate TAVR mortality because of many procedural confounders (for example, general anesthesia is not needed for TF TAVR). Furthermore, many important noncardiac factors such as frailty, malignancy, and neurological status are not part of these risk models. This is in line with our result that one-third of the deaths in our study were due to infection or sepsis, supposing various influencing noncardiac factors not being reflected by the parameters included in the current risk scores. In addition, none of the risk scores take into account anatomical factors such as vessel calcification and procedural aspects, both variables that strongly impact short-term outcome in TAVR.

These findings highlight the need of more precise scoring systems regarding the complex clinical situation of patients with severe aortic valve stenosis. This is why the current guidelines acknowledge the deficient character of the risk scores and recommend a multidisciplinary heart team-based decision for TAVR after detailed clinical evaluation with participation of patients and their families [19].

5. Limitations

The current study is a hypothesis-generating retrospective single-center analysis designed to test the association between single and combined use of risk scores regarding periprocedural adverse events and 30-day mortality. Due to the long time period between 2009 and 2019, there is a high variability in devices and generation of devices. With advances in technique, device, and expansion of TAVR to lower risks groups, the mortality and CVI rates have improved over time. In the present analysis, the measured outcomes were not linked to different antithrombotic and/or antiplatelet regimes. The authors cannot exclude that this absent effect is due to patients' noncompliance in medication intake although all patients had comprehensible medication plans before and after TAVR.

Further studies are warranted to validate our findings, taking other procedural factors and different risk profiles—high, intermediate, and low risk—into account. A propensity-matched score analysis should be considered to clarify the observed differences in risk model-derived prediction of adverse events in TA and TF patients.

6. Conclusion

The combined CHADS-BLED score was a strong predictor for 30-day mortality in TF TAVR patients with AF but failed to predict any adverse event in TA TAVR. Neither a single unified scale or scoring system nor a combination of established risk scores seems to be able to adequately predict both short-term mortality and occurrence of adverse events like MVASC/BARC or CVI in patients with aortic valve stenosis. The complex clinical situation of these patients and different access routes for TAVR require more accurate risk assessment tools, especially regarding noncardiac factors like functional status and frailty as well as anatomical and procedural factors.

Abbreviations

AF:	Atrial fibrillation
AS:	Aortic stenosis
CAD:	Coronary artery disease
CHADS-BLED:	Combined consideration of CHA_2DS_2-VASC and HAS-BLED
CVD:	Cerebrovascular disease
CVI:	Cerebrovascular insults
EuroSCORE:	European System for Cardiac Operative Risk Evaluation
LogES-I:	Logistic EuroSCORE I

MVASC/ BARC:	Major vascular and bleeding events according to VARC-2 criteria
PAo:	Porcelain aorta
PAD:	Peripheral artery disease
STS (PROM):	Society of Thoracic Surgeons (Predicted Risk of Mortality)
TAVR:	Transcatheter aortic valve replacement
TA:	Transapical access
TF:	Transfemoral access
VARC-2:	Valve Academic Research Consortium (2nd update).

Data Availability

The statistical data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

Verena Veulemans, Tobias Zeus, Amin Polzin, and Ralf Westenfeld have received consulting fees, travel expenses, or study fees from Medtronic and Edwards Lifesciences. All other authors have nothing to disclose with regard to this project.

Authors' Contributions

Verena Veulemans and Oliver Maier contributed equally to this work.

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Supplementary Materials

Supplemental Table 1: baseline clinical and functional characteristics. Supplemental Table 2: 30-day outcomes according to VARC-2. Supplemental Table 3: subanalysis of CVI and/or MVASC/BARC positive patients. Supplemental Figure 1: risk model discrimination performance for 30-day mortality, CVI, and MVASC/BARC. Comparative model discrimination (ROC curves) for patients with TF TAVR and TA TAVR only. Receiver operating characteristic (ROC) analysis and the c-index (area under the curve, AUC) were used to identify the sensitivity and specificity of the logistic EuroSCORE I, STS score, CHA_2DS_2-VASC, HAS-BLED, and combined "CHADS-BLED" cutoff points for 30-day mortality, CVI, and MVASC/BARC. The optimal cutoff values were defined by Youden's index, the point at which the value of "sensitivity + specificity − 1" was maximal, leading to a cutoff of >7 points regarding the combined "CHADS-BLED" calculation in every event (30-day mortality, CVI, and MVASC/BARC) and access (TF vs TA TAVR) class. Supplemental Figure 2: risk model discrimination performance for 30-day mortality, CVI, and MVASC/BARC in AF patients. Comparative model discrimination (ROC curves) for patients with AF undergoing TF TAVR and TA TAVR. Receiver operating characteristic (ROC) analysis and the c-index (area under the curve, AUC) were used to identify the sensitivity and specificity of the logistic EuroSCORE I, STS score, CHA_2DS_2-VASC, HAS-BLED, and combined "CHADS-BLED" cutoff points for 30-day mortality, CVI, and MVASC/BARC. The optimal cutoff values were defined by Youden's index, the point at which the value of "sensitivity + specificity − 1" was maximal, leading to a cutoff of >8 points regarding the combined "CHADS-BLED" calculation concerning 30-day mortality and >7 points for every other event (CVI and MVASC/BARC) in TF TAVR patients. (*Supplementary Materials*)

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Research Article

Evaluating the Validity of Risk Scoring in Predicting Pacemaker Rates following Transcatheter Aortic Valve Replacement

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Introduction. Requirement of permanent pacemaker (PPM) implantation is a known and common postoperative consequence of transcatheter aortic valve replacement (TAVR). The Emory risk score has been recently developed to help risk stratify the need for PPM insertion in patients undergoing TAVR with SAPIEN 3 valves. Our aim was to assess the validity of this risk score in our patient population, as well as its applicability to patients receiving self-expanding valves. *Methods*. We conducted a retrospective review of 479 TAVR patients without preoperative pacemakers from November 2016 through December 2018. Preoperative risk factors included in the Emory risk score were collected for each patient: preoperative QRS, preoperative right bundle branch block (RBBB), preoperative syncope, and degree of valve oversizing. Multivariable analysis of the individual variables within the scoring system to identify predictors of PPM placement was performed. The predictive discrimination of the risk score for the risk of PPM placement after TAVR was assessed with the area under the receiver operating characteristic curve (AUC). *Results*. Our results demonstrated that, of the 479 patients analyzed, 236 (49.3%) received balloon-expandable valves and 243 (50.7%) received self-expanding valves. Pacemaker rates were higher in patients receiving self-expanding valves than those receiving balloon-expandable valves (25.1% versus 16.1%, $p = 0.018$). The Emory risk score showed a moderate correlation with pacemaker requirement in patients receiving each valve type, with AUC for balloon-expandable and self-expanding valves of 0.657 and 0.645, respectively. Of the four risk score components, preoperative RBBB was the only predictor of pacemaker requirement with an AUC of 0.615 for both balloon-expandable and self-expanding valves. *Conclusion. In our cohort*, the Emory risk score had modest predictive utility for PPM insertion after balloon-expandable and self-expanding TAVR. The risk score did not offer better discriminatory utility than that of preoperative RBBB alone. Understanding the determinants of PPM insertion after TAVR can better guide patient education and postoperative management.

1. Introduction

Transcatheter aortic valve replacement (TAVR) is now an established alternative to surgical aortic valve replacement for patients with severe aortic stenosis [1–4]. Despite its success and limited complication risk, the occurrence of conduction abnormalities and the need for permanent pacemaker (PPM) implantation remain the most frequent complication of TAVR [5].

Many studies have identified predictors of PPM implantation following TAVR [6–8]. Most recently, Kiani et al. developed the Emory risk score as a tool to aid in the risk stratification of patients undergoing TAVR with SAPIEN 3 balloon-expandable valves. The characteristics of the score include history of syncope, preexisting right bundle branch block (RBBB), QRS duration ≥140 ms, and valve oversizing ≥16% [9].

The aim of this study is to assess the validity of the Emory risk score in our patient population. Moreover, we sought to determine whether the model was applicable to both balloon-expandable and self-expanding valves.

2. Methods

This study was conducted with the approval of the Northwell Health System Institutional Review Board. As this is a retrospective study utilizing de-identified data collected from the New York State and STS databases, specific waiver of the need for individual patient consent was granted by the Institutional Review Board.

All patients who underwent TAVR for severe, symptomatic aortic stenosis from October 2016 to December 2018 were included in this study. All patients were implanted with either a Medtronic Evolut (Medtronic, Minneapolis, MN) or Edwards SAPIEN 3 (Edwards Lifesciences, Irvine, CA) valve. Patients with preexisting PPM or implanted cardiac defibrillators or those undergoing a valve-in-valve procedure were excluded. Preoperative characteristics included in the Emory risk score were collected for each patient, including preoperative QRS duration, preoperative RBBB, the presence of syncope as a symptom, and degree of valve oversizing. A risk score of 0–5 was calculated for each patient, with 1 point allocated for QRS ≥140 ms, syncope, and valve oversizing of ≥16%, and 2 points allocated for preoperative RBBB.

The following baseline preoperative data were also collected for each patient: age, gender, valve type, valve size, Society of Thoracic Surgery Predicted Risk of Mortality (STS-PROM), operator risk stratification, and other risk factors and comorbidities (i.e., dialysis, creatinine, cerebrovascular disease, peripheral artery disease, New York Heart Association heart failure class, diabetes, body mass index, and preoperative ejection fraction). The primary clinical endpoint of interest was the requirement of PPM post-TAVR.

Continuous variables are expressed as mean ± standard deviation and compared using Student's *t*-test. Categorical variables are expressed as percentages and compared using the chi-square test or Fisher's exact test, where appropriate. Differences in preoperative characteristics between patients who required PPM and those who did not were assessed. The association of each individual risk factor with the requirement of PPM was assessed using multivariable logistic regression analysis for both balloon-expandable and self-expanding valves. The accuracy of the Emory risk score and individual factors were assessed with area under receiver-operating characteristic (ROC) curve. Data analysis was performed retrospectively. All statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

Preoperative characteristics and risk factors, including the components of the Emory risk score, are presented in Table 1. Of the 479 patients who underwent TAVR, 99 (20.7%) patients required PPM. Of the patients that underwent PPM, 86 (86.9%) patients required a pacemaker during the index TAVR admission, and 13 (13.1%) patients required a pacemaker following discharge. Among the entire cohort, 236 (49.3%) received balloon-expandable valves and 243 (50.7%) received self-expanding valves. Thirty-eight (16.1%) of patients receiving balloon-expandable valves required PPM, while 61 (25.1%) of patients receiving self-expanding valves required PPM ($p = 0.015$).

Table 1: Baseline patient characteristics: post-TAVR PPM versus no PPM.

Preoperative characteristics	No PPM $N = 380$	PPM $N = 99$	p value
Male	169 (44.6)	52 (52.5)	0.158
Age, years	82.3 ± 7.8	82.2 ± 10.5	0.960
Valve type			0.015
Self-expanding	182 (47.9)	61 (61.6)	—
Balloon-expandable	198 (52.1)	38 (38.4)	—
RBBB	29 (7.7)	30 (30.3)	<0.001
QRS duration	99.5 ± 23.7	115.3 ± 27.6	<0.001
QRS >140 ms	35 (9.2)	23 (23.2)	<0.001
Valve oversizing, %	12.91 ± 10.26	14.62 ± 9.83	0.136
Valve oversizing >16.0%	215 (56.6)	53 (53.5)	0.586
Syncope	13 (3.4)	5 (5.1)	0.447
Emory risk score			<0.001
Score = 0	178 (46.8)	32 (32.3)	—
Score = 1	159 (41.8)	32 (32.3)	—
Score = 2	23 (6.1)	12 (12.1)	—
Score = 3	14 (3.7)	15 (15.2)	—
Score = 4	6 (1.6)	8 (8.1)	—
Score = 5	0 (0.0)	0 (0.0)	—
STS-PROM, %	6.2 ± 6.1	6.3 ± 3.6	0.901
Operator stratification			0.692
Low risk	1 (0.3)	0 (0.0)	—
Intermediate risk	206 (54.2)	49 (50.0)	—
High risk	171 (45.0)	49 (50.0)	—
Heart failure (NYHA)			0.595
Class II	102 (26.9)	22 (22.2)	—
Class III	252 (66.5)	69 (69.7)	—
Class IV	25 (6.6)	8 (8.1)	—
Ejection fraction, %	61.8 ± 13.4	60.4 ± 13.5	0.352
Albumin, g/dL	3.9 ± 0.7	3.9 ± 0.7	0.942
Creatinine, mg/dL	1.3 ± 1.3	1.6 ± 1.7	0.079
Dialysis	13 (3.4)	4 (4.0)	0.766
Cerebrovascular disease	23 (6.1)	8 (8.1)	0.465
Peripheral artery disease	53 (13.9)	13 (13.1)	0.833
Diabetes	125 (32.9)	32 (32.3)	0.914
Body mass index	27.9 ± 5.9	28.4 ± 6.8	0.498

Continuous factors are given as mean (±standard deviation), compared using Student's *t*-test. Frequency and percent are given for categorical factors, compared using the chi-square test. NYHA = New York Heart Association; PPM = permanent pacemaker implantation; RBBB = right bundle branch block; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

The incidence of the elements included in the risk score among all patients was as follows: 12.3% of the patients had RBBB, 12.1% had a QRS duration ≥140 ms, 56% had valve oversizing ≥16%, and 3.8% had a history of syncope. Patients who required PPM post-TAVR were more likely to have preoperative RBBB (30.3% versus 7.7%, $p < 0.001$), had longer mean QRS duration (115.3 ± 27.6 versus 99.5 ± 23.7, $p < 0.001$), and were more likely to have a QRS duration ≥140 ms (23.2% versus 9.2%, $p < 0.001$). There was no significant difference in valve oversizing, presence of preoperative syncope, and other demographics and comorbidities between patients that received PPM versus those that did

not. Patients who required PPM after TAVR had a higher Emory risk score as compared to those who did not require PPM ($p < 0.001$, Table 1).

The components of the Emory risk score assessed using multivariable analysis by valve type are presented in Table 2. Of the four risk score components, preoperative RBBB was the only independent predictor of pacemaker requirement, regardless of valve type. Among patients receiving balloon-expandable valves, 41.4% of patients were with RBBB-required pacemakers (OR 3.89, $p = 0.010$); among those receiving self-expanding valves, 60.0% of patients were with RBBB-required pacemakers (OR 5.75, $p < 0.001$). Although QRS ≥140 ms was associated with PPM insertion after TAVR in the univariate analysis, it was no longer significant in the multivariable analysis for both valve types.

The area under the ROC curve for the Emory risk score to discriminate for patients requiring PPM after TAVR was 0.645 for balloon-expandable valves (Figure 1) and 0.657 for self-expanding valves (Figure 2). The area under the ROC curve for the preoperative RBBB to discriminate for patients requiring PPM after TAVR was 0.615 for both balloon-expandable and self-expanding valves. The Emory risk score did not demonstrate significant superiority in discriminatory power over the presence of RBBB alone in predicting post-TAVR PPM requirements ($p = 0.350$ for balloon-expandable valves and $p = 0.151$ for self-expanding valves).

4. Discussion

Our results demonstrated that the Emory risk score, which stratifies patients based on QRS duration, preexisting RBBB, preoperative syncope, and valve oversizing have similar discriminatory ability for need for PPM after TAVR for balloon-expandable and self-expanding valves. The risk score, however, does not provide significantly increased discriminatory power over presence of preoperative RBBB alone.

The Emory risk score is the first contemporary scoring system to predict the need for PPM among patients undergoing TAVR [9]. It was developed by Kiani et al. and derived from data from a single institution undergoing Edwards SAPIEN 3 valves. It incorporates four characteristics: history of syncope, right bundle branch block, QRS duration ≥140 ms, and valve oversizing ≥16%. Kiani et al. reported an area under the curve for their Emory risk score of 0.778 in the validation cohort of patients undergoing SAPIEN 3 valves. Our study is the first to apply the Emory risk score to patients receiving Evolut balloon-expandable valves. While we found that the Emory risk score has similar discriminatory utility for risk of PPM after TAVR for both balloon-expandable and self-expanding valves, the area under the curve from our patient sample was significantly lower than that obtained by Kiani et al. (0.615 for both balloon-expandable valves and self-expanding valves). Differences in implant technique and institutional guidelines for PPM after TAVR may account for the differences in discriminatory utility of the risk score. This highlights the difficulty in developing universal risk scoring algorithms as algorithms developed in one institution may not be applicable to other institutions secondary to differences in practice patterns.

Incidence of elements of the risk score may vary by institution, further complicating the development of a universal algorithm. This is particularly true in elements of the risk score that are operator dependent. For instance, the incidence of valve oversizing ≥16% was substantially higher in our cohort relative to the Emory derivation cohort (56% versus 23.6%), highlighting likely differences in the valve type and size selection. Notwithstanding, studies have shown that >20% oversizing in self-expanding valves does not significantly increase the rate of PPM insertion [10]; thus, we do not believe that this variation would explain the differences in our outcomes. Further, the incidence of history of syncope was lower in our cohort (3.8% versus 9.4%). While lower than the Emory study, this remains consistent with the literature [11]. The incidence of RBBB (12.3% versus 15.6%) and QRS duration ≥140 ms (12.1% versus 13.6%) were comparable between our cohort and the derivation cohort in the Emory study.

In our sample, 20.7% of patients required PPM implantation after TAVR. In patients receiving balloon-expandable valves, the PPM rate was 16.1% versus 25.1% in self-expanding valves. The finding that PPM insertion rate is higher in patients receiving self-expanding valves is consistent with the literature. Previously published studies have shown the PPM rate to be as high as 17% for balloon-expandable valves [12] and 40% for self-expanding valves [13]. Preoperative RBBB was the only independent predictor of PPM implantation in our cohort, regardless of valve type. This is consistent with existing literature in which preoperative RBBB has been shown to be a well-described predictor of postoperative PPM implantation. In our study, preoperative RBBB offered similar discriminatory utility for need for PPM after TAVR as the Emory risk score [6, 14, 15]. While QRS duration was found to be a significant predictor of PPM on univariate analysis, there was no significance on multivariable analysis. This is likely due to the association between QRS duration and RBBB. Valve oversizing was not an independent predictor of PPM in our study, which is consistent with prior literature [16, 17], albeit not consistent with the Emory study. Similarly, while syncope is an independent predictor of need for PPM in the Emory risk score, we did not find it to be an independent predictor in our study. The low prevalence of syncope in our patient population may not have provided adequate statistical power to show significance.

There are other electrical, procedural, and anatomical factors that have been shown to be associated with an increased need for PPM after TAVR including first-degree heart block, implantation depth, length of the membranous septum, pre and postdilation of the prosthesis, and aortic annulus calcium score [18–22]. Our current study did not evaluate the association of such factors with PPM insertion as the primary objective of this study was to validate the Emory risk score which does not incorporate such factors.

There are several limitations to this study that should be acknowledged. First, there are no specific recommendations for PPM implantation after TAVR. Decisions to proceed

Table 2: Multivariable analysis of predictors of postoperative PPM rates, by valve type.

Variable	Balloon-expandable		Self-expanding	
	OR (95% CI)	p value	OR (95% CI)	p value
Oversize >16%	1.58 (0.66, 3.83)	0.310	0.61 (0.32, 1.16)	0.134
Baseline RBBB	3.63 (1.31, 10.05)	0.013	5.57 (2.20, 14.10)	<0.001
Baseline QRS >140 ms	1.84 (0.62, 5.45)	0.270	1.15 (0.43, 3.06)	0.780
History of syncope	1.93 (0.42, 8.91)	0.400	1.36 (0.26, 7.07)	0.710
AUC of Emory risk score	0.645		0.657	

Odds ratios are given with 95% confidence interval. AUC = area under curve; PPM = permanent pacemaker implantation; RBBB = right bundle branch block.

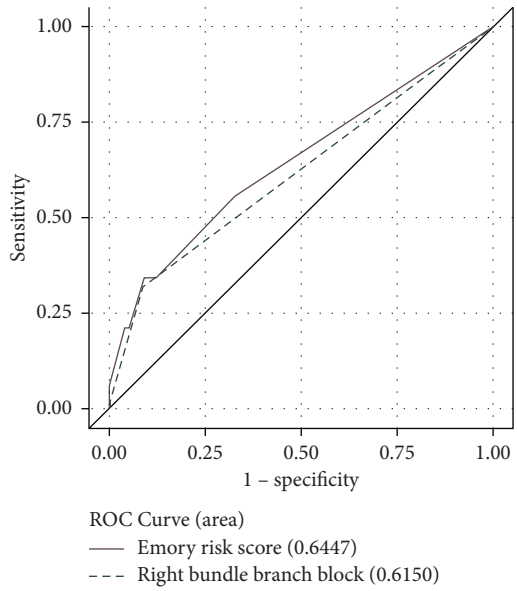

Figure 1: ROC curve for balloon-expandable valves.

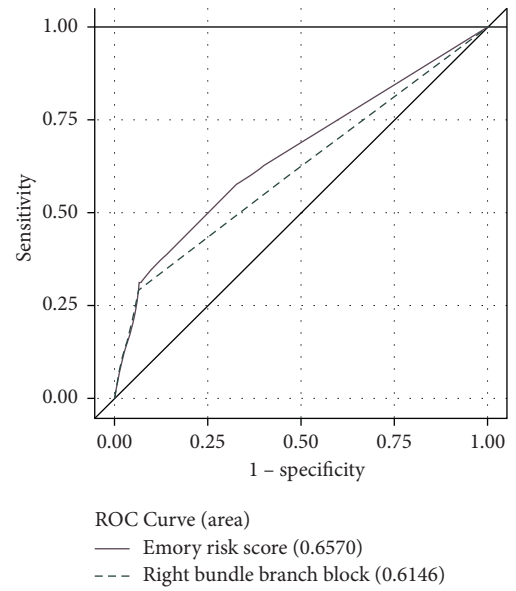

Figure 2: ROC curve for self-expanding valves.

with PPM may therefore be subject to selection bias. Second, while our overall sample size was large, the subset of patients who met specific criteria of the risk score was more limited. This may lead to type II error when evaluating the association of the specific criteria with requirement for PPM. However, the main objective of this study was to validate the Emory risk score, not the individual predictors of PPM placement. Third, although all clinical information relevant to the Emory risk score was independently validated for the purpose of this study, the study remains retrospective in nature and, therefore, has all the limitations of a retrospective study. Fourth, patients in this study received either SAPIEN 3 or Evolut valves. PPM implantation rate varies by both valve type and generation. The new-generation SAPIEN 3 valves have been associated with higher PPM implantation rates relative to the old-generation SAPIEN XT valves [23]. In contrast, the new-generation Evolut valves have lower PPM rates as compared with their first-generation counterparts [24]. As such, the results of this study may not be applicable to valve types and/or generations that are not utilized in our study population. Finally, as with all single-center studies, the results of this study may not be generalizable to other institutions. In fact, our finding that the Emory risk score displayed significantly less discriminatory utility in our patients as compared to its original validation cohort highlights this limitation.

5. Conclusions

In our cohort, the Emory risk score had modest predictive utility for PPM insertion after TAVR for both balloon-expandable and self-expanding prostheses. The risk score did not offer better discriminatory utility than that of preoperative RBBB alone.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

Bruce Rutkin, MD, serves as a consultant for Medtronic. All the other authors have nothing to disclose and have no conflicts of interest.

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Research Article

Clinical Impact of Preexisting Right Bundle Branch Block after Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

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Introduction. Transcatheter aortic valve replacement (TAVR) is now the treatment of choice for patients with severe aortic stenosis regardless of their surgical risk. Right bundle branch block (RBBB) can be a predictor for development of significant atrioventricular (AV) block after TAVR, requiring permanent pacemaker implantation (PPI). However, data related to the risk of PPI requirement with preexisting RBBB is scarce. Hence, this systematic review and meta-analysis aims to assess clinical outcomes of patients undergoing TAVR with RBBB on preexisting electrocardiogram. *Methods*. We performed a systematic literature review to identify randomized and nonrandomized clinical studies that reported any clinical impact of patients undergoing TAVR with preexisting RBBB. A total of eight databases including PubMed (Medline), Embase, Cochrane Library, ACP Journal Club, Scopus, DARE, and Ovid containing articles from January 2000 to May 2020 were analyzed. *Results*. We identified and screened 224 potential eligible publications through the databases and found 14 relevant clinical trials for a total of 15,319 participants. There was an increased 30-day pacemaker implantation rate of 38.1% in the RBBB group compared to 11.4% in the no RBBB group with a risk ratio of 3.56 (RR 3.56 (95% CI 3.21–3.93, $p < 0.01$)). There was an increased 30-day all-cause mortality in the RBBB group of 9.5% compared with 6.3% in the no RBBB group with an odds ratio of 1.60 (OR 1.60 (95% CI 1.14–2.25, $p < 0.01$)). *Conclusion*. This study indicates that patients with preexisting RBBB have higher incidence of PPI and all-cause mortality after TAVR compared with patients without RBBB. Further trials are needed to compare the clinical outcomes based on TAVR valve types and assess the benefit of PPI in patients with new-onset RBBB after TAVR.

1. Introduction

Transcatheter aortic valve replacement (TAVR) has revolutionized the current era of modern medicine by becoming the treatment of choice for patients with symptomatic severe aortic stenosis regardless of their surgical risk [1]. However, the high frequency of conduction disturbances, such as left bundle branch block (LBBB) and atrioventricular block, and the subsequent need for permanent pacemaker implantation (PPI) remain a challenge [2, 3]. Preexisting right bundle branch block (RBBB) has been established as a risk factor for PPI after TAVR [4, 5]. Preexisting RBBB in the general population and in patients with heart disease has been associated with increased risk of mortality [6]. However, data on the prognostic impact of preexisting RBBB on clinical outcomes after TAVR is limited. This systematic review and meta-analysis evaluates the impact of preexisting RBBB on clinical outcomes in patients undergoing TAVR.

2. Methods

The main objective of this review was to assess if preexisting RBBB increased the risk of having PPI after TAVR. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement extension for network meta-analysis. The PRISMA flow diagram was used to depict the four phases of the review including identification, screening, eligibility, and inclusion. The PRISMA statement

contains a checklist of 27 items required of systematic reviews and meta-analyses. The review was not registered a priori. No ethical approval was required since this meta-analysis uses only public published data.

2.1. Search Strategy. We performed a systematic literature review to identify randomized and nonrandomized clinical studies that reported any clinical impact of patients undergoing TAVR with preexisting RBBB. Searches were limited to peer-reviewed primary research articles published in English, French, and Spanish up to May 17th, 2020. This research involved human subjects and described the clinical impact of RBBB on patients who underwent TAVR. We developed the search strategy according to available guidance from the Cochrane Collaboration.

The search strategy in MEDLINE explored Medical Subject Heading (MeSH) terms related to patients with TAVR and history of preexisting RBBB. The following search strategy was applied to search MEDLINE and we adapted it for the other databases: ("transcatheter aortic valve replacement"[MeSH Terms] OR ("transcatheter"[All Fields] AND "aortic"[All Fields] AND "valve"[All Fields] AND "replacement"[All Fields] AND "implantation"[All Fields])) OR "transcatheter aortic valve replacement"[All Fields]) AND ("bundle-branch block"[MeSH Terms] OR ("bundle-branch"[All Fields] AND "block"[All Fields]) OR "bundle-branch block"[All Fields] OR ("right"[All Fields] AND "bundle"[All Fields] AND "branch"[All Fields] AND "block"[All Fields]) OR "right bundle branch block"[All Fields]). The articles found to be relevant during the hand search were stored in EndNote. Selected articles underwent full evaluation to assess their potential inclusion in the systematic review.

2.2. Study Selection. Articles were selected for inclusion based on predefined criteria, which included age, sex, TAVR, and preexisting RBBB, and the primary or secondary outcomes being mortality and clinical outcomes. Exclusion criteria were patients with LBBB and patients with normal sinus rhythm. We excluded case reports and studies with fewer than 10 subjects.

Two authors (GS, SL) independently read the trials and screened the abstracts to choose potentially relevant articles. Risk of bias in the studies was assessed at an individual level of each study. Selected articles underwent full evaluation to assess their potential inclusion in the systematic review.

2.3. Statistical Analysis. Data were analyzed using Review Manager Software 5.3. We used fixed effects to assess the combined risk estimates according to I2 statistics. Analysis to determine sensitivity and publication bias was detected by funnel plots. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Literature Search. Our search yielded 224 abstracts. We excluded 199 studies at the abstract level and selected 24 full-text articles for detailed assessment; 14 studies were ultimately included in our systematic review and 11 studies were included in our meta-analysis. Figure 1 describes the flowchart of included studies.

3.2. Baseline Characteristics of the Studies. Table 1 shows the baseline characteristics of the included studies. All studies were published between 2010 and 2020. The 14 studies included 15,319 patients with 1,654 cases of preexisting RBBB. In nine of the included studies, preexisting RBBB was retrospectively identified as a risk factor for PPI. Therefore, baseline characteristics for patients with preexisting RBBB were not reported in these nine studies. For studies that did report characteristics for both RBBB and non-RBBB patients, the median age of the participants was 82.0 IQR (81.4–84.0). The median percentage of men was 49.1 IQR (39.2–58.4). For studies that reported these selected risk factors, the median percentage of hypertension was 76.1 IQR (74.8–81.9), the median percentage of diabetes was 30.2 IQR (28.9–32.8), the median BMI average was 26.7 IQR (24.3–27.1), the median percentage of coronary heart disease was 56.4 IQR (34.4–64.5), the median percentage of heart failure greater than or equal to New York Heart Association Class III was 74.7 IQR (47–77), and the median percentage of chronic obstructive pulmonary disease was 21.6 IQR (19.2–27.7). Current smoking percentage was 20.6% in the preexisting RBBB group and 19.9% in the no RBBB group for the one study that reported this risk factor. Racial characteristics were not reported by the included studies that used separate preexisting RBBB groups. Multiple centers were used by eight of the included studies and Europe, North America, South America, Japan, and Israel were the geographic regions represented.

3.3. PPI in Patients with Preexisting RBBB after TAVR. Auffrett et al., Husser et al., van Gils et al., Tovia-Brodie et al., and Watanabe et al. reported various clinical outcomes in patients with preexisting RBBB after TAVR as summarized in Table 2 [7–11]. Auffrett et al. found patients with preexisting RBBB to have higher 30-day PPI rates (40.1% vs. 13.5%; $p < 0.001$) [7]. Husser et al. reported a 30-day PPI rate of 39.2% in patients with preexisting RBBB after TAVR and found the ACURATE neo (Boston Scientific, Marlborough, Massachusetts) to have a lower rate of PPI when compared with the Edwards Sapien 3 (Edwards Lifesciences, Irvine, California) [8]. Van Gils et al. reported a 30-day PPI rate of 41.0% in patients with preexisting RBBB after TAVR and found the Boston Scientific Lotus (Boston Scientific, Marlborough, Massachusetts) to have the highest rate of PPI and the Edwards Sapien 3 and XT (Edwards Lifesciences, Irvine, California) to have the lowest rate of PPI [9]. Watanabe et al. found patients with preexisting RBBB to have higher 30-day rates of PPI (17.6% vs. 2.9%; $p < 0.01$) [10]. Tovia-Brodie et al. did not report a 30-day PPI rate as they compared whether prophylactic PPI improved outcomes in patients with preexisting RBBB [11].

The nine remaining studies identified risk factors for 30-day PPI as summarized in Table 2 [12–20]. Meduri et al.

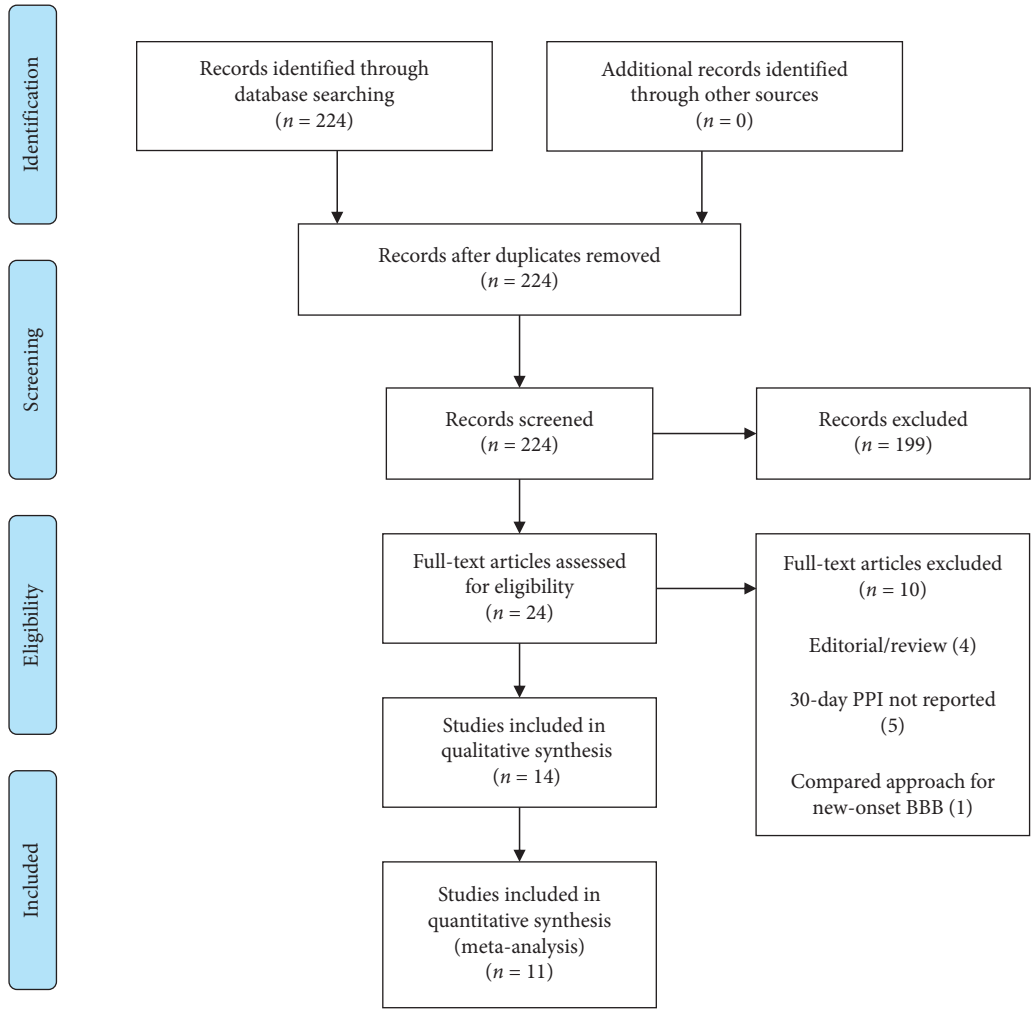

Figure 1: Flowchart of the included studies.

identified preexisting RBBB, female sex, and depth of implantation to be a risk factors for 30-day PPI in their retrospective review of the REPRISE III (The Repositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus Valve System-Randomized Clinical Evaluation) trial [12]. Nazif et al. identified preexisting RBBB, prosthesis to left ventricular outflow tract diameter ratio, and left ventricular end-diastolic diameter as risk factors for 30-day PPI in their retrospective review of the PARTNER (Placement of AoRtic TraNscathetER Valves) trial [15]. Dhakal et al., Roten et al., Erkapic et al., Koos et al., and Fraccarro et al. all identified preexisting RBBB as a risk factor for PPI after TAVR in their retrospective single-center studies [13, 16–19]. Bagur et al. found preexisting RBBB as the only risk factor for PPI after TAVR in their comparison to surgical aortic valve replacement [14]. Guetta el al. identified preexisting RBBB and deep valve implantation as risk factors for PPI after TAVR in their retrospective review at three referral centers in Israel [20].

Meta-analysis of the included studies revealed a higher 30-day PPI rate of 38.1% in patients with preexisting RBBB when compared to a 30-day PPI rate of 11.4% in patients with no RBBB. This is a statistically significant increase in 30-day PPI rate in patients with preexisting RBBB with a risk ratio of 3.56 (95% CI 3.21–3.93, $p < 0.01$). The forest plot for 30-day PPI rate is shown in Figure 2. Husser et al., Tovia-Brodie et al., and van Gils et al. results were not included in the 30-day PPI meta-analysis as these studies only included patients with preexisting RBBB and made no comparisons to patients without RBBB. In the two included studies that reported 30-day mortality as an outcome, meta-analysis revealed a higher 30-day mortality rate of 9.5% in patients with preexisting RBBB compared to a 30-day mortality rate of 6.3% in patients with no RBBB. This is a statistically significant increase in 30-day mortality in patients with preexisting RBBB with a risk ratio of 1.60 (95% CI 1.14–2.25, $p < 0.01$). The forest plot for 30-day morality rate is shown in Figure 3.

4. Discussion

This is the first systematic review and meta-analysis to demonstrate the impact of preexisting RBBB on new pacemaker implantation after TAVR. Our findings are derived from 14 studies reporting clinical outcomes in a total of 1,654 patients with preexisting RBBB after TAVR. The

Table 1: Baseline characteristics of the included studies.

Study author, year	Region	Sample size	RBBB status	Number of patients	Mean age (years)	Men (%)	HTN (%)	Smoking (%)	DM (%)	BMI (kg/m^2)	CHD (%)	NYHA > III (%)	COPD (%)
Watanabe et al., 2016	Japan	749	RBBB	102	85.0 (81.0–89.0)	39.2	80.4	20.6	26.4	22.2 (19.5–24.9)	28.0	52	21.6
			No RBBB	647	85.0 (82.0–88.0)	32.9	74.8	19.9	25.0	21.7 (19.3–24.1)	24.2	47	20.2
van Gils et al., 2017	Europe	2,845	RBBB	306	83 ± 7	63	NR	NR	30	27 ± 5	NR	77	30
Auffrett et al., 2017	Europe, Canada, S. America	3,527	RBBB	362	81.7 ± 7.3	58.4	74.7	NR	28.9	27.2 ± 5.2	59.2	74.7	29.9
			No RBBB	3165	81.4 ± 7.6	49.1	77.2	NR	30.2	26.7 ± 5.1	53.5	74.7	25.5
Husser et al., 2019	Germany and Switzerland	4,305	RBBB -S3	198	82.0 (78.0–85.0)	27.8	86.4	NR	32.8	26.4 (23.7–29.8)	68.2	78.3	18.2
			RBBB -NEO	98	81.0 (78.0–84.0)	39.8	92.9	NR	32.7	27.9 (24.7–31.0)	66.3	79.6	14.3
Tovia-Brodie et al., 2020	Israel	90	RBBB	50	81 ± 8	58	70	NR	34	NR	NR	18	NR
			RBBB -PM	40	84 ± 6	75	75	NR	43	NR	NR	20	NR
Meduri et al., 2019	N. America, Europe, Australia	912	RBBB	85	NR	NR	NR	NR	NR	NR	NR	NR	NR
			No RBBB	827	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dhakal et al. 2020	Arizona, USA	176	RBBB	36	NR	NR	NR	NR	NR	NR	NR	NR	NR
			No RBBB	140	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bagur et al. 2012	Canada	411	RBBB	20	NR	NR	NR	NR	NR	NR	NR	NR	NR
			No RBBB	391	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nazif et al. 2015	United States, Canada, Germany	1,973	RBBB	312	NR	NR	NR	NR	NR	NR	NR	NR	NR
			No RBBB	1661	NR	NR	NR	NR	NR	NR	NR	NR	NR
Roten et al. 2010	Switzerland	67	RBBB	13	NR	NR	NR	NR	NR	NR	NR	NR	NR
			No RBBB	54	NR	NR	NR	NR	NR	NR	NR	NR	NR
Erkapic et al. 2010	Germany	50	RBBB	7	NR	NR	NR	NR	NR	NR	NR	NR	NR
			No RBBB	43	NR	NR	NR	NR	NR	NR	NR	NR	NR
Koos et al. 2011	Germany	80	RBBB	6	NR	NR	NR	NR	NR	NR	NR	NR	NR
			No RBBB	74	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fraccaro et al. 2011	Italy	64	RBBB	8	NR	NR	NR	NR	NR	NR	NR	NR	NR
			No RBBB	56	NR	NR	NR	NR	NR	NR	NR	NR	NR
Guetta et al. 2011	Israel	70	RBBB	11	NR	NR	NR	NR	NR	NR	NR	NR	NR
			No RBBB	59	NR	NR	NR	NR	NR	NR	NR	NR	NR

Values are mean ± SD, median (interquartile range), or *n* (%). NR: not reported; HTN: hypertension; DM: diabetes mellitus; CHD: coronary heart disease; RBBB: right bundle branch block; BMI: body mass index; NYHA: New York Heart Association; COPD: chronic obstructive lung disease.

Table 2: Outcomes of patients with preexisting RBBB after TAVR summary table.

References	Year	Region	Centers	Patients w/RBBB	Valves	Primary outcome	Other outcomes
Watanabe et al.	2016	Japan	8	102	ES-XT	Various clinical outcomes	PPI, mortality, bleeding, etc.
van Gils et al.	2017	Europe	4	306	CoreValve ES-XT ES-3 Lotus	PPI within 30 days	New onset conduction disturbances
Auffrett et al.	2017	Europe, Canada, S. America	Not reported	362	Not reported	All-cause mortality	CV death, SCD, PPI
Husser et al.	2019	Germany and Switzerland	7	296	Neo ES-3	PPI within 30 days	Device failure
Tovia-Brodie et al.	2020	Israel	1	90	CoreValve ES-3 ES-XT Evolute R Lotus	Outcomes comparison for prophylactic PM	Predictors for pacing
Meduri et al.	2019	N. America, Europe, Australia	55	85	CoreValve Lotus	PPI within 30 days	Predictors for pacing, mortality, stroke, rehospitalization
Dhakal et al.	2020	Arizona, USA	1	36	Not reported, balloon expandable and self-expanding	PPI within 30 days	Predictors for pacing
Bagur et al.	2012	Canada	3	20	CE ES ES-XT	PPI within 30 days	Predictors for pacing
Naziif et al.	2015	United States, Canada, Germany	21	312	ES	PPI within 30 days	Predictors for pacing
Roten et al.	2010	Switzerland	1	13	CoreValve ES	PPI within 30 days	Predictors for pacing
Erkapic et al.	2010	Germany	1	7	CoreValve ES	PPI within 30 days	Predictors for pacing
Koos et al.	2011	Germany	1	6	CoreValve ES	PPI within 30 days	Predictors for pacing
Fraccaro et al.	2011	Italy	1	8	CoreValve	PPI within 30 days	Predictors for pacing
Guetta et al.	2011	Israel	3	11	CoreValve	PPI within 30 days	Predictors for pacing

PPI: permanent pacemaker implantation; SCD: sudden cardiac death; CV: cardiovascular; ES-XT: Edwards SAPIEN XT; ES-3: Edwards SAPIEN 3; ES: Edwards SAPIEN; CE: Cribier-Edwards.

incidence of new PPI was significantly increased in patients with preexisting RBBB after TAVR. Increased all-cause and cardiovascular mortality has been demonstrated in patients with preexisting RBBB after TAVR.

The prognostic value of RBBB has shown mixed results in previous studies with healthy participants and with patients with heart disease [21–28]. Bussink et al. found RBBB to be associated with increased all-cause and cardiovascular mortality in both men and women from the general population [21]. Abdel-Qadir et al. found no prognostic value of RBBB in patients hospitalized with heart failure; however, Barshehet et al. found RBBB to be associated with increased long-term mortality risk in hospitalized patients with systolic heart failure [22, 23]. Melgaregjo-Moreno et al. found new permanent RBBB to be associated with increased 30-day and seven-year mortality in patients with acute myocardial infarction [24]. Wong et al. found RBBB accompanying anterior acute myocardial infarction to be associated with increased 30-day mortality [28]. Long-term epidemiological studies in men from the general population have found a higher incidence of RBBB with aging, hypertension, and diabetes mellitus [25, 26]. Zhang et al. found RBBB in women with cardiovascular disease to be associated with an increased risk of coronary heart disease death over 14 years of follow-up. However, RBBB in women free of cardiovascular disease was not associated with increased mortality [27]. Meta-analysis completed by Xiong et al. found RBBB to be associated with an increased risk of mortality in the general population and in patients with heart disease [6]. The exact mechanism by which RBBB increases mortality has not been elucidated, although underlying conduction system disease can predispose patients to various arrhythmias. The association of RBBB with decreased left ventricular ejection fraction in patients with prior myocardial infarction or heart failure may provide a clue towards the underlying mechanism [23, 28]. The various comorbidities and underlying heart disease in patients with RBBB may also explain the increased mortality.

A previous meta-analysis by Siontis et al. demonstrated the significance of RBBB in the requirement for PPI after TAVR. Male sex, first-degree AV block, left anterior hemiblock, and intraprocedural AV block were also found to be predictive of PPI after TAVR [4]. The newer studies highlighted in this meta-analysis emerged to specifically focus on the clinical impact of preexisting RBBB after TAVR, which is important for improving patient outcomes [7–10].

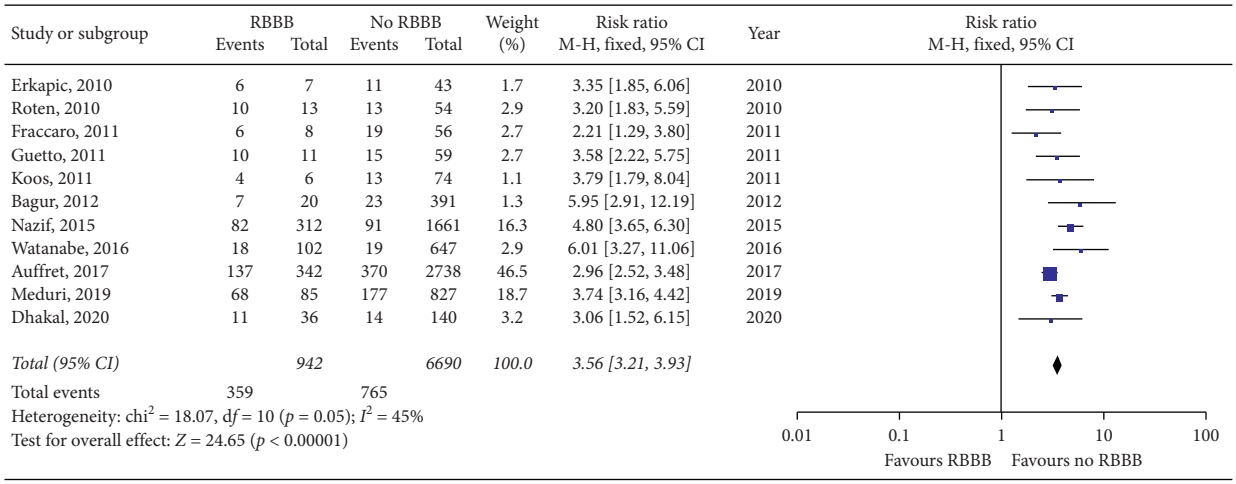

Figure 2: Forest plot of 30-day PPI rates in patients with and without preexisting RBBB after TAVR.

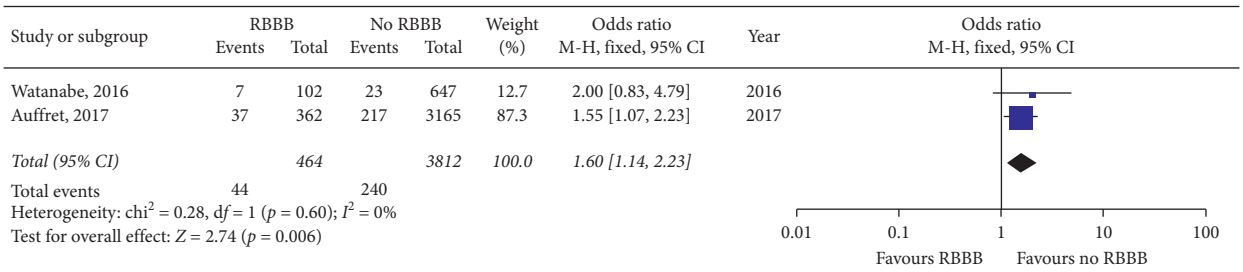

Figure 3: Forest plot of 30-day all-cause mortality rate in patients with and without preexisting RBBB after TAVR.

In TAVR, conduction disturbances are a common complication likely due to direct insult to the left bundle branch because of the anatomical relationship between the aortic annulus and the conduction system [29]. New-onset LBBB develops in 5% to 65% of patients undergoing TAVR, and its persistence can result in PPI in 15% to 20% of cases [29]. New-onset LBBB after TAVR has been associated with increased risk of cardiac death and PPI at one year follow-up [30]. Preexisting RBBB with new-onset LBBB after TAVR will usually generate PPI during the index hospitalization. Chorianopoulos et al. demonstrated that postprocedural bradyarrhythmias develop in 36.2% of patients after TAVR with 3.8% remaining >96 hours after TAVR. Preexisting RBBB was found to be the only predictor of postprocedural bradyarrhythmias [5]. Late-onset new LBBB >3 months after TAVR is a rare complication seen in only 0.8% of patients [31]. Development of high degree AV block is a common complication seen in up to 58.8% of patients with preexisting BBB or BBB occurring during TAVR [32]. These late conduction disorders in patients with preexisting RBBB can lead to cardiac complications such as heart failure and sudden cardiac death.

This systematic review and meta-analysis reveals increased PPI, all-cause mortality, and cardiac mortality in patients with preexisting RBBB after TAVR. This is clinically significant given the recent trend towards early discharge after TAVR [33]. Patients with preexisting RBBB may need additional monitoring after TAVR to detect conduction disturbances and ensure safe discharge. Early electrocardiographic monitoring may be beneficial as part of the TAVR work-up as Urena et al. found that newly diagnosed preprocedural arrhythmias are common and associated with higher rates of PPI after the procedure [34]. Additional strategies for managing preexisting RBBB in patients undergoing TAVR may emerge as we understand more about conduction disturbances following TAVR.

Preexisting RBBB is a common underlying conduction disturbance in patients undergoing TAVR and is associated with increased risk of PPI at 30 days and all-cause and cardiovascular mortality. Future studies will be needed to evaluate optimal management of patients with preexisting RBBB undergoing TAVR. Larger prospective studies are needed to investigate the optimal timing for PPI after TAVR and to evaluate prophylactic PPI in patients with preexisting RBBB prior to TAVR. Larger prospective studies are needed to investigate strategies for early detection of conduction disturbances in patients with preexisting RBBB. Until more data is available, there are many multicenter and literature-based decisional algorithms to guide PPI decision-making [35]. Careful monitoring to detect arrhythmias after TAVR may be necessary to improve clinical outcomes in patients with preexisting RBBB.

5. Limitations

The limitations for this systematic review and meta-analysis are influenced by the limitations of the included studies. Auffrett et al. used a nonrandomized study design that may

lead to confounders influencing the relationship between preexisting RBBB and outcomes [7]. The studies by Husser et al. and van Gils et al. are limited by their observational design [8, 9]. Tovia-Brodie et al. used a single-center retrospective design and did not use randomization to determine prophylactic pacemaker implantation [11]. The results from Watanabe et al. are limited by the relatively small size of the cohort ($n = 749$) and the relatively short median follow-up of 16 months [10]. The retrospective studies of existing data are subject to all of the limitations inherent to this study design [12–20]. Availability of specific data points, such as medication that could influence cardiac conduction, is a common limitation for retrospective studies. Roten et al., Erkapic et al., Koos et al., Fraccaro et al., and Guetta et al. all had small sample sizes of less than 100 patients in their studies [16–20]. All of the included studies are likely influenced by between-center variability and the lack of centralized independent assessment of procedural results and outcomes. The various valve types used in each study likely influence the generalizability of the aggregate data as specific valve types have shown different rates of procedural complications.

6. Conclusion

Conduction issues after TAVR continue to remain a common complication during the management of severe aortic stenosis. This current systematic review and meta-analysis indicates that patients with preexisting RBBB have a higher incidence of PPI and all-cause mortality after 30 days after TAVR compared with patients without RBBB. Further trials are needed to compare the clinical outcomes based on TAVR valve types and assess the benefit of PPI in patients with RBBB after TAVR. In addition, understanding the progression and prevention of electrical conduction disease are necessary for appropriate risk stratification, interventional strategy, and avoidance of pacemaker implantation.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare no conflicts of interest.

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Research Article

Incidence, Predictors, and Outcome of Paravalvular Leak after Transcatheter Aortic Valve Implantation

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Background. Paravalvular leak (PVL) is common after transcatheter aortic valve implantation (TAVI) and has been linked with worse survival. This study aimed to investigate the determinants and outcome of PVL after TAVI and determine the role of aortic valve calcification (AVC) distribution in predicting PVL. *Methods and Results*. This was a retrospective cohort study of 270 consecutive patients who underwent TAVI. Determinants and outcomes of ≥mild PVL were assessed. Matching rates of PVL jet with AVC distribution were calculated. AVC volume, larger annulus dimensions, and transvalvular peak velocity were risk factors for ≥mild PVL after TAVI. AVC volume was an independent predictor of ≥mild PVL. On the other hand, annulus ellipticity, left ventricular outflow tract nontubularity, and diameter-derived prosthesis mismatch were not found to predict PVL after TAVI. PVL jet matched, in varying proportions, with calcification at all aortic root regions, and the highest matching rate was with calcifications at body of leaflets. Moreover, matching rates were less with commissure compared to cusp calcifications. Mild or greater PVL was not associated with all-cause and cardiovascular mortality up to 1-year follow-up. *Conclusion*. ≥mild PVL after TAVI is common and can be predicted by aortic root calcification volume, larger annulus dimensions, and pre-TAVI transvalvular peak velocity, with calcification volume being an independent predictor for PVL. However, annulus ellipticity, left ventricular outflow tract nontubularity, and diameter-derived prosthesis mismatch had no role in predicting PVL. Importantly, body of leaflet calcifications (versus annulus and tip of leaflet) and cusp calcifications (versus commissure calcification) are more important in predicting PVL. No association between ≥mild PVL and increased risk of all-cause and cardiovascular mortality at 1-year follow-up.

1. Introduction

Transcatheter aortic valve implantation (TAVI) is a well-established first-line therapy for severe symptomatic aortic stenosis (AS) patients who are at intermediate or higher surgical risk [1, 2]. Paravalvular leak (PVL) is common after TAVI and has been linked with worse survival [3]. Pre-procedural multislice computed tomography (MSCT) is considered the most reliable method for measuring aortic root parameters in patients undergoing TAVI and has shown to be more advantageous in decreasing rates of PVL compared to echocardiography and, hence, has become the preferred imaging method for TAVI patients [4]. Some risk factors for developing PVL after TAVI have been identified [3, 5–8]. However, there is currently no integrated method which includes all parameters that may predict PVL after TAVI. We sought to conduct the present study to investigate the determinants and outcome of PVL after TAVI and to evaluate the role of aortic valve calcification (AVC) distribution in predicting PVL.

2. Materials and Methods

2.1. Patient Population. Data from 270 consecutive patients with severe symptomatic AS who underwent TAVI at west China hospital of Sichuan University, Sichuan, China, from

April 2012 to November 2017 were retrospectively analyzed. Of these, 3 patients had preexisting surgical valve and 11 patients had no prostheses implantation due to potential risk of coronary occlusion or annulus rupture found during the procedure of predilatation. Thus, 256 patients were finally included. All included patients have undergone MSCT and transesophageal or transthoracic echocardiography (TEE, TTE) before TAVI for prosthesis sizing and selection of vascular access and TEE or TTE during the procedure for PVL assessment. The baseline surgical operative risk was calculated using the Surgeons Risk Score for Prediction of Mortality (STS score) [9].

Based on the severity of PVL after TAVI, patients were divided into two groups: ≥mild PVL group or <mild PVL group. In patients with ≥mild PVL, AVC distribution and PVL jet location were analyzed. Then we calculated the matching rates of AVC distribution and PVL jet for each aortic root region (annulus, body of leaflet, and tip of leaflet) first for all patients and then for each tricuspid aortic valve (TAV), bicuspid aortic valve (BAV) type I, and BAV type 0 subgroups. Finally, matching rates of cusps calcifications and commissures calcifications with PVL jet were analyzed. The study was approved by the institutional review board, and all patients provided written signed consent.

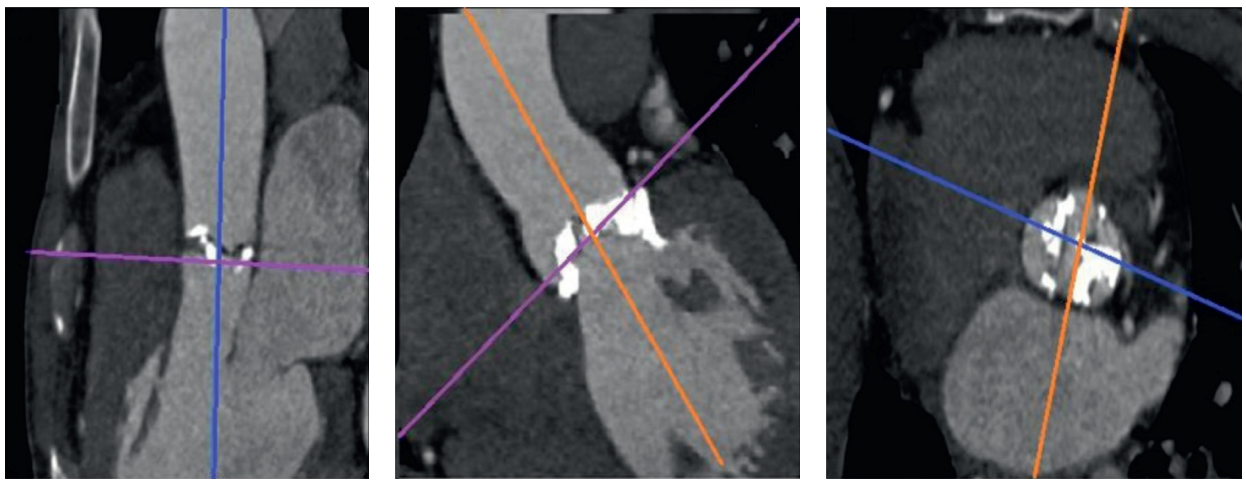
2.2. MSCT Acquisition and Image Analysis. CT scans were performed using a 64-MSCT scanner (SOMATOM Definition Flash; Siemens Healthineers, Erlangen, Germany). Aortic root measurements were accomplished by analyzing pre-TAVI MSCT with OsiriX (OsiriX Foundation, Geneva, Switzerland) (Figure 1). The aortic valve annulus was defined as a plane including the lowest basal attachment points of the aortic valve leaflets in the left ventricular outflow tract (LVOT). MSCT measurements included minimum and maximum annular diameters, area, and circumference, as well as LVOT area. The mean annular diameter was calculated by taking the average of the minimum and maximum diameters. Measurements were performed using midsystolic MSCT images (Figure 2). The area of a completely expanded transcatheter heart valve (THV) was calculated by the following formula: ($3.14 \times \text{radius}^2$ measured in mm^2). On this basis, prosthesis mismatch was calculated using the method described by Buzzatti et al. [10] as follows: ([mean diameter of the prosthesis/mean annulus diameter] × 100). Annular cover index was calculated as follows: ([THV area × area of the annulus/THV area] × 100). Annular ellipticity was calculated as ([maximum annular diameter – minimum annular diameter/maximum annular diameter] × 100) and LVOT nontubularity as ([annular area – LVOT area/annular area] × 100) using a method introduced by Condado et al. [11].

2.3. Analysis of Aortic Valve Calcification. The analysis of calcification was performed using diastolic MSCT images at 75% of the RR interval using calcium volume scoring system [5, 12]. An adjusted threshold of 550 Hounsfield units was used for calcification quantification for most patients [5, 7]. Calcium quantification was performed by a cardiologist experienced in cardiovascular imaging. The aortic root was divided into the following regions in the craniocaudal axis along the long axis of the aortic valve/LVOT: annulus (from 3 mm above to 2 mm below the annular plane) and leaflet (from 3 mm above the annular plane to the superior edge of leaflets). Then each leaflet was visually divided into three-thirds; one-third near the edge of leaflet was considered "tip of leaflet" and the remaining two-thirds were considered "body of leaflet" (Figure 3). Each anatomical region was divided into 4 or 6 sectors to correspond to the leaflets and commissures distribution in BAV and TAV patients, respectively. The total AVC volume was calculated; then AVC distribution was analyzed for each region.

2.4. PVL Assessment. Evaluation of PVL severity was performed at the end of the procedure. PVL was considered positive if it was present after completing all interventions. Echocardiographic assessment was performed by a board-certified echocardiographer experienced in TAVI imaging. PVL was classified using color Doppler imaging into trace, mild, moderate, or severe as suggested by the Valve Academic Research Consortium-2 (VARC-2) consensus recommendations [13]. The location of the PVL jets was determined retrospectively by a board-certified echocardiographer and was blinded to the results of AVC volume and distribution analysis.

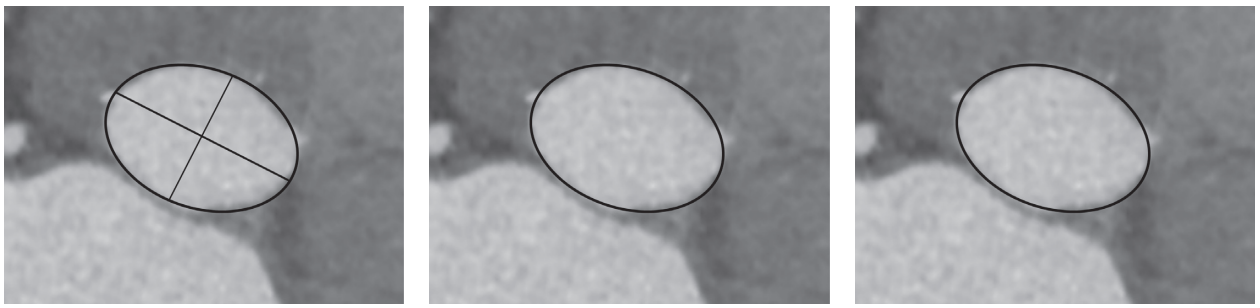
2.5. The Procedure. Implanted prostheses included the self-expandable prosthesis (the first-generation CoreValve, Medtronic, Inc., Minneapolis, Minnesota. Venus A-Valve, Venus MedTech, Inc., Hangzhou, China. VitaFlow Valve, MicroPort, Inc., Shanghai, China; and Taurus One Valve; Peijia, Inc., Suzhou, China), the mechanical-expandable prosthesis (Lotus Valve; Boston Scientific, Inc., Natick, MA, USA), and Edwards SAPIEN XT or SAPIEN3 valves (Edwards LifeSciences, Inc., Irvine, California, USA) (Figure 4). Prosthesis selection depended on prosthesis availability. Based on the agreement of the heart team, all the patients underwent TAVI using the transfemoral access, except for two patients in whom the transsubclavian and transcarotid approach were used due to unfavorable femoral anatomy. Valve sizing was based on the consensus of a multidisciplinary heart team that includes senior interventional cardiologists, cardiovascular surgeons, and imaging specialists. The need for predilatation was decided by the heart team. Similarly, the choice of postdilatation was at the discretion of the heart team and was generally based on the postdeployment echocardiographic imaging showing significant PVL.

2.6. Statistical Analyses. Mean ± standard deviation was used for continuous variables and numbers with percentages for categorical variables. Comparisons between groups were performed with the Chi-square test for categorical variables and Student's *t*-test or Wilcoxon rank-sum test for continuous variables as appropriate. Exploratory multivariable analysis by logistic regression was performed to evaluate the



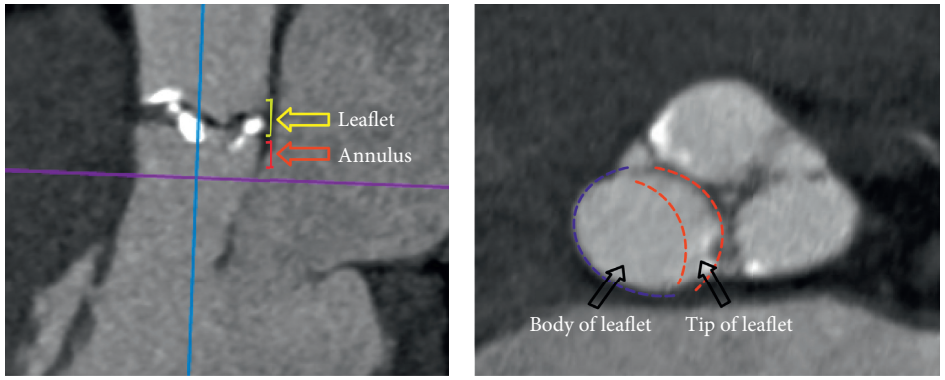
(a) (b) (c)

Figure 1: Multiplanar reconstruction used for the assessment of aortic root. (a) Single oblique sagittal view; (b) coronal view; (c) double oblique transverse view.



(a) (b) (c)

Figure 2: Aortic annular measurements on the MSCT. (a) Maximum and minimum annular diameters; (b) annular area; (c) annular circumference.



(a) (b)

Figure 3: Anatomical regions of the aortic root. (a) Regions of the aortic valve in the craniocaudal axis along the long axis of the aortic valve/LVOT: annulus (from 3 mm above to 2 mm below the annular plane) and leaflet (from 3 mm above the annular plane to the superior edge of leaflets); (b) parts of aortic valve leaflet.

Table 1: Baseline characteristics of patients based on the severity of PVL.

Clinical characteristics	All ($n = 256$)	≥mild PVL ($n = 75$)	<mild PVL ($n = 181$)	p value
Age (year)	74 ± 6	73.68 ± 5.89	74.17 ± 6.19	0.56
Female gender	111 (43.4%)	29 (38.7%)	82 (45.3%)	0.33
Body mass index	22.12 ± 3.44	21.88 ± 3.30	22.35 ± 3.59	0.33
STS SCORE	8.01 ± 4.4	8.1 ± 4.01	7.93 ± 4.78	0.80
History of dyspnoea	230 (89.8%)	65 (86.7%)	165 (91.2%)	0.27
History of chest pain	74 (28.9%)	19 (25.3%)	55 (30.4%)	0.42
History of syncope	41 (16.4%)	13 (17.3%)	28 (15.5%)	0.71
Hypertension	114 (44.5%)	37 (49.3%)	77 (42.5%)	0.32
Diabetes mellitus	46 (17.9%)	15 (20%)	31 (17.1%)	0.59
Chronic obstructive pulmonary disease	162 (63.2%)	50 (66.7%)	112 (61.9%)	0.47
Coronary artery disease	110 (42.9%)	32 (42.7%)	78 (43.1%)	0.95
Previous myocardial infarction	5 (1.9%)	2 (2.7%)	3 (1.7%)	0.61
Peripheral vascular disease	143 (55.8%)	35 (46.7%)	108 (59.7%)	0.057
Prior stroke or transient ischemic attack	34 (13.2%)	8 (10.7%)	26 (14.4%)	0.43
Chronic kidney disease	36 (14.0%)	13 (17.3%)	23 (12.7%)	0.33
Atrial fibrillation	37 (14.4%)	9 (12%)	28 (15.5%)	0.47
NYHA			0.88	
Class I	1 (0.4%)	0	1 (1.6%)	
Class II	21 (8.2%)	6 (8%)	15 (8.3%)	
Class III	113 (44.1%)	35 (46.7%)	78 (43.1%)	
Class IV	121 (47.2%)	34 (45.3%)	87 (48.1%)	
NYHA III/IV	234 (91.4%)	69 (92%)	165 (91.2%)	0.82
Echocardiographic factors				
Left ventricular ejection fraction (%)	54.7 ± 15	52.93 ± 14.98	56.48 ± 15.12	0.088
Aortic valve peak velocity (m/s) 5 ± 0.73	5.15 ± 0.75	4.94 ± 0.71	0.035	
Aortic valve mean pressure gradient (mm Hg)	64.32 ± 19.3	66.56 ± 20.57	62.08 ± 17.97	0.084
Aortic regurgitation (moderate to severe)	60 (23.4%)	24 (26.3%)	36 (19.9%)	0.19
Mitral regurgitation (moderate to severe)	43 (16.8%)	17 (19.5%)	26 (16%)	0.42

Data are presented as mean ± SD or percentages. NYHA: New York Heart Association; STS score: Society of Thoracic Surgeon score.

predictors of ≥mild PVL after TAVI. The final model included variables associated with univariate analysis (all variables with a $p$value < 0.1). Statistical analysis was performed using the Statistical Package for Social Sciences, version 21.0, for Windows (SPSS. Chicago, Illinois). All reported $p$values are two-sided and were considered statistically significant if <0.05.

3. Results

3.1. Baseline Characteristics. Overall, median age was 74 ± 6 years old, and 43.4% were females. The mean STS score was 8 ± 4.35 and NYHA ≥ III in 234 (91.4%) patients. At baseline, the median left ventricular ejection fraction was 54.7 ± 15%, and the mean transvalvular peak velocity was 5 m/s. We observed that those with higher transvalvular peak velocity were associated with PVL after TAVI. The mean pressure gradient dropped from 64 mmHg to 13.7 mmHg immediately after the procedure. Before the procedure, 60 (23.4%) patients had moderate to severe aortic regurgitation, and 43 (16.8%) had moderate to severe mitral regurgitation. Baseline characteristics of patients are shown in Table 1.

3.2. Procedural and MSCT Characteristics. Seventy-five patients (29.3%) had ≥mild PVL after the procedure. Of them, 15 patients had moderate PVL and PVL was severe in 2 patients. Among included patients, 213 (83.2%) patients received self-expandable prostheses, 32 (12.5%) received mechanically expandable prostheses, and the remaining 11 (4.3%) patients received balloon-expandable prostheses (Figure 4). By univariate analysis, neither prosthesis type nor size was significantly associated with the occurrence of ≥PVL. MSCT-derived maximum, minimum, mean annular diameters, and annulus area were 27.1 ± 3.14 mm, 21.3 ± 2.75 mm, 24.2 ± 2.63 mm, and 462.7 ± 101.2 mm^2, respectively. All these annulus parameters were significantly associated with PVL. Interestingly, annular ellipticity, annular area cover index, prosthesis-mismatch index, and LVOT nontubularity were not associated with PVL. The mean total AVC volume was 798 ± 594.5 mm^3. The overall analysis indicates that AVC volume was strongly associated with PVL (Table 2).

3.3. Multivariate Analysis. By multivariate analysis, calcification volume (OR: 1.001 [95% CI: 1.000, 1.002] $p = 0.01$) and prosthesis type (self-expandable versus non-self-expandable) (OR: 3.489 [95% CI: 1.096, 11.105] $p = 0.034$) were found to be independent predictors of ≥mild PVL after TAVI, although prosthesis type was not associated with PVL by univariate analysis. Multivariate analysis is shown in Table 3.

3.4. Calcification Distribution and PVL Jet Location. An example illustrating PVL jet location on postprocedural TEE short axes view matching with the location of aortic valve

Table 2: Procedural and MSCT characteristics of patients based on the severity of PVL.

Procedural factors	All ($n = 256$)	≥mild PVL ($n = 75$)	<mild PVL ($n = 181$)	p value
Annular maximum diameter (mm)	27.1 ± 3.14	27.67 ± 3.19	26.52 ± 3.10	0.01
Annular minimum diameter (mm)	21.3 ± 2.75	21.67 ± 2.71	20.85 ± 2.80	0.03
Annular mean diameter (mm)	24.2 ± 2.63	24.67 ± 2.66	23.69 ± 2.59	0.01
Annular area (mm^2)	462.7 ± 101.2	481.09 ± 103.24	444.38 ± 99.21	0.001
Annular ellipticity	21.17 ± 8.9	21.33 ± 8.46	21.02 ± 9.47	0.81
Diameter derived prosthesis mismatch (%)	12.8 ± 9.9	12.09 ± 10.46	13.62 ± 9.26	0.25
Prosthesis/mean annulus diameter ratio	1.13 ± 0.10	1.12 ± 0.10	1.14 ± 0.09	0.25
Calcification volume (mm^3)	798 ± 594.5	991.64 ± 709.94	604.37 ± 479.05	<0.001
Presence of predilatation		150 (82.9%)	66 (88%)	0.30
Area cover index	19.9 ± 14.6	18.66 ± 15.52	21.14 ± 13.66	0.21
Depth of implantation (mm)	6.8 ± 4.43	7.21 ± 4.47	6.40 ± 4.39	0.27
LVOT nontubularity	−5.3 ± 18.46	−7.15 ± 18.59	−3.46 ± 18.33	0.15
Second valve implantation	28 (10.9%)	7 (9.3%)	21 (11.6%)	0.59
Postdilatation	115 (44.9%)	45 (60%)	70 (38.7%)	0.002
Size of the prosthesis (mm)				0.23
23	46 (19.9%)	9 (12.0%)	37 (20.4%)	
26	109 (42.6%)	30 (40%)	79 (43.6%)	
29	74 (28.9%)	26 (34.7%)	48 (26.5%)	
31/32	27 (10.5%)	10 (13.3%)	17 (9.9%)	
Prosthesis type				0.054
Self-expandable	213 (83.2%)	69 (91.9%)	144 (79.6%)	
Mechanically expandable	32 (12.5%)	4 (5.4%)	28 (15.5%)	
Balloon expandable	11 (4.3%)	2 (2.7%)	9 (5.0%)	
Type of native valve				0.61
Tricuspid	114 (44.5%)	31 (41.3%)	83 (45.9%)	
Bicuspid type I	58 (22.6%)	16 (21.3%)	42 (23.2%)	
Bicuspid type 0	84 (32.8%)	28 (37.3%)	56 (30.9%)	

Data are presented as mean ± SD or percentages. LVOT: left ventricular outflow tract.

Table 3: Multiple regression analysis.

Variable	OR (95% CI)	p value
Peripheral vascular disease	0.644 (0.335–1.237)	0.18
Calcification volume (mm^3)	1.001 (1.000–1.002)	0.010
Prosthesis type (self-expandable versus non-self-expandable)	3.489 (1.096–11.105)	0.034
Left ventricular ejection fraction (%)	0.981 (0.959–1.004)	0.097
Transvalvular peak velocity (m/s)	1.826 (0.334–9.985)	0.488
Transvalvular mean pressure gradient (mmHg)	0.991 (0.928–1.058)	0.789
Annular maximum diameter (mm)	1.105 (0.835–1.461)	0.486
Annular minimum diameter (mm)	1.118 (0.844–1.483)	0.437
Annular mean diameter (mm)	1.251 (0.712–2.199)	0.437
Annular area (mm^2)	0.995 (0.982–1.009)	0.50

calcification (AVC) on MSCT is shown in Figure 5. PVL jet location matched, in varying proportions, with calcification at all regions of the aortic root, and the highest matching rate was with calcification at body of leaflets compared to calcification at the annulus or tip of leaflets as shown in Figure 6. Matching rates of PVL jet were higher with cusp calcifications than commissure calcifications, particularly in TAV subgroup (Figure 7).

3.5. Outcome. At discharge, left ventricular ejection fraction was higher in patients with <mild PVL compared to those with ≥PVL, but no difference was observed in transvalvular valve peak velocity or mean pressure gradient. No statically significant difference in the rate of all-cause and cardiovascular mortality between patients with ≥mild PVL and those with a lesser degree of PVL at 30-day, 6-month, and 1-year follow-up (Table 4).

4. Discussion

The main findings of the current study include the following. (1) Risk factors for ≥ mild PVL include AVC volume, larger annulus dimensions, and pre-TAVI transvalvular peak velocity. AVC volume and prosthesis type (self-expandable versus non-self-expandable) were independent predictors of ≥mild PVL. (2) PVL jet matched, in varying proportion, with calcification at all aortic root regions, and the highest

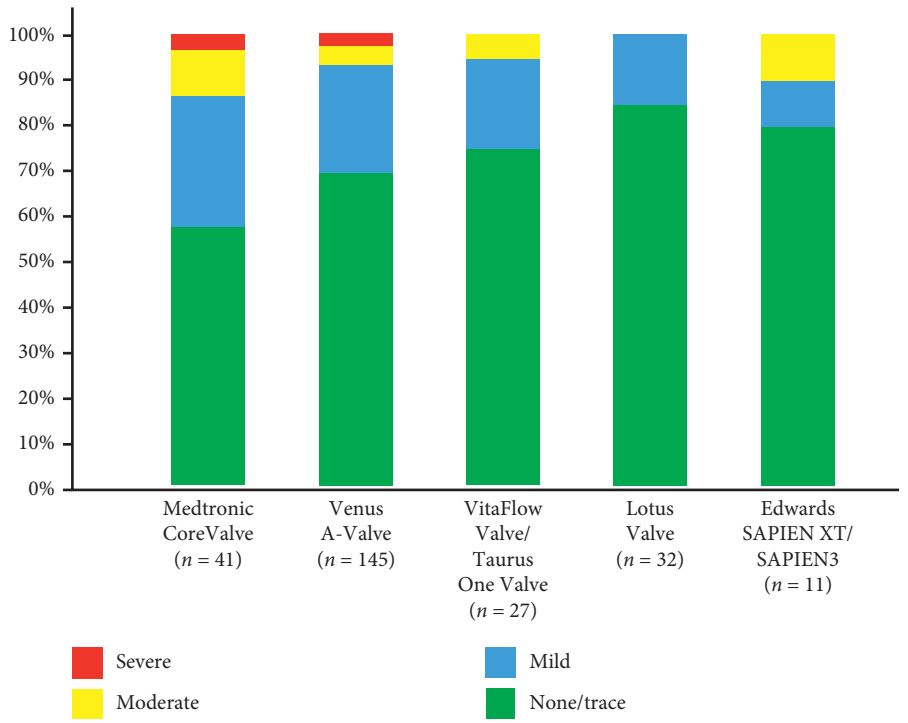


Figure 4: Degree of PVL for each prosthesis type.

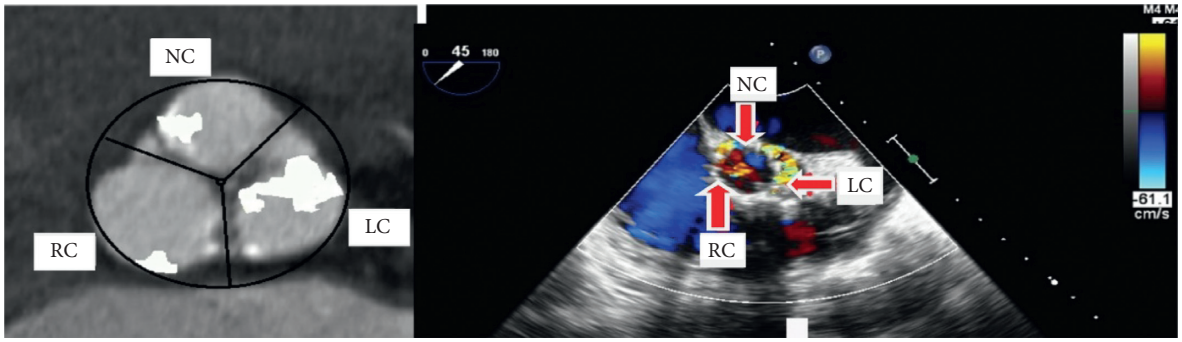


Figure 5: Example showing paravalvular leak jet location on echocardiography matching with the location of AVC on MSCT (image of the MSCT is rotated to be easily compared with the corresponding view of echocardiography). LC: left coronary cusp; RC: right coronary cusp; NC: noncoronary cusp.

matching rate was with calcification at body of leaflets. Moreover, matching rates of PVL jet were higher with cusp calcifications than commissure calcifications, particularly in TAV subgroup. (3) No association between ≥ mild PVL and all-cause and cardiovascular mortality at 1-year follow-up.

4.1. Incidence of PVL after TAVI. Despite improvements in TAVI technology, PVL after TAVI remains commonly reported with variable frequencies [3, 14]. This variability was assumed to be due to differences in the imaging modalities used in different centers, evaluation timing, the grading system, and variability in prostheses type [15]. In the current study, 29.3% of patients had ≥mild PVL, which is consistent with several reports [8, 10, 16].

4.2. Risk Factors for PVL. Smaller annulus size has been reported to be protective against the presence of PVL, explained by the better congruence between the small annulus and THV. However, the prostheses might be undersized in patients with larger aortic annuli [17]. Results from REVIVAL trial showed that larger aortic annulus was a predictor of post-TAVI central aortic regurgitation rather than PVL due to the requirement of larger postdilatation balloon leading to possible leaflet distortion [18]. Conversely, some publications have reported that larger annulus dimensions were not predictors of PVL [7, 8]. In the present study, larger annulus dimensions were significantly associated with ≥mild PVL. As well as that, a meta-analysis study found that undersizing of the prosthesis relative to the annulus size was the main cause of PVL [3]. However, most

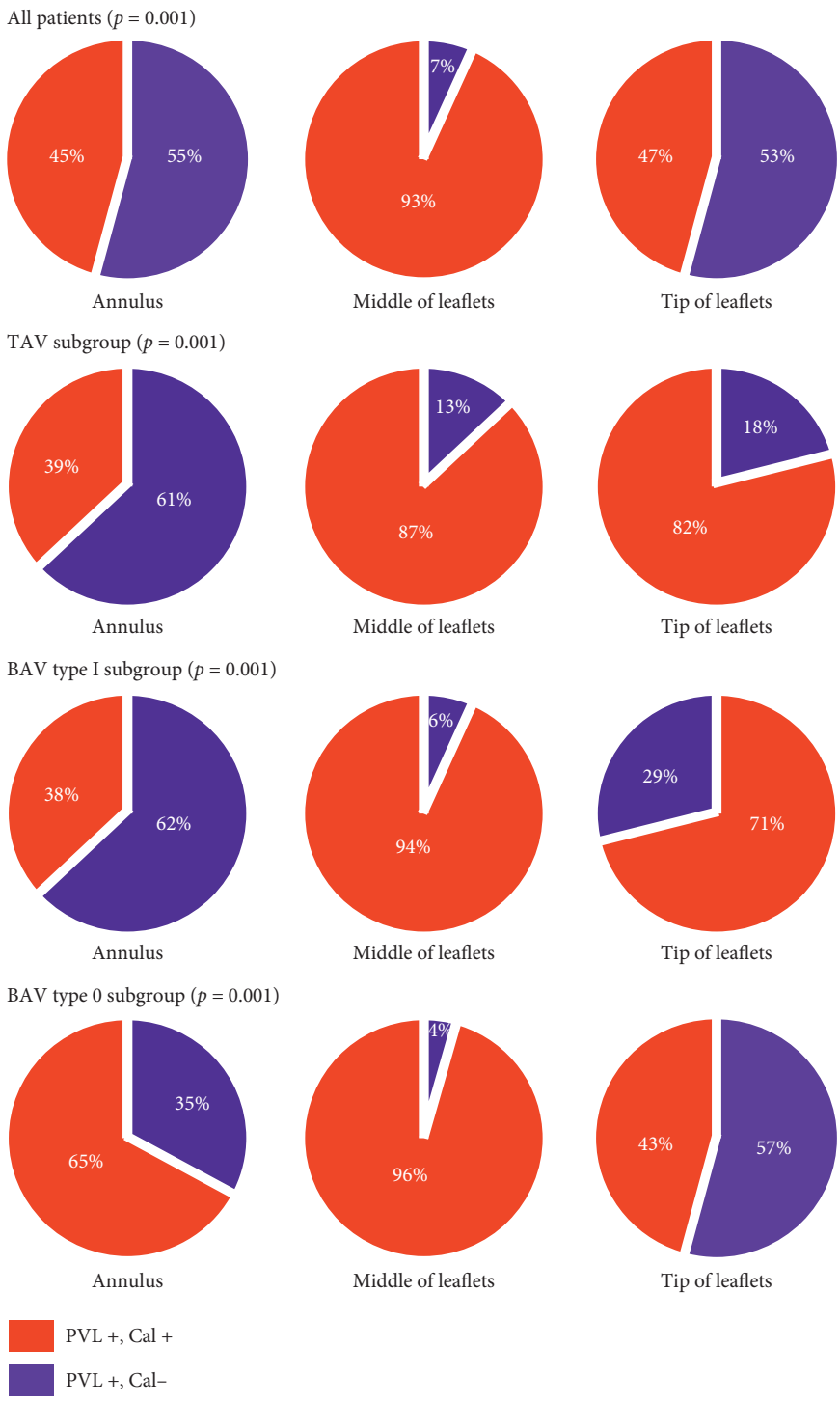


Figure 6: Matching rates of calcification distribution and PVL jet location based on the site of calcification on the aortic root. PVL+, Cal+: paravalvular leak present at the specific location and calcification present at the corresponding location; PVL+, Cal–: paravalvular leak present at a specific location without calcification at the corresponding location; BAV: bicuspid aortic valve; TAV: tricuspid aortic valve.

of the studies included in their meta-analysis measured aortic annulus using TEE rather than MSCT, which has been proven to underestimate the annulus size [4]. In the present study, however, no statistically significant correlation was found between these parameters and the incidence of PVL, which can be explained by the proper oversizing in our study, as the prosthesis size was always greater than that of the annulus (Table 2). Therefore, these results indicate that an appropriate oversizing based on accurate MSCT-derived annulus measurement is crucial to minimize the incidence of

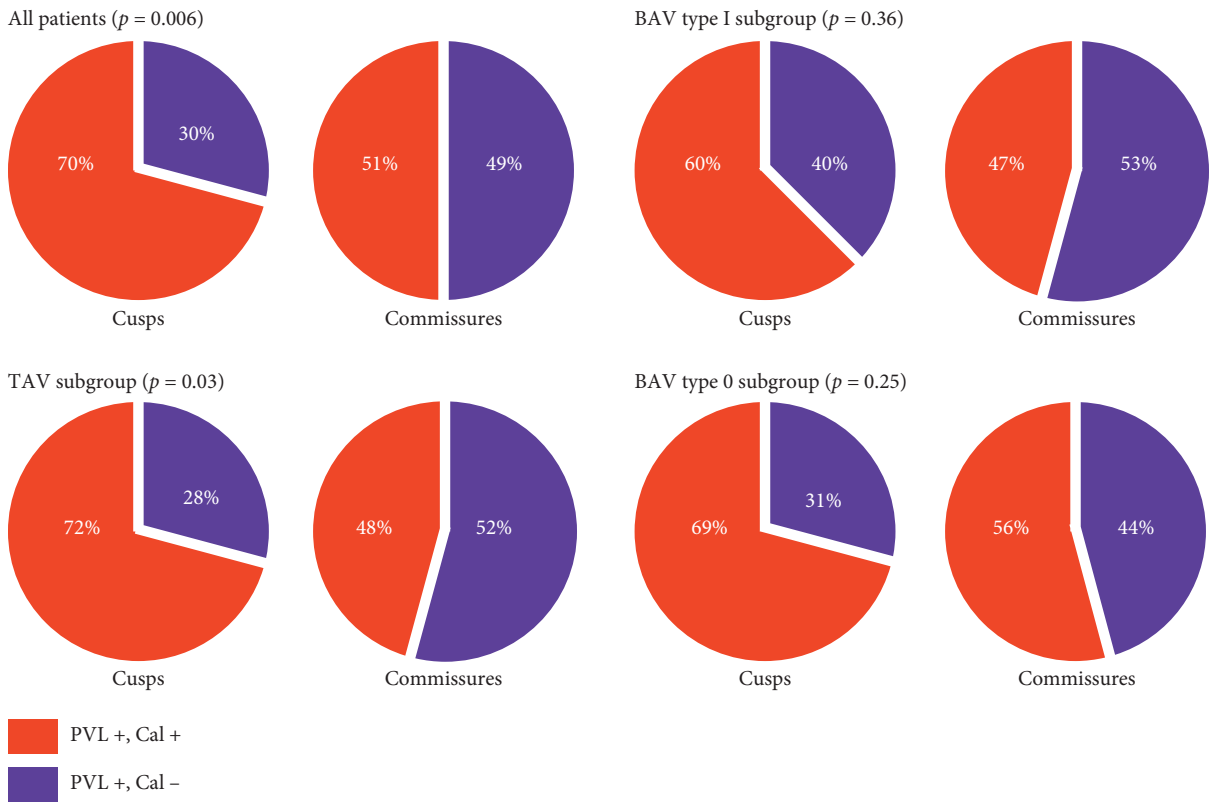


Figure 7: Matching rates of calcification distribution and PVL jet location (Cusps versus commissures). PVL+, Cal+: paravalvular leak present at the specific location and calcification present at the corresponding location; PVL+, Cal–: paravalvular leak present at a specific location without calcification at the corresponding location; BAV: bicuspid aortic valve; TAV: tricuspid aortic valve.

Table 4: Follow-up outcome data.

At discharge	All ($n = 256$)	≥mild PVL ($n = 75$)	<mild PVL ($n = 181$)	p value
Transvalvular peak velocity	2.44 ± 1.1	2.39 ± 0.52	2.49 ± 1.59	0.61
Transvalvular mean pressure gradient	13.7 ± 5.9	13.85 ± 5.82	13.49 ± 6.13	0.66
Left ventricular ejection fraction	55.87 ± 12.1	53.67 ± 12.17	58.07 ± 12.04	0.008
30 days				
All-cause morality		5 (6.7%)	5 (2.8%)	0.16
Cardiac-related mortality		4 (5.3%)	3 (1.7%)	0.19
6-months				
All-cause mortality		8 (10.7%)	8 (4.4%)	0.08
Cardiac-related mortality		5 (6.7%)	4 (2.2%)	0.13
1 year				
All-cause mortality		8 (10.7%)	9 (5.0%)	0.11
Cardiac-related mortality		5 (6.7%)	5 (2.8%)	0.16

Data are presented as mean ± SD or percentages.

PVL after TAVI. Wong et al. [19] reported that elliptical aortic annulus as a predictor of PVL after TAVI. However, several other studies found no correlation, which is consistent with our results [3, 8].

4.3. Calcification Volume and Distribution. The present study evaluated both severity of PVL and PVL location in relation to the distribution of aortic valve calcification. We found that patients with ≥mild PVL had significantly greater calcification in all regions of the aortic valve. Similarly, previous studies have shown that aortic root calcification predicts significant PVL after TAVI [5, 7]. Importantly, several studies suggested that the distribution of calcification on the aortic root is more important than the calcification volume in determining PVL after TAVI [5–7, 20]. However, results of these studies varied; Koos et al. [6] showed that calcium distribution asymmetry had no role in predicting the severity of PVL after TAVI. Ewe et al. [20] found that calcification at the aortic wall near the annulus level was of

more importance compared to leaflet calcification in predicting PVL. Marwan et al. [7] reported that annulus calcification was an important determinant in predicting PVL. In addition, they reported no difference in commissure calcification between patients with and without PVL. Khalique et al. [5] used similar methodology like the one we used for classifying the calcification of aortic valve complex and confirmed that both leaflet and annulusLVOT calcification predict significant PVL. The current study found that calcification at all regions of the aortic valve may predict the presence of PVL at the corresponding location. However, calcifications at the body of leaflets were found to be the main determinant in predicting PVL after TAVI. Annulus calcifications and calcifications at the tip of leaflets were less important in predicting PVL. Interestingly, cusp calcifications were found to be more important than commissure calcification in predicting PVL, particularly in TAV and BAV type 0 patients. We believe that leaflet calcification, as suggested by our results and results of a study by Khalique et al. is as important as annular and LVOT calcifications in predicting PVL [5]. The underlying mechanism may be leaflet and annulus/LVOT calcifications causing prosthesis underexpansion and incomplete contact between the prosthesis and its landing zone. In addition, our results suggested that, compared to cusp calcification, commissural calcification is less important in predicting PVL. This finding as suggested by previous report [5] could probably be explained by the fact that contrary to cusp calcifications, commissure calcifications are easier to be pushed outward during the predilatation and deployment procedure and, hence, do not affect the sealing of the prosthesis to its landing zone. We compared the number of patients who underwent predilatation and found that 95% of BAV patients underwent predilatation, in contrast to TAV patients where only 71% ($p < 0.001$) were predilated which may further explain the lower contributing effect of commissure/raphe calcification, in BAV patients, to the development of PVL.

Operators should be cautious when dealing with heavily calcified aortic valves, especially calcifications on areas found to predict PVL after TAVI. In such patients, significant PVL should be anticipated and hopefully prevented by a wise selection of the prosthesis type and proper predilatation to help spread calcified leaflets and preparation for balloon postdilatation and even implantation of a second valve in case of significant PVL.

4.4. Prosthesis Type. Widely variable incidence of PVL after TAVI has been observed among patients with both balloon-expandable and self-expandable prostheses. Athappan et al., in their meta-analysis study, found that the incidence of ≥moderate aortic regurgitation after the implantation of self-expandable and balloon-expandable valves was 16% and 9%, respectively [3]. Similarly, a recent study confirmed that aortic regurgitation after TAVI was found to be more frequent in patients with self-expandable prosthesis compared to those with balloon-expandable ones [21]. Conversely, some other studies reported no significant association between prosthesis type and incidence of PVL [8]. In our study, by univariate analysis, prosthesis type had no role in predicting PVL. However, in multivariate analysis, the prosthesis type (self-expandable prosthesis versus non-self-expandable prosthesis) was a predictor of PVL. It should be mentioned that, in the present study, the number of patients who received a self-expandable prosthesis (83%) is significantly greater than those who received another type of prostheses (17%). Hence, it cannot be concluded that a certain prosthesis predicts PVL. Further evaluation of the outcome of different prosthesis types in terms of PVL is warranted using a large and equal number of patients for each prosthesis type.

Yoon et al. found that, in patients with BAV anatomy, new-generation devices were associated with less moderate or severe PVL compared to early-generation devices [22]. Similarly, our results showed that around 40% and 30% of patients who underwent TAVI using CoreValve and Venus A-Valve, respectively, had ≥mild PVL. On the other hand, only less than 25% of those who received new-generation devices had ≥mild PVL after TAVI (Figure 4). Although new-generation devices have less incidence of PVL and, hence, should be preferred over early-generation ones, nevertheless, mild PVL still occur and minimizing PVL is crucial for better outcome of TAVI, particularly in an intermediate-to-low risk patients.

4.5. Outcome. There was no difference in terms of all-cause and cardiovascular mortality at 1-year follow-up. This may be explained by the relatively younger age of included patients (mean age was 74 years) and the relatively short follow-up period.

5. Conclusions

Risk factors for PVL after TAVI include AVC volume, larger annulus dimensions, and pre-TAVI transvalvular peak velocity. AVC volume is an independent predictor of PVL. Body of leaflet calcifications (versus annulus and tip of leaflet) and cusps calcifications (versus commissures) were more important in predicting PVL. There was no association between ≥mild PVL and 30-day, 6-month, or 1-year all-cause and cardiovascular mortality.

6. Limitations

We acknowledge that our study has some limitations. First, this is a retrospective study at one center; we need to be cautious when extrapolating the present findings to other cohorts. Second, most of the included patients underwent TAVI using self-expandable prosthesis. Hence, the study is insufficient to assess the impact of prosthesis type on the incidence of PVL. Third, a relatively short follow-up period makes it hard to estimate mortality, and longer follow-up is warranted. Finally, the number of patients in whom the correlation between calcification distribution and PVL was analyzed was relatively small. This will need to be explored in a larger population.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Abdullah Hagar and Yijian Li contributed equally to this work.

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