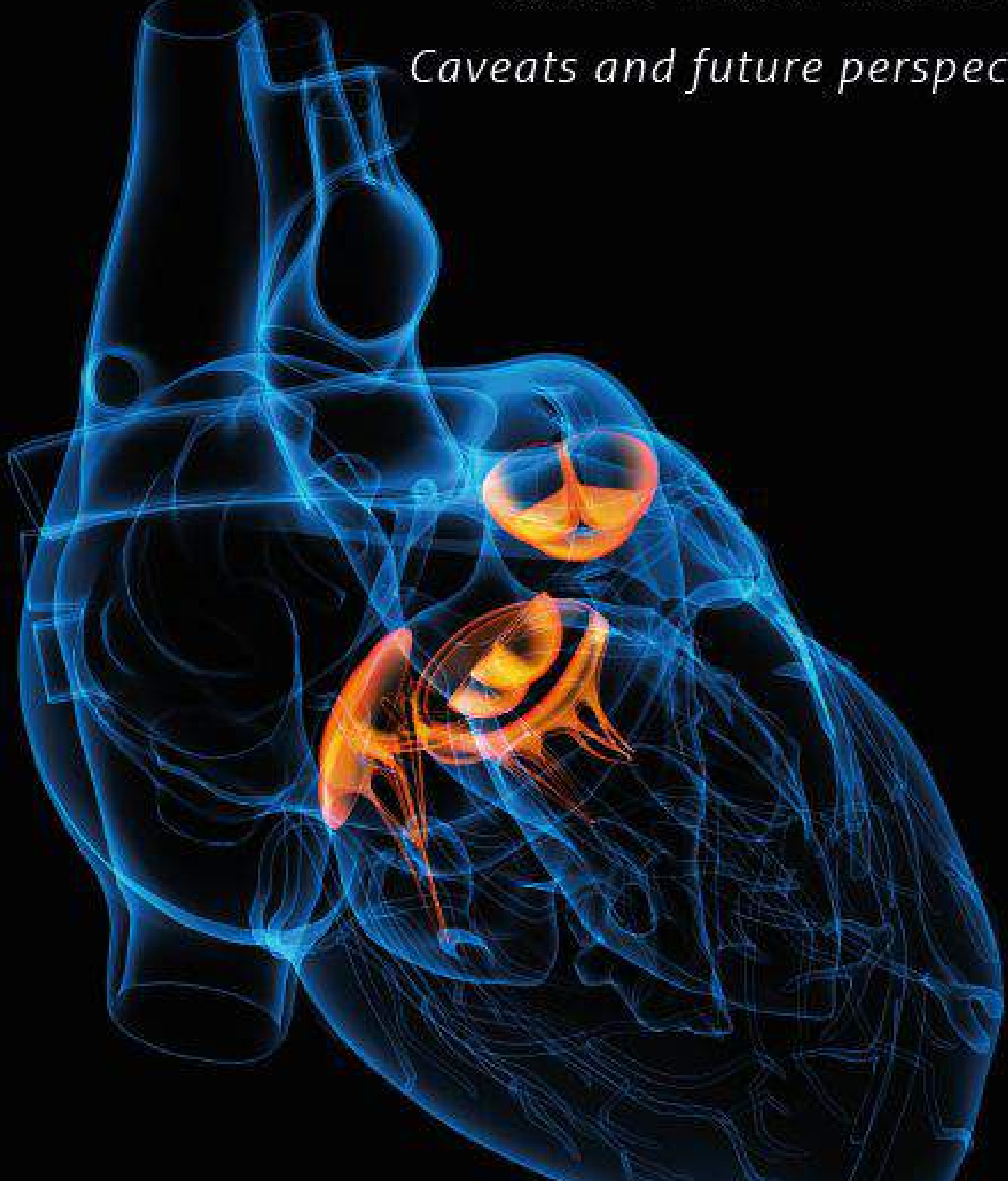
Contemporary Footprint of Transcatheter Left-Sided Heart Valve Interventions

Caveats and future perspectives



Zouhair Rahhab

Contemporary footprint of transcatheter left-sided heart valve interventions – Caveats and future perspectives

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Contemporary Footprint of Transcatheter Left-Sided Heart Valve Interventions – caveats and future perspectives

Hedendaagse voetafdruk van transcatheter gebonden linkszijdige hartklep interventies – kanttekeningen en toekomst perspectieven

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Voor mijn ouders

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Introduction

Aortic stenosis

Aortic stenosis (AS) is a frequently seen valvular heart disease and its prevalence is increasing with age [1, 2]. Surgical aortic valve replacement (SAVR) was for a long time the ‘’gold standard’’. However, a significant proportion of patients (≥30%) was denied/not referred for SAVR mainly due to advanced age, left ventricular (LV) dysfunction or comorbidities [3-5]. Symptomatic severe AS left untreated is a lethal disease with a 1-year mortality of ≈ 25% [6]. Transcatheter aortic valve implantation (TAVI) was introduced for the inoperable and high-risk patients. TAVI is a percutaneous treatment option in which a crimped valve is delivered through a sheath (via transfemoral or other transarterial or transapical approach) and advanced to the native aortic valve. Subsequently, the crimped bioprosthetic transcatheter heart valve (THV) will be deployed, the frame will expand and anchor within the underlying calcified aortic valve annulus. The newly implanted THV will take over the function of the native aortic valve. This procedure precludes sternotomy and cardiopulmonary bypass and is thus less invasive than SAVR. Professor Alain Cribier performed the first-in-human TAVI in 2002 [7]. Over the past 2 decades multiple randomized clinical trials demonstrated TAVI non-inferiority as compared to SAVR across the entire risk spectrum in terms of clinical outcome out to 2 (for low risk) and 5 years for intermediate and high risk. Society guidelines on both sides of the Atlantic have formulated strong recommendations for TAVI in elderly patients with symptomatic severe AS [8-10].

Comprehensive three-dimensional computed tomography planning, multi-disciplinary patient selection, growing operator experience and the introduction of refined transcatheter valve platforms improved procedural safety and bioprosthetic valve performance. TAVI has now matured into a lean procedure under local anaesthesia that catalyses early ambulation and early discharge protocols. The attractive TAVI paradigm also spurs the entertainment of expanding indications beyond symptomatic severe AS (Chapter 5).

Nevertheless, despite the spectacular surge of TAVI adoption in clinical practice, some lingering issues remain and need to be addressed to justify further expansion towards truly low risk (and younger) patients and new indications. The first part of this dissertation will zoom in on some of these limitations:

- *Paravalvular leakage (PVL) (Chapter 1 and 2)*

Paravalvular leakage (PVL) (i.e. backflow of blood around the bioprosthesis during diastole) is conceptually associated with TAVI because the degenerated calcified and elliptic native valve may prevent a homogenous circular transcatheter valve expansion and leave uncovered gaps between the native anatomy and the bioprosthetic frame. More than mild PVL is associated with worse outcome [11, 12]. PVL rates vary from 9% to 67% for trivial-mild leaks and from 0.8% to 20% for moderate-severe leaks [13, 14]. The wide variability of these frequencies can partly be explained using different methodologies for PVL assessment, different definitions and different THV types. Valve Academic Research Consortium (VARC) consensus documents have been created to standardize definitions [15-17]. Furthermore, it is important to understand the underlying mechanisms to be able to prevent/minimize PVL. The underlying mechanisms and determinants of PVL are extensively discussed in Chapter 1 and 2 and are classified into patient-specific, procedural and post-procedural related factors.

- *Vascular complications (VC) (Chapter 3)*

TAVI requires a large bore arteriotomy to accommodate the delivery system, which make it prone to vascular access site complications (VCs) [12, 18]. VCs are associated with mortality, prolonged hospitalization and need for blood transfusion [18-20]. Important determinants are the sheath to femoral artery ratio, femoral artery calcium score, low body weight and female gender [19-22]. The VARC document proposed VC definitions and it is important that TAVI reports follow these consensus definitions for comparison purposes [15-17]. VC reports also suffer from self-reporting and underreporting. We therefore performed a meta-analysis of all prospective studies in which VC were adjudicated by an independent clinical event committee. This meta-analysis could provide a TAVI related VC benchmark for other centers and trials and helps to assess the impact of device iterations with a lower profile and operator experience on the incidence of VC (Chapter 3).

- *Myocardial injury (Chapter 4)*

It is controversial whether myocardial injury, i.e. cardiac biomarker rise, after TAVI is associated with mortality and impaired recovery of left ventricular ejection fraction (LVEF) [23-26]. The exact patho-mechanism of myocardial injury is not clear although several studies hypothesize that factors such as global myocardial ischemia due to balloon valvuloplasty, acute aortic regurgitation, rapid ventricular pacing induced hypotension, micro-embolization of aortic valve debris in the coronary arteries, myocardial tissue compression by the expansion of the device and coronary obstruction should be considered as potential mechanisms for myocardial injury [20, 23]. In Chapter 4, we studied whether prosthesis expansion mechanism (balloon expandable vs. self-expanding vs. mechanically expanding) is an independent predictor for myocardial injury and whether myocardial injury is associated with 30-day mortality.

Mitral regurgitation and transcatheter edge-to-edge repair

Mitral regurgitation (MR) has a prevalence of 2% in the general population and is more frequent in the elderly [27, 28]. The etiology of MR can be classified into degenerative/primary or functional/secondary MR. Degenerative MR is an intrinsic valve problem affecting the mitral valve leaflets while functional MR is a consequence of annular dilatation and distortion of the subvalvular mitral apparatus.

Mitral valve surgery is the treatment of choice for symptomatic patients with severe MR [8, 9]. Surgical mitral valve repair is preferred over mitral valve replacement if technically feasible [8, 9]. However, in the Euro Heart Survey of 2001 surgery was denied in a significant proportion (49%) of eligible patients because of age, comorbidities or poor left ventricular function [29]. Percutaneous mitral valve edge-to-edge repair (MitraClip) was introduced as a less invasive alternative to surgery and complement this unmet clinical need for such patients who are not deemed suitable surgery candidates. The Italian surgeon Ottavio Alfieri introduced the surgical edge-to-edge technique (Alfieri stitch) in which he approximated the free edges of the leaflets at the site of regurgitation and created a double mitral orifice in the early 1990s [30]. The MitraClip mimics the Alfieri stitch in a percutaneous way.

The MitraClip, a V-shaped Clip consisting of two movable grippers and arms, is delivered through the femoral vein advanced to the left atrium after transseptal puncture and positioned above the origin of the regurgitant jet. The arms of the Clip are opened and advanced into the left ventricle. Then the Clip is gradually pulled back towards the left atrium to grasp both leaflets. The grippers are lowered, the clip is closed, and the leaflets are approximated resulting in a double mitral orifice.

The efficacy and safety of the MitraClip has been demonstrated in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST I) [31]. In the EVEREST II, MitraClip was compared with conventional surgery in operable patients with moderate-to-severe or severe, predominantly degenerative MR. MitraClip was associated with superior safety and similar improvements in clinical outcomes. However, it was less effective in reducing MR [32]. As a result, MitraClip received CE mark in 2008 and gained FDA approval in 2013 for high-risk patients with symptomatic degenerative MR. Importantly, contemporary guidelines formulate strong recommendations for surgical repair or replacement in the context of primary/degenerative MR but not for secondary/functional MR (FMR) [8, 9]. Indeed, surgical FMR treatment did not affect survival in a randomized trial of patients with at least moderate FMR who also underwent CABG [33]. Conversely, the randomized COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial demonstrated the clinical benefit of FMR treatment with MitraClip in patients with heart failure [34]. Patient selection (e.g. excluding end-stage heart failure with extensively dilated ventricles), optimized guideline directed heart failure treatment and skilled MitraClip execution seem important for the overall clinical benefit of MitraClip therapy. These principles were reinforced by the conflicting MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial results that showed no clinical impact of MitraClip therapy but patients in MITRA-FR had more dilated LV dimensions, were not optimally medically treated and seemed to have subpar MitraClip procedural results (with more residual MR) [35].
In this thesis, we report a global overview of the complete Dutch MitraClip experience from its inception in 2009 until 2016 (Chapter 6).

MitraClip after failed surgical mitral valve repair

As mentioned earlier, surgical mitral valve repair is treatment of first choice for symptomatic patients with severe MR [8, 9]. However, recurrence of MR after surgical mitral valve repair is common and may require reoperation [36]. Reoperation can be technically challenging and is associated with increased risk of mortality [37]. Percutaneous mitral valve edge-to-edge repair with MitraClip can be an alternative treatment option in selected patients who are denied for redo-surgery. In Chapter 7, we report the safety and efficacy of this alternative treatment option as well as some 'tips and tricks' to overcome procedural challenges (i.e. shadowing from the annuloplasty ring).

Creative solutions to complex interventions

Structural heart interventions may require improvisation and ''out-of-the box'' thinking to address therapeutic challenges. Patients with aortic stenosis often have advanced atherosclerotic disease including peripheral arterial disease that may add complexity to the TAVI procedure and sometimes need focused treatment. Transcatheter mitral valve interventions can be very complex given the anatomical substrate (the entire mitral apparatus, vulnerable cors, presence of calcium) and may result in complications. Comprehensive 3D planning may help obtain detailed insights into a patient's anatomy and may help execute complex mitral valve implantations and anticipate or avoid complications (such as LV outflow obstruction).

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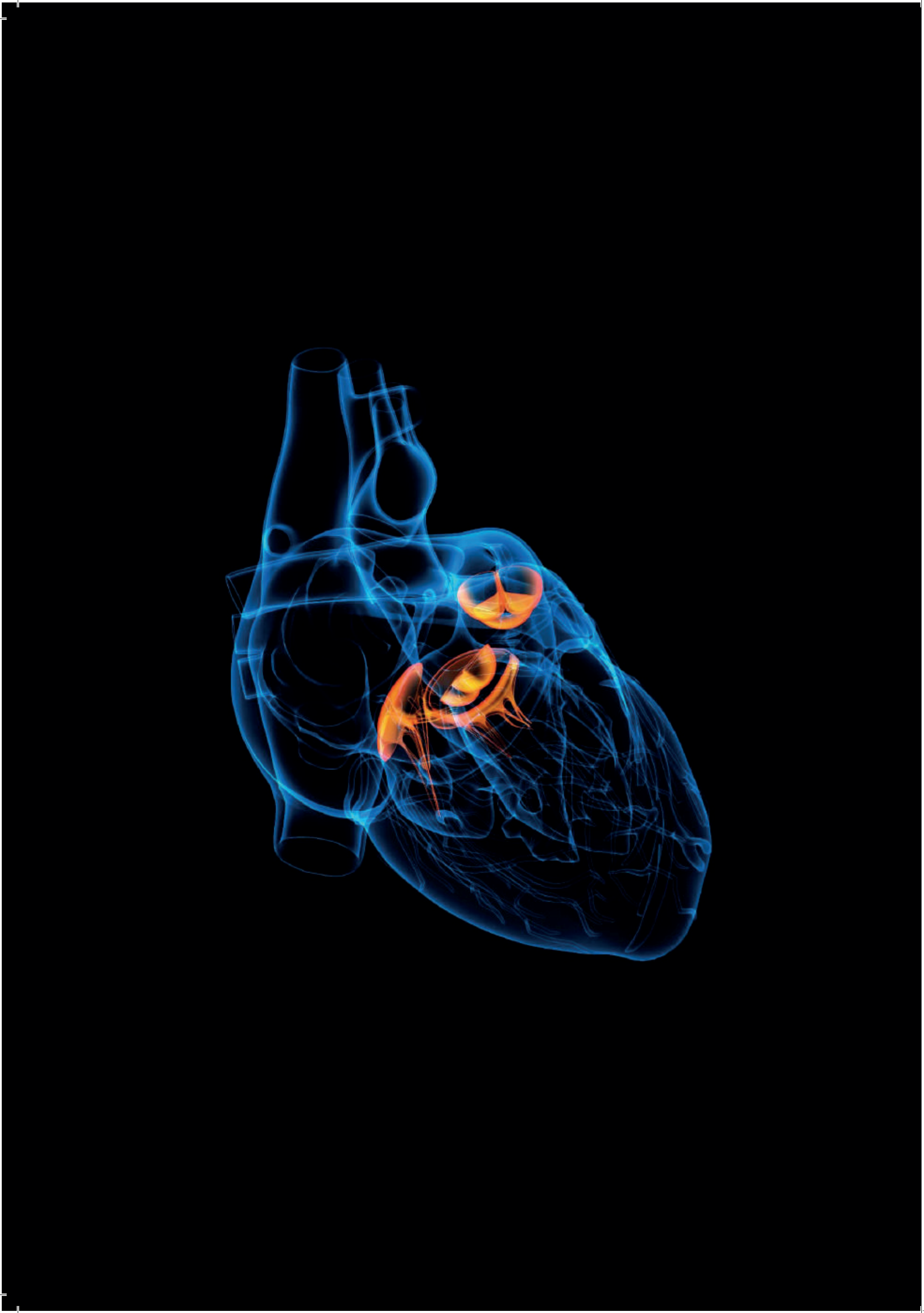

Part I: Aortic valve

CHAPTER 1 Paravalvular leakage after transcatheter aortic valve implantation

Zouhair Rahhab; Nicolas M. Van Mieghem

Textbook;Transcatheter Paravalvular Leak Closure: Paravalvular leakage after transcatheter aortic valve implantation. Bookchapter 9 page 135-152. (2017)

Introduction

Transcatheter aortic valve implantation (TAVI) is the treatment of choice for inoperable or high-risk patients with severe aortic stenosis and is now expanding to intermediate and low-risk patients [1-3]. A frequently seen complication after TAVI is paravalvular leakage (PVL), which is considered the Achilles' heel of TAVI since several studies have shown an association with worse outcome [4-6]. Several trials and registries reported PVL rates ranging from 40 to 67% for trivial-mild leaks and from 7 to 20% for moderate-severe leaks [1,7]. The wide variability of these frequencies may be partly related to the transcatheter heart valve (THV) design but may also reflect different methodologies for PVL assessment. Accurate PVL quantification remains challenging since there is no standardized method yet.

It is important to understand the underlying mechanisms in order to prevent/minimize and treat PVL. In recent years the PVL incidence may have declined because of growing experience, improved implantation techniques and the incorporation of sealing fabric around the valve frame with newer generation THVs.

Assessment of PVL

Angiographic assessment

Contrast angiography can be used for semi-quantitative assessment of aortic regurgitation (AR). AR severity is visually assessed according to the Sellers classification which is based on the density of left ventricular opacification: Grade 1 (mild) corresponds with a small amount of contrast entering the left ventricle (LV) in diastole without filling the entire cavity and clearing with each cardiac cycle; Grade 2 (moderate) corresponds with contrast filling of the entire LV in diastole with faint opacification of the entire LV; Grade 3 (moderate to severe) corresponds with contrast filling and opacification of the entire LV in diastole, equal in density to the ascending aorta; Grade 4 (severe) corresponds with contrast filling of the entire LV in diastole on the first beat with denser opacification than the ascending aorta [8].

Limitations

AR interpretation by aortography is subjective and has high inter-observer variability. Several technical factors (e.g. position of the pigtail catheter and contrast volume/injection rate) may contribute to this variability. Furthermore, aortography weighs the total amount of contrast leaking into the LV ventricle, and cannot distinguish between trans- and paravalvular leakage. In addition, iodinated contrast is needed which increases the risk of acute kidney injury (AKI).

Video densitometry

Dedicated software for semi-automated AR quantification may improve inter- en intra-observer variability of contrast aortography. The principle relies on time dependent changes in contrast distribution and density within the LV during diastole [9]. The software produces five time-density curves ((aortic root (reference area), left ventricular base, mid, apex and overall) and measures the relative area under the curve to obtain the quantified aortic regurgitation index (qAR index) with values ranging from 0.0 (no AR) to 4.0 (severe AR).

Suboptimal contrast angiography studies including incomplete visualization of the LV apex and superposition of the spine and the abdominal aorta may affect its feasibility and accuracy. To address these issues, a simplified video densitometric analysis restricted to the LVOT (LVOT-AR) has been proposed with acceptable results. A recent study showed that LVOT-AR was feasible in 64.8% of aortograms vs. 29.7% for qAR index. Inter-observer variability for LVOT-AR was low (mean difference ± standard deviation; 0.01± 0.05, p=0.53) and inter-observer correlation was high (r= 0.95, p<0.001) [10].

Hemodynamic assessment

The aortic regurgitation index (AR-index) relies on the difference between the invasively measured diastolic central blood pressure (DBP) and the left ventricle end diastolic pressure (LVEDP) divided by the systolic blood pressure (SBP) x100 [(DBP-LVEDP/SBP]x100) (Figure 1) [11]. The seminal paper on this topic illustrated that AR-index decreases in parallel with increasing severity of PVL, from 31.7 ± 10.4 in patients without PVL to 28.0 ± 8.5 in patients with mild PVL, 19.6 ± 7.6 in patients with moderate PVL, and 7.6 ± 2.6 in patients with severe PVL (p < 0.001). AR-index < 25 was an independent predictor for 1 year mortality (hazard ratio: 2.9, 95% confidence interval: 1.3 to 6.4; p = 0.009) [11]. Elevation of the LVEDP due to e.g. volume loading, diastolic dysfunction or peri-procedural myocardial ischaemia can result in a lower diastolic transvalvular gradient and thus a “false positive” AR-index [11]. Diastolic hemodynamic parameters can be influenced by heart rate and this is not taken into account in the AR-index [12]. Finally, the AR-index does not differentiate between transvalvular and paravalvular leakage.

ARI ratio correlates ARI before and after transcatheter valve implantation. The ARI ratio with a cutoff < 0.60 improved the specificity for the prediction of more than mild PVL and 1-year mortality from 75.1% to 93.2% and from 75.0% to 93.3%, respectively [13].

The diastolic pressure-time (DPT) index is calculated by measuring the area between the aortic and left ventricular pressure-time curves during diastole and divided by the duration of diastole. DPT index is adjusted for the SBP. (DPT $index_{adj=}$ (DPT/ SBP) x 100) [14].

DPT $index_{adj}$ decreases with significant PVL (grade ≥2) and a value ≤ 27.9 seems associated with 1-year mortality (hazard ratio: 2.5, 95% confidence interval; 1.3 to 6.4); p<0.001) (Figure 2) [14].

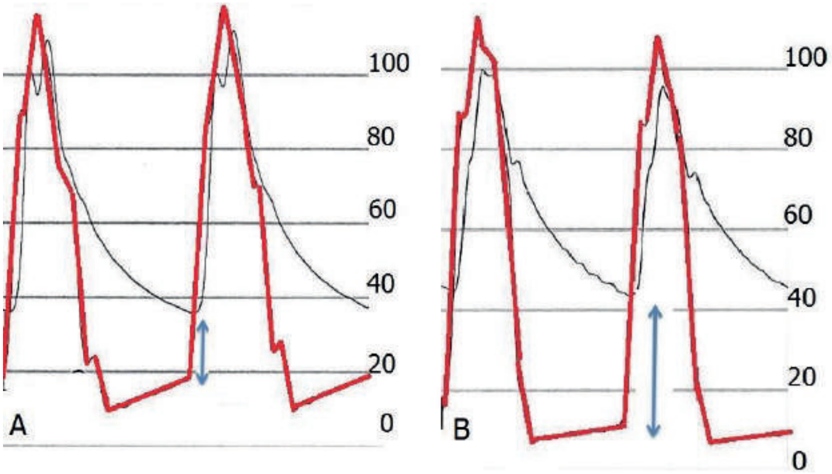

Figure 1: Hemodynamic assessment of a patient (A) with and (B) without PVL.

A) AR-index patient A= (37-18)/111 *100=17. B) AR-index patient B = (42-10)/105 *100=30.

Index	Definition	Cut-off	PVL > mild Specificity	1-year mortality Specificity
AR-index (ARI)	$\frac{\text{Diastolic blood pressure – Left ventricle end diastolic pressure}}{\text{Systolic blood pressure}}$ x100	<25	75.1%	75%
ARI ratio in addition to ARI post	$\frac{\text{ARI post}}{\text{ARI pre}}$; ARI post	<0.60 ; <25	93.2%	93.3%
Diastolic pressure time $index_{adj}$	$\frac{\text{Diastolic pressure time index}}{\text{Systolic blood pressure}}$ x100	≤ 27.9	N.A.	N.A.

Figure 2 Overview of different hemodynamic indices with their definition, cut-off values and specificity.

N.A. not available

Echocardiographic assessment

The valve Academic Research Consortium-2 (VARC-2) recommends Doppler echocardiography for the quantitative and semi-quantitative assessment of PVL [15]. Color Doppler echocardiography can distinguish between trans- and paravalvular leakage; for the evaluation of PVL Color Doppler should be performed just below the valve stent, whereas for the evaluation of transvalvular leakage it should be performed at the coaptation point of the leaflets [15]. All imaging windows should be assessed in order to ensure complete visualization of PVL, however the parasternal short axis view is critical in assessing the number and severity of paravalvular jets [15].
Transoesophageal echocardiography (TEE) may improve PVL assessment in patients in whom poor images are obtained by transthoracic echocardiography (TTE), however TEE is more invasive.
Current trends to perform TAVI under local anesthesia or (mild) conscious sedation limit TEE feasibility. Furthermore TTE assessment in the cathlab is challenging because the patient is in the supine position (no left lateral decubitus). In addition, TTE may mask PVL jets located posteriorly whereas TEE may mask jets located anteriorly.

Limitations

Most echocardiographic parameters (Figure 3) used for the assessment of PVL, are based on surgical heart valves and are not validated in transcatheter heart valves. In addition, several studies suggest that echocardiography underestimates the severity of PVL when compared to cardiac magnetic resonance (CMR) [16-17]. Recently, Geleijnse et al. showed that the parasternal short axis analysis of the circumferential extent of PVL, which is recommended by the VARC-2 and is considered critical in assessing PVL, was false negative in 14% of cases. This may imply underestimation of PVL in prior studies relying on circumferential PVL extent [18].

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

PW, Pulsed wave; EROA, effective regurgitation orifice area

Figure 3: Echocardiographic parameters for the assessment of paravalvular leakage

Cardiac Magnetic Resonance (CMR)

Cardiac Magnetic Resonance is a non-invasive imaging modality allowing accurate and reproducible quantification of aortic regurgitation (AR) by using phase-contrast velocity mapping technique [16-17]. A phase-contrast view in a short axis plane just above the THV is obtained for quantification of the forward and reversed flow volumes (Figure 4) [16]. The regurgitation fraction (RF), which is defined as the diastolic reversed flow volume/ systolic forward volume x100, can be used as a parameter for the stratification of the severity of PVL. None/trivial corresponds with a RF of <8%; mild corresponds with a RF of 9-20%; moderate corresponds with a RF of 21-39%; Severe corresponds with a RF of >40% [16-17].

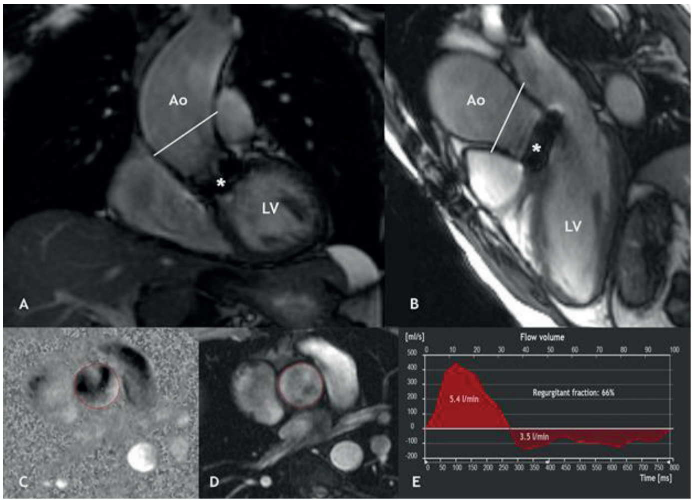

Figure 4: Example of aortic regurgitation quantification with cardiac magnetic resonance (CMR) by using phase-contrast velocity technique. (A and B) Coronal and 3-chamber views (white line represents the level of flow measurement and asterisk (*) the valve in aortic position); (C and D) Phase-contrast velocity and anatomic images; (E) Graphic of flow measurement showing a regurgitation fraction of 66%. Image courtesy of Raluca Chelu, MD, Department of Radiology, Erasmus Medical Center.

Limitations

Since CMR is not available in the catheterization room, intra-procedural assessment of PVL is not possible and thereby not contributing in the decision making whether to perform additional corrective maneuvers. In addition, CMR does not differentiate between transvalvular and paravalvular leakage. The cut-off values of the RF, used for the stratification of PVL, are not validated.
Also, TAVI induced conduction abnormalities may require a permanent pacemaker or Implantable Cardioverter Defibrillator (ICD) which is at least a relative contra indication for CMR (even for the MR compatible devices).

Biomarkers

Recently van Belle et al. demonstrated that changes in von Willebrand factor during TAVI can predict the presence of PVL [19]. Defects in von Willebrand factor high-molecular-weight (HMW) multimers occur in patients with PVL, through turbulent blood flow caused by paravalvular leakage. The HMW multimer conformation changes lead to proteolytic cleavage [19]. This may shorten HMW multimers that are less hemostatically competent and cause a prolongation of the closure time with adenosine diphosphate (CT-ADP).

CT-ADP decreased in patients with no regurgitation post- TAVI from 235 ± 62 (baseline) to 129 ± 54 seconds (end of procedure), while in patients with persistent AR CT-ADP remained high throughout the procedure. In the corrected regurgitation group (i.e. post balloon dilatation or second valve), the CT-ADP did not change markedly from 250 ± 53 (baseline) to 223 ± 49 seconds (after valve implantation) but decreased after the corrective procedure to 124 ± 59 seconds. These findings were also confirmed in a validation cohort: The CT-ADP at the end of the procedure was significantly higher in patients with aortic regurgitation than in those without regurgitation (244±64 seconds vs. 118±53 seconds, P<0.001 [19].

Determinants of PVL

Patient related factors

- *Native aortic valve calcification*

In contrast to surgical aortic valve replacement, the calcified native aortic valve is not excised with TAVI. In fact, valvular calcification is needed to ensure anchoring of the THV. We previously demonstrated that patients with valve dislodgement had significantly less aortic root calcification (Agatston score median 1951 AU (IQR, 799-3103) vs. 3289 AU (IQR 2097-4481), P = 0.016) with an Agatston score< 2359 AU as a single independent predictor for valve dislodgement (OR 3.10, 1.09-8.84) [20]. However, excessive calcification of the aortic annulus (Figure 5) might lead to frame under expansion and incomplete circumferential apposition (of the THV) to the native annulus [21-23]. Amount and distribution of annular calcification is a predictor for PVL [24-27]. A study on 112 consecutively treated patients confirmed a significant association between the aortic valve calcium score (AVCS) and PVL [odds ratio (OR; per AVCS of 1000), 11.38; 95% confidence interval (CI) 2.33–55.53; *P* = 0.001) [27]. The mean AVCS in patients without PVL (n=66) was 2704 ± 151, 3804 ± 2739 (P=0.05) in mild PVL (n=31) and 7387±1044 (P=0.002) with PVL (n=4). An increase of the Agatston calcium score with 100 HU is associated with increased risk for PVL (odds ratio 1.09; 95% confidence interval: 1.01 to 1.17; p = 0.029) [25].

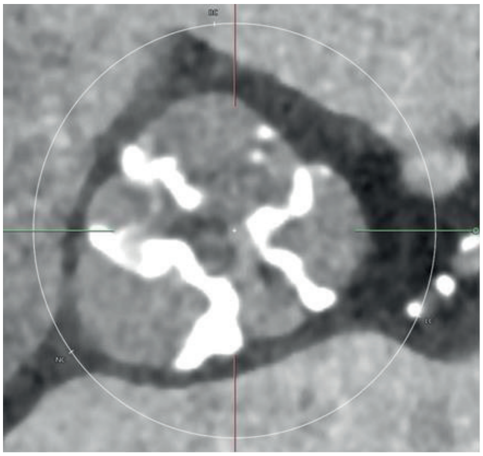

Figure 5: MSCT image of a severely calcified tricuspid aortic valve.
NC= non-coronary cusp, RC= right coronary cusp, LC= left coronary cusp

- *Bicuspid aortic valve*

Bicuspid aortic valve (BAV) phenotype (Figure 6) is the most common congenital valvular abnormality, occurring in 0.5% to 2% of the general population and is associated with accelerated valve degeneration [28]. BAV has so far been an exclusion criterion in randomized TAVI trials so limited data about TAVI in BAV is available [1,2]. TAVI in BAV may suffer from uneven frame expansion and subpar function, including PVL [29]. A systematic review on TAVI in BAV reported a 31% incidence of ≥ moderate PVL [30]. The rate of at least moderate PVL post TAVI seems consistently higher with BAV vs. tricuspid aortic stenosis (25% vs 15%, $p = 0.05$) [31]. BAV tends to have a higher degree of root calcification (Agatston score 1262.7 ± 396.0 vs. 556.4 ± 461.9, $P < 0.01$) [32]. The self-expandable Medtronic CoreValve seems more underexpanded in BAV than in degenerated tricuspid aortic valves (underexpansion at base of the stent frame in 81.7% ± 14.9% vs. 94.7% ± 15.0%, $P = 0.06$, at annulus level, 74.3% ± 16.7% vs. 89.9% ± 10.5%, $P = 0.03$, at leaflet level 64.6% ± 13.1% vs. 81.2% ± 13.2%, $P < 0.01$) [32].

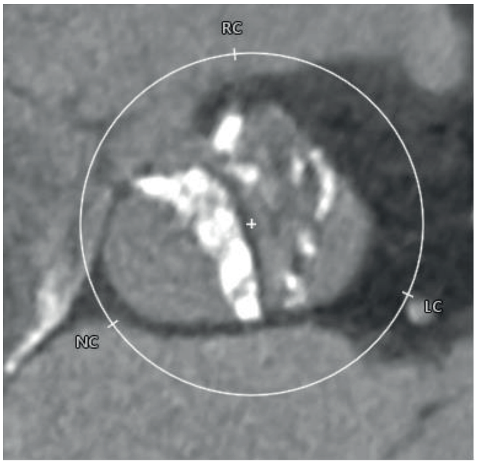

Figure 6: MSCT image of a calcified bicuspid aortic valve type I L-R, with fusion of the left and right coronary cusp. NC= non- coronary cusp, RC= right coronary cusp, LC= left coronary cusp

Procedural factors

- *Valve type*

Several meta-analyses suggest that the frequency of PVL is higher with self-expandable valves (SEV) than with the balloon-expandable valves (BEV) [7,33]. In the randomized Comparison of Transcatheter Heart Valves in high Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN XT (CHOICE) trial PVL assessed by contrast aortography and TTE was more frequent with Medtronic Corevalve SEV as compared to SAPIEN XT [34]. The nitinol SEV frame has lower radial force than the stainless steel BAV frame which may explain a more ellipsoid and underexpanded frame configuration with SEV by rotational angiography and a higher incidence of ≥ moderate PVL [35-36].

- *Patient prosthesis mismatch*

Sizing for TAVI relies on a detailed aortic root assessment by non-invasive imaging techniques. Oversizing relative to the native annulus may provoke conduction abnormalities, or more rarely annulus rupture and coronary obstruction whereas undersizing may increase the risk for valve embolization and PVL. Three-dimensional, volume rendered multi sliced computed tomography (MSCT) is currently ‘’the gold standard” for aortic annulus measurement and device sizing.

Echocardiography typically underestimates annular dimensions and may thus predispose to valve undersizing and PVL [37,38]. Indeed MSCT-guided annular sizing reduced the incidence of >mild PVL when compared with two-dimensional TEE guided annular sizing (7.5% vs 21.9%; p= 0.045) [38].

- *Prosthesis malpositioning*

Appropriate positioning of THV is essential. Various THVs have a sealing mechanism (i.e. skirt) (Figure 7), located at the lower part of the frame, to minimize retrograde blood flow into the LV. However, in too deep implantations (too ventricular) (Figure 8A), the sealing fabric ends up below the native annulus. In case of a too high (aortic) implantation (Figure 8B), the THV may not cover the native annulus.

Figure 7: example of a sealing mechanism at the inflow portion of the frame of the transcatheter heart valve.

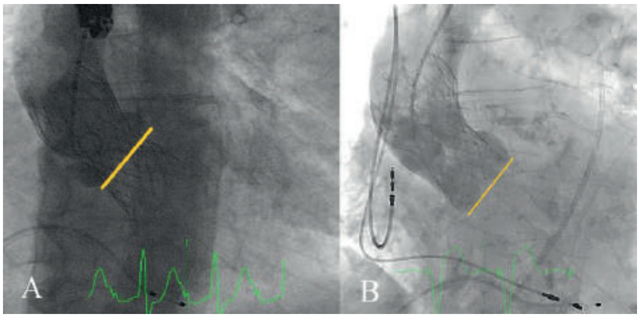

Figure 8: Angiographic view of (A) a too deep (too ventricular) and (B) a too high (too aortic) implantation of a transcatheter aortic heart valve. Yellow line= native aortic annulus.

Post-procedural factor

Prosthetic valve endocarditis

Prosthetic valve endocarditis (PVE) is diagnosed according to the modified Duke criteria [39]. PVE is a rare but serious complication after TAVI, with an incidence varying in the literature from 0.6% to 3.4% [1,40-41]. A large multicenter registry reported an 1.13% PVE incidence [42]. PVE may damage the leaflets and/or framework and extend into paravalvular tissue causing AR (transvalvular and/or paravalvular). A multi-center study reported new or worsening AR in 15.1% of TAVI patients with PVE [43].

Treatment

Balloon postdilatation

Balloon postdilatation may (partly) correct frame underexpansion (Figure 9). Balloon postdilatation can improve frame expansion and reduce PVL in the majority of patients with ≥ moderate PVL [44].

However, balloon postdilatation may be associated with a higher risk for THV migration, trauma to the conduction system, rupture of the aortic annulus and cerebrovascular embolism.

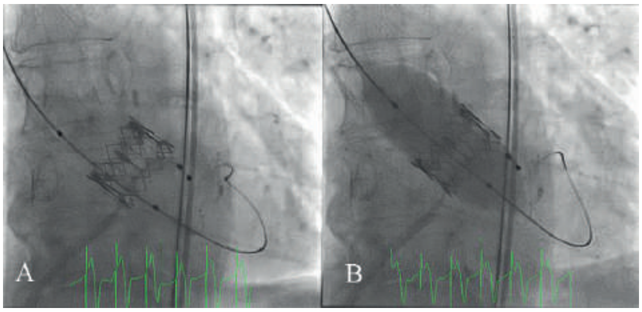

Figure 9: Angiographic image of (A+B) post balloon dilatation in a transcatheter heart valve.

Snaring

Snaring may correct valve malpositioning (Figure 10). A snare catheter can be advanced through a femoral or radial/brachial approach. Potential risks of this maneuver are valve embolization, cerebral embolization and aortic tear/dissection.

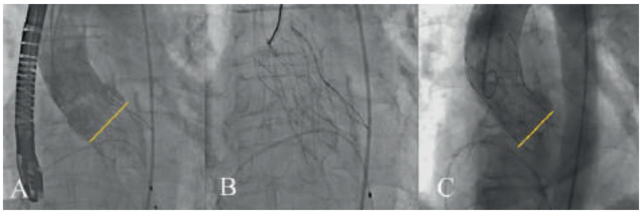

Figure 10: Angiographic image of (A) a too deep implantation of transcatheter heart valve (B) snare catheter is engaged to the hook of the prosthesis. Yellow line: native aortic annulus.

Valve in Valve

A viable treatment option for patients with a malpositioned valve (i.e. too deep or too high) is the Valve-in-Valve (VinV) technique. A second valve is then implanted several millimeters above or below the first malpositioned valve allowing the skirt of the stent frame to seal the native annulus (Figure 11). In the Italian CoreValve registry VinV technique was required in 24 of 663 patients (3.6%) [45]. The procedural, 30-day and 12-month outcome of the VinV group was not different from the no-VinV group. V-in-V was safe with no impingement of the coronary ostia, embolic events, or excess intra-procedural or 30-day mortality. Importantly no significant increase in transvalvular gradient was observed. At 12-months, PVL grade ≥2 was seen in 1 of the 24 patients (4.2%) in the VinV group [45]. Patients with V-in-V had a higher need for permanent pacemaker implantation (33.3% vs. 14.5%, p=0.020) because in the majority of cases the first THV had been implanted too deep [45-46].

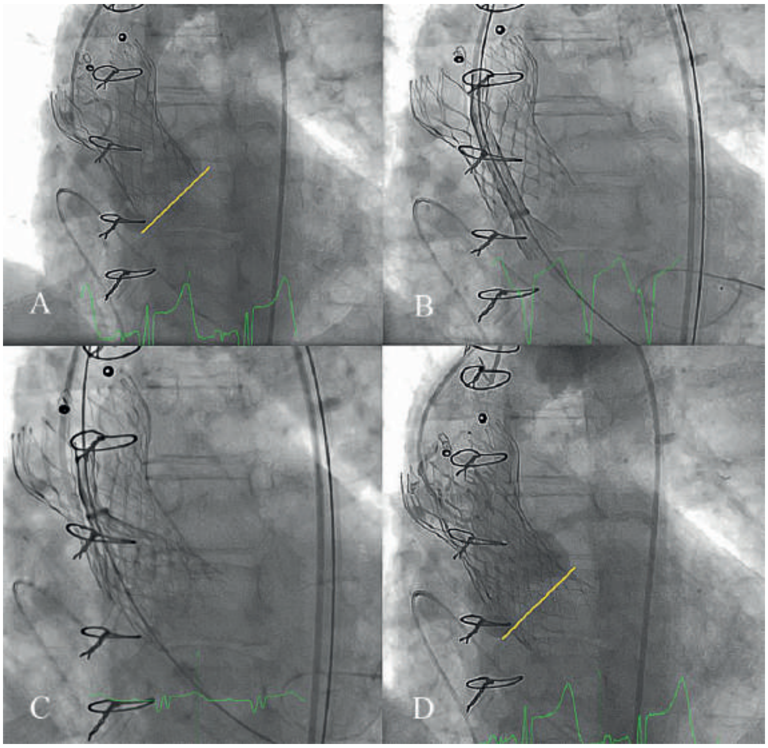

Figure 11: Aniographic image of (A) a too high (too aortic) implantation of a transcatheter heart valve (THV), (B+C) implantation of a second valve several millimeters below the first THV. (D) fully expanded second THV several millimeters below the native aortic annulus. Yellow line: native aortic annulus.

Percutaneous closure with a plug

Vascular plugs, can be used for percutaneous closure of PVL (off-label). The implantation of the vascular plug is generally performed under fluoroscopy with or without TEE guidance. Briefly, the PVL is crossed with wire and catheter. The plug is then advanced to fill the periprosthetic space. A systematic review on this technique confirmed a relatively high success rates (86.9%) with both self-expandable and balloon-expandable THVs (100% vs. 77.8%, p=0.095) [46]. Valve embolization occurred in one patient [47].

New technologies

- Second generation valves

Second generation valves (Figure 12) introduce repositionability/retrievability, sealing fabric and/or frame adjustments to address the limitations of first generation valves (e.g. PVL). THV repositionability may improve overall THV positioning. So far repositioning with these next generation THVs seems a safe concept. Notably, no excess in cerebrovascular events were reported [48]. In a propensity matched analysis ≥ moderate PVL was more frequent with first generation THVs vs. 2nd generation THVs (17.5% vs 5.8%; odds ratio, 0.30; 95% CI, 0.13-0.69; P<.001) with no difference in 30-day all-cause mortality (5.2% vs 3.2%; odds ratio, 0.61; 95% CI, 0.20-1.92; P=.40) [49].

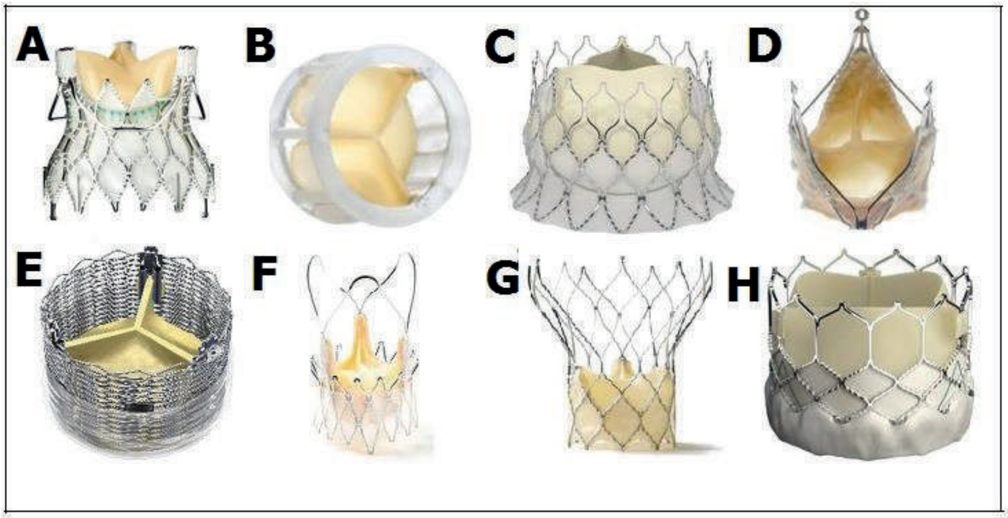

Figure 12: Second-generation transcatheter aortic heart valves: (A) Engager valve (B) Direct Flow (C) Edwards Centera Valve (D) JenaValve (E) Lotus Valve (F) Symetis ACURATE (G) Portico Valve (H) Edwards Sapien 3 Valve

THV simulation

MSCT datasets can be used to simulate and predict device-host interactions by performing a virtual THV implantation in a 3D annular reconstruction. Simulation models accurately predicted calcium displacements and final PVL location and severity (Figure 13) [50-51]. This concept can help determine the optimal valve size and implantation depth and support a true patient-tailored approach in the future.

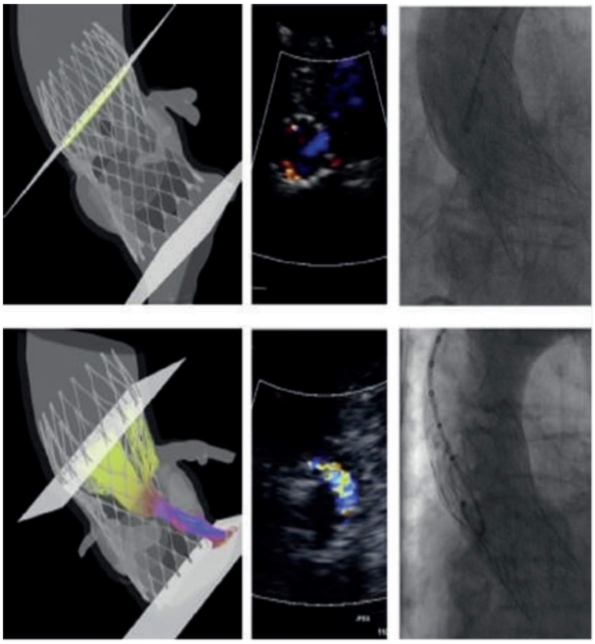

Figure 13: Top row: example of a prediction model of a patient in which no PVL was predicted corresponding well with echocardiography and angiography (both grade 0).
Bottom row: example of a prediction model of a patient in which PVL of 16ml/s was predicted corresponding well with echocardiography (grade 2) and angiography(grade 3).
Image courtesy of Prof. Dr. Peter de Jaegere, MD, PhD; Department of Cardiology, Erasmus Medical Center.

Conclusion

The issue of paravalvular leakage with TAVI has multiple dimensions. Where challenges in accurate assessment and treatment remain, current generation transcatheter heart valve technologies, experience and improved implantation techniques have dramatically reduced PVL frequency making TAVI a valid treatment for a growing number of patients justifying extended adoption in clinical practice.

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CHAPTER 2 Determinants of aortic regurgitation after transcatheter aortic valve implantation. An observational study using Multi Slice Computed Tomography (MSCT) guided sizing

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ABSTRACT

Background: To explore the determinants of aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI) using Multi Slice Computed Tomography (MSCT) instead of echocardiography-guided sizing.

Methods: Determinants of AR were assessed in 313 consecutive patients who underwent TAVI with the Medtronic (MCS, n=259) or Edwards Sapien or XT (ESV, n=54) using MSCT guided sizing. AR was assessed by angiography immediately after TAVI (n=313, Sellers) and by echocardiography at discharge (n=285, VARC-2). Distinction was made between patients with grade 0-1 and grade ≥2 AR post-TAVI.

Results: AR≥2 post TAVI was seen in 91 patients or 29% (MCS 85/259:33% vs ESV 6/54:11%) by angiography and 94 patients or 33%(MCS 87/239:36% vs ESV 7/46:15%) by echocardiography. By univariable analysis, patients with AR≥2 post TAVI had more AR≥2 at baseline (70% vs. 52%,p=0.003), a larger mean and maximal annulus diameter (25.0 [23.5-26.3] vs. 24.0 [22.6-26.0],p=0.025 and 27.9 ± 2.7 mm vs. 27.0 ± 2.8 mm,p=0.018, respectively) and a higher Agatston score(3.9[2.9-5.3] vs 2.6[1.8-3.8], p= <0.001). AR≥2 post TAVI was more frequent after MCS than ESV (33% vs. 11%, p=0.001). There was no difference in nominal valve size relative to the patient's annulus, nor depth of implantation. By propensity score adjusted multivariable analysis, AR≥2 at baseline (odds 2.407 [95%CI: 1.472-3.938]) but above all MCS (odds: 6.047 [95%CI; 1.307- 27.976]) were independent determinants of AR≥2 post TAVI. The latter was also confirmed by propensity score adjusted multivariable analysis in the echocardiography population (n=285) (odds: 5.259 [95%CI; 1.070-25.851]).

Conclusion: AR≥2 is more prevalent after MCS valve implantation and is an independent determinant of AR also when using MSCT guided sizing.

List of abbreviations

AR = Aortic Regurgitation

Dmax = maximal annulus diameter

Dmean = mean annulus diameter

Dmin = minimal annulus diameter

ESV = Edwards Sapien Valve

MCS = Medtronic CoreValve System

MSCT = Multi Slice Computed Tomography

TAVI = Transcatheter Aortic Valve Implantation

Introduction

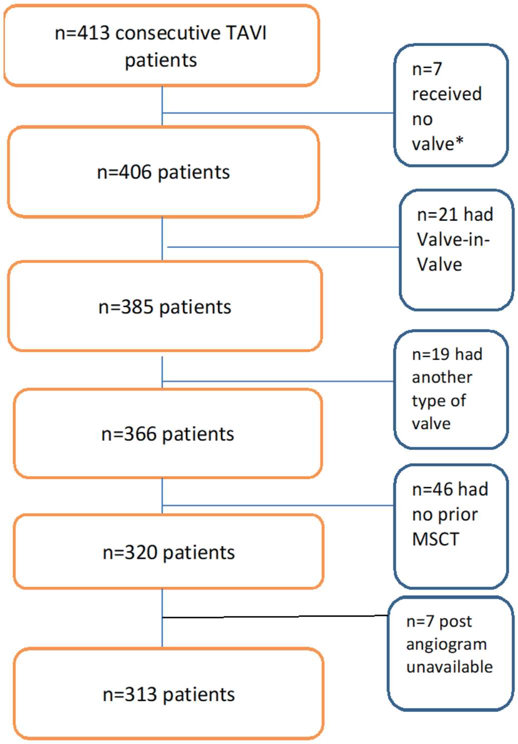
Transcatheter aortic valve implantation (TAVI) is increasingly used in patients with aortic stenosis and has been shown to be superior to medical treatment in patients who are ineligible for surgical aortic valve replacement (SAVR) and at least equally effective in high risk patients [1-6]. Aortic regurgitation (AR) post TAVI frequently occurs and is associated with increased mortality during follow-up [7-10]. Patient - procedure- and operator related variables such as the amount and distribution of aortic root calcification, annulus dimensions, depth of implantation and sizing have been identified as determinants of AR post TAVI [11-22]. AR post TAVI is more frequent with the self-expanding Medtronic CoreValve System (MCS) as compared to the balloon expandable Edwards Sapien valve (ESV) [7-9,22-24]. In most of these studies except the CHOICE randomised study, sizing was based upon echocardiographic assessment of the aortic annulus while Multi Slice Computed Tomography (MSCT) has been recommended to improve sizing, thereby reducing AR post TAVI [21,24,25]. We studied the determinants of AR post TAVI in a consecutive cohort of patients who were treated with the MCS or ESV (Sapien, Sapien XT) after heartteam clinical consensus using MSCT guided sizing [26].

Methods

Patients

The study population consists of 313 consecutive patients (figure 1) who had undergone MSCT before TAVI. For the assessment of AR post TAVI contrast angiography according to a predefined protocol (details below) and echocardiography before discharge were used. TAVI was performed under general anesthesia using the MCS or ESV (Sapien, Sapien XT) via the femoral, axillary artery or the apex of the heart. Sizing was performed in accordance with the industry guidelines using MSCT-derived mean diameter, perimeter and/or area of the patient’s annulus. Additional post balloon dilatation was performed in case of moderate to severe or severe AR . All patients gave written informed consent before admission for anonymised prospective data collection for clinical research purposes (data analysis and publication).

Figure 1. Flowchart study population



MSCT

A Second generation Dual Source (Somatom Definition FLASH, Siemens Healthcare, Forchheim, Germany) MSCT, was used for the selection of access site, optimal valve plane and valve size as described before [26] . For the assessment of the calcium load of the aortic root a non-contrast scan was performed in an ECG-gated, prospective, sequential (step and shoot) mode with a reference tube current of 80 mAs/rotation, a tube voltage of 120kV and slice thickness of 3mm at 1.5mm interval with B35f filtered back projection kernel in the early systolic heart phase depending on the heart rate. The threshold for the detection of calcium was set at 130HU using the SYNGO VIA Calcium score software (Siemens, Forchheim, Germany). The aortic root was defined as the stretching from the caudal aspect of the aortic annulus to the origin of the left main stem as seen on axial images. Agatston score, calcium volume and mass were measured [27]. In cases where aortic root calcification was confluent with adjacent structures (mitral annulus, ascending aorta, coronary arteries) only the stack of images that contained the aortic root were selected.

Angiography

Contrast angiography was performed immediately after TAVI for the assessment of AR post TAVI. For that purpose 20 ml non-diluted Iodixanol [Visipaque™] at a flow rate of 20 ml/sec was injected via a 6 Fr pigtail that was positioned just above the bioprosthetic leaflets. Cineruns were recorded at a speed of 30 frames/sec. AR post TAVI was assessed in accordance to the Sellers classification and graded as follows; 0= none, 1= mild, 2=moderate, 3=moderate to severe and 4=severe [28]. Two observers independently from one another scored the angiograms. In case of discrepancy, consensus was reached by consulting a senior cardiologist. The intra- and interobserver variability for the assessment of AR post TAVI according to the Sellers classification were κ 0.07, 0.60 and 0.78 respectively. For the purpose of the study, the population was divided into patients with none-mild (Sellers grade 0-1) and moderate, moderately severe and severe PVL (Sellers grade 2-4). The contrast angiogram was also used for the quantification of the depth of implantation (distance between the inflow or ventricular end of the valve and the nadir of the non- and left coronary sinus – mm).

Echocardiography

In 285 patients echo-Doppler cardiography was performed before discharge. AR severity was assessed by an independent cardiologist and was defined by the circumferential extent of the echo-doppler signal in the parasternal short axis view according to the VARC-2 criteria [29]. Distinction was made between patients with non and mild (<10%) and those with moderate and severe (10-29 and ≥30%) AR.

Statistical analysis

The main analysis consisted of the assessment of the determinants of AR based by comparing patients with Sellers grade 0-1 and 2-4 on angiography immediately after implantation. The secondary analysis consisted of the assessment of the determinants of AR by comparing patients with none or mild (<10%) and those with moderate or severe (10-29 and ≥ 30%) AR on echocardiography before discharge.

Categorical variables are presented as frequencies and percentages and, compared with the use of the Pearson Chi Square Test or the Fisher's exact test, as appropriate. Continuous variables are presented as means (±SD) (in case of normal distribution) or medians (IQR) (in case of skewed distribution) and compared with the use of the Student's t-test or MannWhitney U test. Normality of the distributions was assessed using the Shapiro-Wilk test. To study the independent predictors of AR ≥2 post TAVI logistic regression was performed. All characteristics judged to be clinically relevant or to have a pathophysiologic role in AR post TAVI were included in a multivariable adjusted logistic regression model, taking into account the observed frequency of the dependent variable y (n/10). Additionally, a propensity score was computed based on baseline characteristics which were different between the MCS and ESV population or those which were considered to be clinically relevant. The first consisted of age (p=<0.001), hypertension (p=0.031), peripheral vascular disease (p=0.023), baseline aortic valve area (p=0.039) and baseline AR index (p=0.001). The second were mean annulus diameter and Agatston score. This propensity score was also entered into the multivariable adjusted logistic regression model. A two-sided alpha level of 0.05 was used to indicate significance. Statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline

The baseline clinical and procedural details of the total population and of the patients with absent or mild (Sellers grade 0-1) and those with moderate to severe (Sellers grade 2-4) AR post TAVI are summarised in Table 1 and 2. AR ≥2 post TAVI was seen in 91 (29%) of the patients. By univariable comparison, these patients had more AR ≥ 2 at baseline (70% vs. 52%, p=0.003), a larger maximal and mean annulus diameter (27.9 ± 2.7 mm vs. 27.0 ± 2.8 mm, p=0.018 and 25.0 (23.5-26.3) vs. 24.0 (22.6-26.0), p=0.025 respectively) and a higher Agatston score (3.9 (2.9-5.3) vs. 2.6 (1.8-3.8), p=<0.001).

Table 1. Baseline characteristics of patients undergoing transcatheter aortic valve implantation.

	Entire cohort n = 313	AR post TAVI-Sellers grade 0-1 n = 222	AR post TAVI-Sellers grade 2,3,4 n = 91	p-value
Age (yrs), median (IQR)	81 (76-85)	80 (75-84)	81 (77-86)	0.12
Male, n (%)	166 (53)	109 (49)	57(63)	0.029
Height (cm), median (IQR)	168 (162-174)	168 (160-174)	169 (164-175)	0.094
Weight (kg), median (IQR)	74 (65-85)	74 (65-85)	72 (64-81)	0.14
Body mass index (kg/m2), median (IQR)	26 (24-29)	26 (24-30)	26 (23-27)	0.006
Body surface area (m2), mean ± SD	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.62
New York Heart Association class ≥ III, n (%)	239 (78)	170 (78)	69(78)	0.93
Previous cerebrovascular event, n (%)	66(21)	41(19)	25(28)	0.076
Previous myocardial infarction, n (%)	73(23)	55(25)	18(20)	0.34
Previous coronary artery bypass graft surgery, n (%)	73(23)	52(23)	21(23)	0.95
Previous percutaneous coronary intervention, n (%)	91(29)	64(29)	27(30)	0.88
Diabetes mellitus, n (%)	87(28)	67(30)	20(22)	0.14
Hypertension, n (%)	210 (67)	153 (69)	57(63)	0.28
Peripheral vascular disease, n (%)	68(22)	46(21)	22(24)	0.50
Pulmonary Hypertension, n (%)	19 (6)	13 (6)	6 (7)	0.80
Severe Pulmonary Hypertension, n (%)	8(3)	5(2)	3 (3)	0.70
Chronic obstructive pulmonary disease, n (%)	91(29)	63(28)	28(31)	0.67
Atrial fibrillation, n (%)	75(24)	57(26)	18(20)	0.27
Permanent pacemaker, n (%)	28 (9)	21(10)	7 (8)	0.62
<u>Laboratory results</u>				
Creatinine (umol/L), median (IQR)	95 (77-120)	93 (75-115)	97 (80-126)	0.17
Hemoglobin (g/dl), median (IQR)	7.6 (7.1-8.3)	7.6 (7.1-8.3)	7.7 (7.1-8.4)	0.51
<u>Echocardiography</u>				
Left ventricular ejection fraction, mean ± SD	50 ± 14	50 ± 15	50 ± 13	1.00
Aortic valve area (cm2), median (IQR)	0.7 (0.5-0.8)	0.7 (0.5-0.8)	0.7 (0.5-0.8)	0.42
Peak gradient, median (IQR)	68 (54-85)	67 (53-85)	76 (55-88)	0.093
Mitral regurgitation grade ≥ II, n (%)	163 (52)	118 (54)	45(50)	0.50
Aortic regurgitation grade ≥ II, n (%)	150 (48)	107 (49)	43(48)	0.89
AR grade ≥ II baseline, n (%)	179 (57)	115 (52)	64(70)	0.003
AR index baseline, median (IQR)	28 (20-35)	28 (21-36)	26 (20-34)	0.40
Logistic Euroscore, median (IQR)	13 (9-22)	13 (9-21)	13 (10-23)	0.68
Multi-sliced Computed Tomography				
Bicpusid aortic valve, n (%)	20 (6)	13 (6)	7 (8)	0.58
Type 0	4(1)	2(1)	2 (2)	
Type 1 L-R	9(3)	6(3)	3 (3)	
Type 1 R-N	4(1)	3(1)	1 (1)	
Type 1 N-L	3(1)	2(1)	1 (1)	
minimal annulus diameter (mm), median (IQR)	21.7(20.0-23.3)	21.4(19.9-23.2)	22.1(20.4-23.4)	0.060

maximal annulus diameter (mm), mean ± SD	27.3 ± 2.8	27.0 ± 2.8	27.9 ± 2.7	0.018
mean annulus diameter (mm), median (IQR)	24.3 (22.9-26.1)	24.0 (22.6-26.0)	25.0 (23.5-26.3)	0.025
aortic valve Agatston (/1000) score, median (IQR)	3.0 (2.0-4.3)	2.6 (1.8-3.8)	3.9 (2.9-5.3)	<0.001
aortic eccentricity, median (IQR)	0.20 (0.16-0.25)	0.21 (0.16-0.25)	0.20 (0.15-0.24)	0.68

Table 2. Procedure related factors in patients undergoing transcatheter aortic valve implantation.

	Entire cohort n = 313	AR post TAVI-Sellers grade 0-1 n = 222	AR post TAVI-Sellers grade 2,3,4 n = 91	p-value
Device, n (%)				
Medtronic CoreValve	259(83)	174 (78)	85(93)	0.001
Edwards Sapien	54(17)	48(22)	6(7)	0.001
Access strategy, n (%)				
Trans-femoral	281(90)	200 (90)	81(89)	0.78
Trans-apical	16(5)	13 (6)	3(3)	0.41
Trans-subclavian	16(5)	9(4)	7(8)	0.26
Trans-iliacal	1(0)	1(1)	0(0)	1.00
Circulatory support , n (%)	7(2)	3(1)	4(4)	0.20
Prosthesis size, n (%)				
23, 26 –mm	101(32)	74(33)	27(30)	0.53
29, 31-mm	179(57)	118 (53)	61(67)	0.024
Pre- implantation balloon dilation, n (%)	303(97)	215 (97)	88(98)	1.00
Ratio Ballon/Annulus (Dmean), median (IQR)	0.92(0.86-0.97)	0.93(0.87-0.98)	0.89(0.85-0.95)	0.013
Ratio Ballon/Annulus (Circumference), median (IQR)	0.90(0.85-0.95)	0.90(0.85-0.95)	0.88(0.84-0.93)	0.018
Post implantation balloon dilation, n (%)	57(18)	28(13)	29(32)	<0.001
Depth of implantation NCC (mm), median (IQR)	6 (4-9)	6 (4-9)	7 (5-9)	0.53
Depth of implantation LCC (mm), median (IQR)	7 (5-10)	7 (5-10)	7 (5-10)	0.93
Ratio Valve/Annulus(Dmin), median (IQR)	1.29 (1.21-1.37)	1.29 (1.21-1.37)	1.28(1.21-1.35)	0.35
Ratio Valve/Annulus(Dmax), median (IQR)	1.03(0.98-1.07)	1.04(0.98-1.08)	1.02(0.98-1.07)	0.17
Ratio Valve/Annulus(Dmean), median (IQR)	1.15(1.10-1.20)	1.15(1.10-1.21)	1.14(1.09-1.19)	0.24
Ratio Valve/Annulus(Circumference), median (IQR)	1.12(1.07-1.17)	1.13(1.07-1.18)	1.12(1.08-1.15)	0.15

Procedural characteristics

From a procedural perspective, AR ≥2 post TAVI was more often seen after MCS implantation than after ESV (33% vs 11%, p=0.001). There was a similar use of balloon dilatation after MCS and ESV valve implantation (46 (18%) vs 11 (20%), p= 0.65). In patients with AR ≥2 post TAVI, the balloon used for predilatation was smaller (0.89 (0.85-0.95) vs 0.93 (0.87-0.98) , p=0.013) relative to the patient's annulus (mean annulus diameter (Dmean)) and balloon dilatation post valve implantation was more often performed (32% vs 13%, p=<0.001). There was no difference in valve sizing (i.e. nominal valve size relative to the patient's annulus; minimal annulus diameter (Dmin), maximal annulus diameter (Dmax), Dmean, Circumference) nor depth of implantation between the 2 groups.

Propensity score adjusted multivariable analysis

As patients were not randomly allocated to valve type, a propensity score adjusted multivariable analysis was performed. The baseline clinical and procedural details of the total population and of the patients with MCS and those with ESV are summarised in supplemental Table 1 and 2.

Table 3. Multivariable propensity score adjusted analysis for the determination of AR ≥2 post TAVI (Sellers) in the entire cohort (n=313).

	OR (95% CI)	p-value
Male gender	1.194 (0.577-2.472)	0.63
AR grade ≥ II at baseline	2.407 (1.472-3.938)	<0.001
Maximal annulus diameter (Dmax,mm)	0.913 (0.755-1.104)	0.35
Medtronic Corevalve System	6.047 (1.307-27.976)	0.021
Ratio Balloon/Annulus (Circumference)	0.014 (0.000-73.524)	0.33
Ratio Valve/Annulus(Circumference)	0.003 (0.000-2.326)	0.088
Bicuspid aortic valve	0.767 (0.228- 2.575)	0.67

In the propensity score adjusted multivariable analysis, valve type (i.e. MCS) (odds: 6.047 [95%CI; 1.307- 27.976], p=0.021) and AR ≥2 at baseline (odds: 2.407 [95%CI; 1.472 –3.938], p<0.001) were found to be independent determinants of AR ≥2 post TAVI (Table 3). Repeat analysis using echo-Doppler cardiography to discern patients with non-mild and those with moderate-severe AR confirmed the above findings and in particular that the MCS valve (odds:5.259 [95%CI; 1.070-25.851], p=0.041) was an independent determinant of AR≥2 post TAVI (Table 4, supplemental Table 3).

Table 4. Multivariable propensity adjusted analysis for the determination of AR≥2 post TAVI (echocardiography) in n=285.

	OR (95% CI)	p-value
Male gender	1.935 (0.899-4.162)	0.091
AR grade ≥ II at baseline	1.321 (0.800-2.180)	0.28
Maximal annulus diameter (Dmax,mm)	1.178 (0.943-1.471)	0.15
Medtronic Corevalve System	5.259 (1.070-25.851)	0.041
Ratio Balloon/Annulus (Circumference)	7.872 (0.001- 103680)	0.6745
Ratio Valve/Annulus(Circumference)	0.028 (0.00-29.315)	0.31
Aortic Peak Gradient (mmHg)	1.021 (1.006-1.037)	0.005
Bicuspid aortic valve	1.767 (0.523-5.962)	0.36

Discussion

This study confirms that valve type (i.e. MCS) is an important determinant of AR post TAVI also when using CT guided sizing. This is noteworthy given the fact that MSCT has been shown to be superior to 2D echocardiography for a more accurate and reproducible definition of the annular geometry and dimensions leading to improved sizing and, thereby, reducing AR [12,16,17,21,25,26].

With respect to the present findings, we acknowledge that the majority of the patients in this study received the self-expanding MCS while a smaller fraction received the balloon expandable ESV. Also, the observational nature precludes a direct comparison between valves as confounders may have played a role in addition to time bias (experience) since the ESV was used later than the MCS. Yet, the findings were confirmed by a propensity score adjusted multivariable analysis in the angiography as well as in the echocardiography population. The higher incidence of AR after MCS implantation can be explained by the findings of CT revealing that the MCS valve – especially at the inflow or ventricular end - is more often elliptical while the ESV is more often circular [12,30-32]. In a series of 30 patients who underwent MSCT after TAVI, symmetrical expansion of the MCS valve was seen in only 5 patients (17%) while circularity of the ESV was seen in all but 2 out of 89 patients (98%) and was independent of the native annular anatomy [30,31]. This indicates that the MCS conforms to the geometry of the patient's annulus while the ESV dictates the geometry of the annulus.

Moreover, in a series of 110 patients treated with MCS, aortic root calcification had a higher discriminatory power for the prediction of balloon dilatation after MCS valve implantation than annulus dimensions or prosthesis to annulus ratio [14]. In another 56 patients treated with the MCS, mal-apposition was seen in 35 (63%) and occurred at specific anatomic locations of the left ventricular outflow tract coinciding with AR that did not only depend on depth of implantation but also the calcium load of the aortic root [15]. Asymmetrical expansion is also seen at higher levels of the MCS frame and may also contribute to AR post TAVI [30,33].

Aetiology AR post TAVI

AR after ESV implantation appears to be predominantly the result of inappropriate sizing rather than frame geometry or apposition [11,12,16,17,20,21]. As mentioned above, the ESV is more often circular and a low cover index has consistently been reported to be associated with AR post TAVI. This has recently been confirmed by the French registry revealing an inverse relationship with cover index and degree of AR [22]. This was not the case for the MCS valve in which no association between AR and cover index was found. The question is, however, whether the cover index can adequately be measured for the MCS valve given the hourglass configuration of the frame and the varying degree of depth of implantation. These data indicate the importance of correct sizing when using the ESV (i.e. neither under- nor oversizing) while some degree of oversizing may be needed when using the MCS valve to overcome the calcium load and/or to compensate for variations in position.

Assessment of AR post TAVI

Similar to the CHOICE study that compared valve function between the MCS and ES valve, contrast angiography was the principal method to address the current study objective [24]. The reason is twofold; contrast angiography is used during every TAVI procedure for guidance and evaluation and because of the recognized limitations of echo-Doppler cardiography for AR assessment post valve implantation [34,35]. Although contrast angiography has been reported to overestimate the AR severity in comparison to echo-Doppler, it has conceptually the advantage over echo-Doppler cardiography - analogous to MRI – to represent the accumulation of contrast in the left ventricle that is the sum effect of all regurgitant jets irrespective of number, location, direction, regurgitation path and/or eventual signal attenuation in the presence of calcium and frame [34-39].

Even when using multiparametric echo analysis, echo-Doppler has recently been shown to inaccurately estimate AR severity following TAVI [38,39]. Obviously, the question is how contrast angiography compares to MRI and is subject of ongoing research. Noteworthy, irrespective of the former discussion, repeat analysis using echo-Doppler assessment (VARC-2 criteria) confirmed the angiographical analysis. In addition to the limitations summarised above, the herein reported findings only relate to the MCS and ESV (Sapien, XT) but not to other type of valves such as among others the novel generation self-expanding CoreValve Evolut R valve. Also, the explanation why AR is more frequent after MCS than ESV (Sapien, XT) implantation is deduced from MSCT analysis of the frame from different populations and studies. It remains to be seen whether the present explanation will be confirmed when analysing novel generations of valves. Device-host interaction is complex and novel generations of devices may interact in a different way with the host. Yet, the findings of this observational study complement those of the randomised CHOICE study, thereby, enforcing the role of valve type in the aetiology of AR.

Conclusion

AR≥2 is more prevalent after MCS valve implantation and is an independent determinant of AR also when using MSCT guided sizing. This is most likely due to the intrinsic biomechanical properties and design of the valve indicating room for improvement.

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Supplementary material

Supplemental table 1. Baseline characteristics of patients undergoing transcatheter aortic valve implantation. Distinction between patients with MCS and ESV.

	Entire cohort n = 313	MCS n=259	ESV n=54	p-value
Age (yrs), median (IQR)	81 (76-85)	81 (77-85)	77 (72-81)	<0.001
Male, n (%)	166 (53)	139 (54)	27 (50)	0.62
Height (cm), median (IQR)	168 (162-174)	168 (162-175)	167 (162-172)	0.78
Weight (kg), median (IQR)	74 (65-85)	73 (65-84)	77 (63-90)	0.35
Body mass index (kg/m2), median (IQR)	26 (24-29)	26 (24-29)	27 (23-31)	0.24
Body surface area (m2), mean ± SD	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.68
New York Heart Association class ≥ III, n (%)	239 (78)	197 (78)	42 (79)	0.79
Previous cerebrovascular event, n (%)	66 (21)	56 (22)	10 (19)	0.61
Previous myocardial infarction, n (%)	73 (23)	56 (22)	17 (32)	0.12
Previous coronary artery bypass graft surgery,n (%)	73 (23)	63 (24)	10 (19)	0.36
Previous percutaneous coronary intervention,n (%)	91 (29)	75 (29)	16 (30)	0.92
Diabetes mellitus, n (%)	87 (28)	70 (27)	17 (32)	0.51
Hypertension, n (%)	210 (67)	167 (65)	43 (80)	0.031
Peripheral vascular disease, n (%)	68 (22)	50 (19)	18 (33)	0.023
Pulmonary Hypertension, n (%)	19 (6)	13 (5)	6 (11)	0.11
Severe Pulmonary Hypertension, n (%)	8 (3)	7 (3)	1 (2)	1.00
Chronic obstructive pulmonary disease, n (%)	91 (29)	77 (30)	14 (26)	0.58
Atrial fibrillation, n (%)	75 (24)	66 (26)	9 (17)	0.17
Permanent pacemaker, n (%)	28 (9)	25 (10)	3 (6)	0.44
Laboratory results				
Creatinine (umol/L), median (IQR)	95 (77-120)	94 (75-120)	97 (81-120)	0.50
Hemoglobin (g/dl), median (IQR)	7.6 (7.1-8.3)	7.6 (7.1-8.4)	7.6 (7.1-8.2)	0.70
Echocardiography				
Left ventricular ejection fraction, mean ± SD	50 ± 14	50 ± 14	48 ± 13	0.48
Aortic valve area (cm2), median (IQR)	0.7 (0.5-0.8)	0.7 (0.5-0.8)	0.7 (0.6-0.9)	0.039
Peak gradient, median (IQR)	68 (54-85)	67 (54-85)	71 (57-85)	0.81
Mitral regurgitation grade ≥ II, n (%)	163 (52)	131 (51)	32 (60)	0.20
Aortic regurgitation grade ≥ II, n (%)	150 (48)	118 (46)	32 (59)	0.079
AR Pre Sellers grade ≥ II, n (%)	179 (57)	148 (57)	31 (57)	0.97
AR index Pre, median (IQR)	28 (20-35)	28 (21-36)	23 (16-29)	0.001
Logistic Euroscore, median (IQR)	13 (9-22)	13 (10-22)	13 (7-20)	0.14
Multi-sliced Computed Tomography				
Bicpusid aortic valve, n (%)	20 (6)	17 (7)	3 (6)	1.00
Type 0	4 (1)	4 (2)	0 (0)	
Type 1 L-R	9 (3)	7 (3)	2 (4)	
Type 1 R-N	4 (3)	3 (1)	1 (2)	
Type 1 N-L	3 (1)	3 (1)	0 (0)	
minimal annulus diameter (mm), median (IQR)	21.7 (20.0-23.3)	21.7 (20.0-23.3)	21.4 (20.1-23.2)	0.81
maximal annulus diameter (mm), mean ± SD	27.3 ± 2.8	27.3 ± 2.8	27.2 ± 2.8	0.76
mean annulus diameter (mm), median (IQR)	24.3 (22.9-26.1)	24.4 (22.9-26.1)	23.9 (22.8-26.1)	0.63
aortic valve Agatston 1000 score, median (IQR)	3.0 (2.0-4.3)	3.0 (2.0-4.3)	2.6 (1.9-4.0)	0.65
aortic eccentricity, median (IQR)	0.20 (0.16-0.25)	0.20 (0.16-0.25)	0.21 (0.15-0.25)	0.91

Supplemental table 2. Procedure related factors in patients undergoing transcatheter aortic valve implantation. Distinction between patients with MCS and ESV.

	Entire cohort n = 313	MCS n=259	ESV n=54	p-value
Access strategy, n (%)				
Trans-femoral	281 (90)	243 (94)	38 (70)	<0.001
Trans-apical	16 (5)	0 (0)	16 (30)	<0.001
Trans-subclavian	16 (5)	16 (6)	0 (0)	0.084
Trans-iliacal	1 (0)	1 (0)	0 (0)	1.00
Circulatory support , n (%)	7 (2)	7 (3)	0 (0)	0.61
Prosthesis size, n (%)				
23, 26 –mm	101 (32)	69 (27)	32 (59)	<0.001
29, 31-mm	179 (57)	174 (67)	5 (9)	<0.001
Pre- implantation balloon dilation, n (%)	303 (97)	251 (97)	52 (96)	0.66
Ratio Ballon/Annulus (Dmean), median (IQR)	0.92 (0.86-0.97)	0.92 (0.86-0.97)	0.93 (0.86-0.98)	0.52
Ratio Ballon/Annulus (Circumference) median (IQR)	0.90 (0.85-0.95)	0.90 (0.84-0.94)	0.91 (0.87-0.96)	0.087
Post implantation balloon dilation, n (%)	57 (18)	46 (18)	11 (20)	0.65
Depth of implantation NCC (mm), median (IQR)	6 (4-9)	7 (4-10)	5 (4-6)	0.002
Depth of implantation LCC (mm), median (IQR)	7 (5-10)	8 (5-11)	5 (4-6)	<0.001
Ratio Valve/Annulus(Dmin), median (IQR)	1.29 (1.21-1.37)	1.32 (1.24-1.38)	1.21 (1.13-1.26)	<0.001
Ratio Valve/Annulus(Dmax), median (IQR)	1.03 (0.98-1.07)	1.04 (1.00-1.08)	0.95 (0.92-1.00)	<0.001
Ratio Valve/Annulus(Dmean), median (IQR)	1.15 (1.10-1.20)	1.16 (1.11-1.21)	1.07 (1.03-1.11)	<0.001
Ratio Valve/Annulus(Circumference), median (IQR)	1.12 (1.07-1.17)	1.13 (1.09-1.18)	1.03 (1.00-1.07)	<0.001

Supplemental table 3. Baseline and procedural characteristics of patients undergoing transcatheter aortic valve implantation with AR severity based on echocardiography.

	Entire cohort n = 285	AR < 10% of circumference by echocardiography n = 191	AR ≥ 10% of circumference by echocardiography n = 94	p-value
Age (yrs), median (IQR)	81 (76-85)	81 (77-84)	81 (72-85)	0.64
Male, n (%)	150 (53)	84 (44)	66 (70)	<0.001
Height (cm), median (IQR)	168 (162-174)	165 (160-172)	170 (164-178)	<0.001
Weight (kg), median (IQR)	74 (64-84)	74 (64-85)	73 (64-83)	0.59
Body mass index (kg/m2), median (IQR)	26 (23-29)	27 (24-30)	25 (22-27)	0.005
Body surface area (m2), mean ± SD	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.55
New York Heart Association class ≥ III, n (%)	220 (77)	151 (79)	69 (73)	0.18
Previous cerebrovascular event, n (%)	62 (22)	33 (17)	29 (31)	0.009
Previous myocardial infarction, n (%)	66 (23)	48 (25)	18 (19)	0.26
Previous coronary artery bypass graft surgery,n (%)	67 (24)	44 (23)	23 (25)	0.79
Previous percutaneous coronary intervention,n (%)	81 (28)	57 (30)	24 (26)	0.45
Diabetes mellitus, n (%)	79 (28)	56 (29)	23 (25)	0.39
Hypertension, n (%)	192 (67)	131 (69)	61 (65)	0.53
Peripheral vascular disease, n (%)	58 (20)	39 (20)	19 (20)	0.97
Pulmonary Hypertension, n (%)	18 (6)	12 (6)	6 (6)	0.97
Severe Pulmonary Hypertension, n (%)	8 (3)	6 (3)	2 (2)	1.00
Chronic obstructive pulmonary disease, n (%)	78 (27)	53 (28)	25 (27)	0.84
Atrial fibrillation, n (%)	70 (25)	44 (23)	26 (28)	0.39
Permanent pacemaker, n (%)	27 (10)	19 (10)	8 (9)	0.70
Laboratory results				
Creatinine (umol/L), median (IQR)	94 (76-120)	93 (75-119)	96 (82-122)	0.26
Hemoglobin (g/dl), median (IQR)	7.7 (7.1-8.4)	7.6 (7.1-8.2)	7.8 (7.1-8.6)	0.12
Echocardiography				
Left ventricular ejection fraction, mean ± SD	50 ± 14	50 ± 14	51 ± 13	0.76
Aortic valve area (cm2), median (IQR)	0.70 (0.50-0.80)	0.70 (0.50-0.80)	0.70 (0.51-0.81)	0.89
Peak gradient, median (IQR)	67 (53-85)	64 (52-85)	77 (60-89)	0.014
Mitral regurgitation grade ≥ II, n (%)	146 (51)	100 (52)	46 (49)	0.62
Aortic regurgitation grade ≥ II, n (%)	136 (48)	92 (48)	44 (47)	0.77
AR Pre Sellers grade ≥ II, n (%)	167 (59)	103 (54)	64 (68)	0.023
AR index Pre, median (IQR)	28 (20-35)	27 (20-35)	28 (21-35)	0.44
Logistic Euroscore, median (IQR)	13 (9-22)	13 (10-24)	13 (8-20)	0.17
Multi-sliced Computed Tomography				
Bicpusid aortic valve, n (%)	19 (7)	7 (4)	12 (13)	0.004
Type 0	4 (1)	1 (1)	3 (3)	
Type 1 L-R	8 (3)	3 (2)	5 (5)	
Type 1 R-N	4 (1)	2 (1)	2 (2)	
Type 1 N-L	3 (1)	1 (1)	2 (2)	
minimal annulus diameter (mm), median (IQR)	21.7 (20.0-23.2)	21.3 (19.6-23.0)	22.4 (20.8-24.1)	<0.001

maximal annulus diameter (mm), mean ± SD	27.3 ± 2.8	26.8 ± 2.7	28.4 ± 2.6	<0.001
mean annulus diameter (mm), median (IQR)	24.3 (22.9-26.0)	23.8 (22.5-25.7)	25.1 (23.9-27.0)	<0.001
aortic valve Agatston 1000 score, median (IQR)	3.0 (2.0-4.4)	2.6 (1.7-3.7)	4.1 (2.7-5.5)	<0.001
aortic eccentricity, median (IQR)	80 (75-84)	80 (75-84)	80 (75-84)	0.65
Device, n (%)				
Medtronic CoreValve	239 (84)	152 (80)	87 (93)	0.005
Edwards Sapien	46 (16)	39 (20)	7 (7)	0.005
Access strategy, n (%)				
Trans-femoral	261 (92)	172 (90)	89 (95)	0.19
Trans-apical	10 (4)	9 (5)	1 (1)	0.17
Trans-subclavian	14 (5)	10 (5)	4 (4)	1.00
Trans-iliacal	1 (0)	1 (1)	0 (0)	1.00
Circulatory support , n (%)	6 (2)	6 (3)	0 (0)	0.18
Prosthesis size, n (%)				
23, 26 –mm	91 (32)	74 (39)	17 (18)	<0.001
29, 31-mm	165 (58)	92 (48)	73 (78)	<0.001
Pre- implantation balloon dilation, n (%)	275 (97)	186 (97)	89 (96)	0.48
Ratio Ballon/Annulus (Dmean), median (IQR)	0.92 (0.87-0.97)	0.93 (0.87-0.98)	0.90 (0.84-0.95)	0.002
Ratio Ballon/Annulus (Circumference), median (IQR)	0.90 (0.85-0.94)	0.90 (0.85-0.95)	0.88 (0.82-0.93)	0.007
Post implantation balloon dilation, n (%)	53 (19)	22 (12)	31 (33)	<0.001
Depth of implantation NCC (mm), median (IQR)	6 (4-9)	6 (4-9)	7 (4-10)	0.58
Depth of implantation LCC (mm), median (IQR)	7 (5-10)	7 (5-10)	7 (4-10)	0.87
Ratio Valve/Annulus(Dmin), median (IQR)	1.29 (1.21-1.37)	1.30 (1.22-1.37)	1.29 (1.19-1.36)	0.32
Ratio Valve/Annulus(Dmax), median (IQR)	1.03 (0.98-1.07)	1.04 (0.98-1.08)	1.02 (0.98-1.06)	0.056
Ratio Valve/Annulus(Dmean), median (IQR)	1.15 (1.10-1.20)	1.15 (1.10-1.21)	1.13 (1.09-1.18)	0.099
Ratio Valve/Annulus(Circumference), median (IQR)	1.12 (1.07-1.17)	1.13 (1.08-1.18)	1.11 (1.06-1.15)	0.070

CHAPTER 3 Vascular Complications after Transfemoral Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Vascular complications (VCs) after transcatheter aortic valve implantation (TAVI) are associated with impaired outcome. We performed a meta-analysis to determine in-hospital/30-day major VCs rate after transfemoral TAVI adjudicated by an independent clinical event committee, and to compare the major VCs rate with regard to consecutive generations of balloon-expandable and self-expanding platforms, device profile, experience and patient risk-profile.

Methods: A systematic, computerized search with predefined criteria was performed in PubMed, Embase and Cochrane on March 27, 2018. The overall pooled proportion of VC was calculated using a random-effects model. Subgroups were examined based on sheath size, STS-score and start-date of inclusion (early-phase (< January 2012); late-phase (≥ January 2012) studies).

Results: A total of 24 studies with 14308 patients were included. The pooled major VCs rate was 7.71% and was lower in low-profile vs. high-profile device studies (5.51% vs. 8.46%, p = 0.0015). Major VCs rate decreased significantly with transition to newer generation balloon-expandable valves ((Sapien vs. Sapien XT (15.18% vs. 8.48%, p < 0.00001); Sapien XT vs. Sapien 3 (8.48% vs. 4.48%, p = 0.005)) and there was a tendency towards fewer major VCs in EvolutR vs. CoreValve (5.98% vs. 7.97%, p = 0.094). Major VC rate was lower in late-phase vs. early-phase studies (5.82% vs. 7.84%, p = 0.048) and a tendency towards a lower rate was seen in intermediate vs. high-risk studies (7.09% vs. 9.62%, p = 0.059).

Conclusion: The pooled rate of independently adjudicated major VCs after transfemoral TAVI was 7.71%. Experience and device profile are associated with fewer major VCs.

Introduction

Transcatheter aortic valve implantation (TAVI) is an established treatment for inoperable/high and intermediate-risk patients with severe aortic stenosis [1–4]. Compared to surgical aortic valve replacement (SAVR), TAVI is associated with fewer major bleedings and less new-onset atrial fibrillation, similar survival rates but more vascular complications and conduction abnormalities [3,4]. Several studies have correlated TAVI-induced vascular complications with mortality, increased length of stay and reduced quality of life [5–7].

Over the last decade, device iterations have introduced novel features and smaller profiles. Also, operators gained more experience in performing TAVI. These factors may affect the incidence of vascular complications (VCs) [8].

We sought to perform a meta-analysis of studies that reported in-hospital/30-day rate of major VCs after transfemoral TAVI adjudicated by an independent clinical event committee (CEC), and to compare the rate of major VCs with regard to consecutive generations of balloon-expandable and self-expanding platforms, device profile, experience, and patient risk profile.

Materials and methods

Study design, search, inclusion, and definitions

The study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for meta-analyses [9]. A systematic, computerized search was performed in PubMed, Embase and the Cochrane Library on 27 March 2018. The following search term was used: (“Transcatheter Aortic Valve Replacement” [Mesh] OR “Transcatheter Aortic Valve Replacement” [All Fields] OR “TAVR” [All Fields] OR “Transcatheter Aortic Valve Implantation” [All Fields] OR “TAVI” [All Fields]) AND (“Treatment Outcome” [Mesh] OR “Postoperative Complications” [Mesh] OR “Vascular complications” [All Fields] OR “independent adjudication” [All Fields] OR “cardiovascular events” [All Fields] OR “cardiovascular” [All Fields]). The language was restricted to English and only multicenter studies were included. Two reviewers (ZR and KRM) screened abstracts, methods and results section of every study. Conflicts between reviewers were solved by consensus. If consensus was not reached a senior researcher (NVM) was consulted.

Studies were included if they met all the following criteria:
(1) Multicenter studies (2) including >100 TAVI patients and (3) reporting the incidence of in-hospital or 30-day major vascular complications after transfemoral TAVI (4) adjudicated by an independent clinical events committee. Studies that only included non-transfemoral access were excluded. In case of studies with overlapping patient cohorts, only the study with the largest cohort was retained (Figure 1).

Corresponding authors of studies with transfemoral and non-transfemoral TAVI were approached to obtain relevant data specific to the transfemoral cohort. Only studies with independent CEC endpoint adjudication were selected for this analysis as these studies arguably have the most reliable data reporting avoiding site reporting and limit reporting bias.

Studies were further stratified based on device profile (i.e., sheath inner diameter) into low (≤16 French) and high profiled (>16 French) device studies and based on Society of Thoracic Surgeons score (STS) into intermediate (STS 4–8%) and high risk (STS > 8%) studies. In case the STS score was absent the Logistic EuroScore I was used. A score of 10–20% and >20% were considered intermediate and high risk, respectively. In order to compare the rate of major VCs over time studies were divided into early and late-phase studies: Early-phase studies were defined as studies that started to include patients before January 2012 and late-phase studies as studies that started to include patients ≥ January 2012. Edwards device was pooled with balloon-expandable valves (BEV), CoreValve and Evolut R were pooled with self-expanding devices (SEV).

Statistical analysis

Baseline and procedural characteristics as well as in-hospital/30-day outcome were pooled in a random effects model using the Der Simonian and Laird method. The Cochrane Q statistic and I^2 were used to test for heterogeneity. A p-value of ≤0.1 was considered significant for the Cochrane Q statistic. An I^2 statistic value of <25%, 25%–50% and >50% was considered to denote low, moderate and substantial heterogeneity, respectively. Comparison of subgroups was performed according to the method of Borenstein [10]. In case of three subgroups, a Bonferroni correction for multiple testing was applied (with a threshold for p= 0.05/3). MedCalc (version 17.8.6) and Excel were used to calculate the pooled estimates.

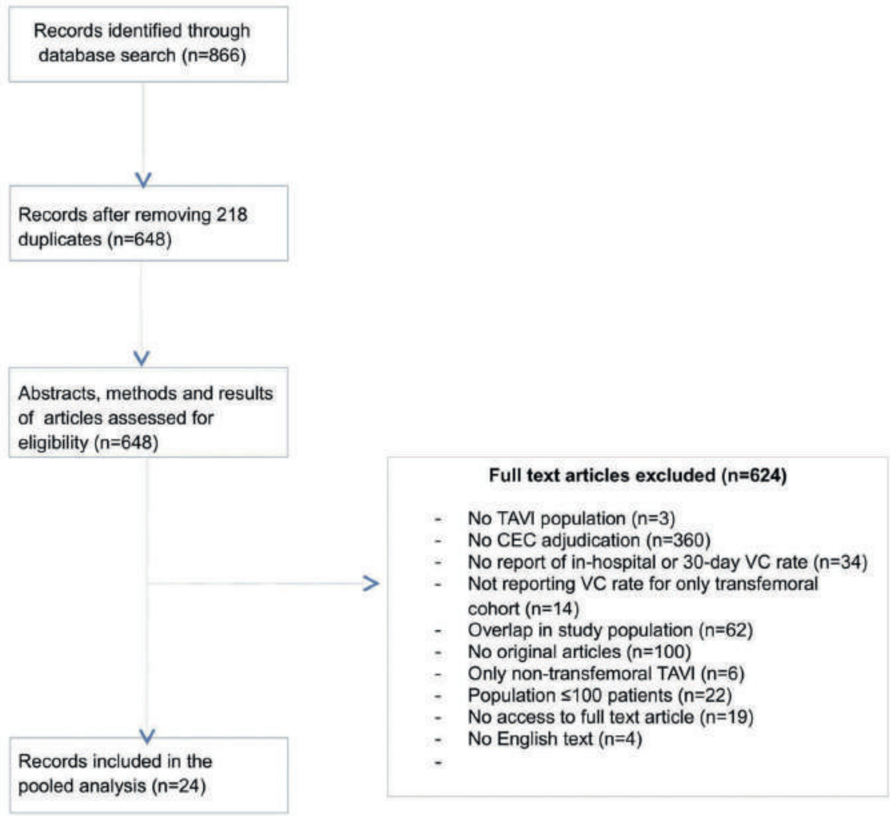


Figure 1. Flow diagram of the study.

TAVI: Transcatheter aortic valve implantation; CEC: Clinical events committee; VC: Vascular complication.

Results

A total of 24 unique studies and 14308 patients were included (Table 1) [1,3,4,11–28]. The pooled mean age was 82.6 years, 43.9% was male and 25.1% had peripheral artery disease. The 30-day logistic EuroSCORE I and Society of Thoracic Surgeons score were 18.7% and 7.2%, respectively. The pooled mean left ventricular ejection fraction was 56.3%, the mean aortic gradient was 45.8 mmHg and aortic valve area was 0.69 (cm^2) (Table 1).

The Medtronic CoreValve was implanted in 33.8%, Evolut R in 14.7%, Edwards Sapien in 8.1%, Edwards XT in 23.8%, Edwards Sapien 3 in 8.7%, Lotus in 5.9%, Direct Flow Medical in 1.7%, Portico in 2.3%, and other (not specified) valve types in 0.9% of the patients (Table 1).

Major VCs were defined according to valve academic research consortium (VARC) 1 or 2 in 87.5% of the studies (Table 1) [29,30].

In-hospital or 30-day outcome

The overall pooled rate of major VCs was 7.71% (95% CI 6.81% to 8.67%); for major bleeding this was 11.58% (95% CI 8.86–14.52%), for life-threatening bleeding 5.79% (95% CI 4.52–7.21%) and for all-cause mortality 3.38% (95% CI 2.73– 4.09%) (Table 2, Figure 2 and Supplemental Figure 1).

The event rate of major VCs was significantly lower in low profile (≤16 Fr) vs. high-profile studies (>16 Fr) (5.51% (95% CI (4.10−7.10)) vs. 8.46% (95% CI (7.44–9.53)), p = 0.0015) (Figure 3). When comparing different generations of BEV studies, the rate of major VCs decreased significantly with the transition to newer generation BEV (Sapien vs. Sapien XT (15.18% (95% CI (12.62–17.93) vs. 8.48% (95% CI (7.56–9.45)), p < 0.00001) and Sapien XT vs. Sapien 3 (8.48% (95% CI (7.56– 9.45) vs. (4.48% (95% CI (2.21–7.50), p = 0.005) (Figure 4a). In the SEV studies, there was a tendency toward fewer major VCs with Evolut R vs. Corevalve ((7.97% (95% CI (7.20–8.80) vs. 5.98% (95% CI (3.98–8.36), p = 0.094) (Figure 4b).

The major VC rate was lower in late-phase (≥ January 2012) vs. early-phase studies (< January 2012) (6.52% vs. 9.38%, p = 0.0011) (Figure 5) and there was a tendency toward fewer major VCs in intermediate-risk vs. high-risk studies (7.09% vs. 9.62%, p = 0.059) (Figure 6).

Discussion

So far this is the first systematic review and meta-analysis, which included only multicenter studies in which vascular complications after transfemoral TAVI were independently adjudicated by a CEC. A total of 24 unique studies with 14308 patients were included. The main findings are:

(1) The pooled rate of major VCs is 7.71% and
(2) is significantly lower with low profile vs. high-profile devices (5.51% vs. 8.46%).
(3) The rate of major VCs decreased significantly with the transition to newer generation BEV.
(4) A tendency toward fewer major VCs with Evolut R vs. Medtronic CoreValve studies was seen.
(5) There was a tendency toward fewer major VCs in intermediate vs. high-risk studies.
(6) There were fewer major VCs in late-phase vs. early-phase studies, suggesting an experience effect.

The pooled rate of 7.71% for major vascular complications may serve as a benchmark and is, despite similar baseline characteristics, lower than the reported 11.9% rate in the meta-analysis by Genereux et al. that studied the earlier TAVI experience [31]. Technology has evolved over the years including smaller profiles and different sheath concepts. Importantly operators gained more experience.

In line with the study of Barbanti et al., we have shown that low-profile sheaths are associated with a lower incidence of major VCs [32]. A lower profile will decrease the sheath to femoral artery ratio (SFAR), which is defined as the ratio of the sheath outer diameter (in millimeters) to the minimal femoral artery diameter (in millimeters). Hayashida et al. identified the SFAR as an important independent predictor for major VC (hazard ratio [HR]: 186.20, 95% CI 4.41 to 7,855.11); a SFAR threshold of 1.05 (area under the curve = 0.727) was associated with a higher rate of major VC [7].

The rate of major VCs decreased significantly with the transition to newer generation BEV (Sapien vs. Sapien XT (15.18% vs. 8.48%, p < 0.00001)) and Sapien XT vs. Sapien 3 (8.48% vs. 4.48%, p = 0.005). Webb et al. randomized 560 patients to either Sapien or Sapien XT and showed, similar to our study, a higher major VC rate in Sapien group [18]. Mussardo et al. showed a threefold higher complication rate in the Sapien group compared to Sapien XT group [33]. The first-generation Sapien valve was 22 or 24 Fr compatible (depending on valve size) and the second-generation Sapien XT 18 or 19 Fr compatible. The Sapien 3 introduced the 14 or 16Fr e-sheath with its dynamic expansion mechanism [34]. Binder et al. compared the Sapien XT with Sapien 3 and showed a lower rate of major VC in Sapien 3 group [12].

With SEV there was a tendency toward fewer major VCs with Evolut R vs. Medtronic CoreValve studies (5.98% vs. 7.97%, p = 0.094). CoreValve is 18 Fr compatible while the InLine™ sheath of the Evolut R is equivalent to 14 Fr. The InLine™ sheath is integrated in Enveo R delivery system and allows valve delivery without requirement of an external sheath [35,36]. The Solopath™ sheath (Terumo Interventional Systems, Somerset, NJ) is another sheath concept that is introduced with a 13Fr profile and exhibits a full expandable (to 19Fr) and recollapsible mechanism, which may facilitate sheath handling during TAVI [37,38].

Our data demonstrate that rate of major VCs was significantly lower in later studies suggesting more operator experience. This ‘learning curve’ was also seen by Ando et al. who showed initially an increase of the overall VC rate from 2011 to 2012 and then a significant decrease from 2012 to 2014 [39]. Lunardi et al. suggested 54 cases were required to reach “acceptable performance’’ and to control the most relevant complications [40]. Minha et al. showed that the occurrence of major VC in the PARTNER-I trial rapidly decreased from nearly 25% to less than 5% by case 135 (p < 0.0001) [41]. The Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC Plus) study showed a significant reduction of major VC over time (15% vs. 7.9%, p = 0.023) and showed that almost 2/3 (64%) of the major VC were related to closure device failure (suture-based) [5,8]. New closure devices (e.g., collagen-based) might reduce the rate of major VCs [42].

Finally, we have shown a tendency toward fewer major VCs in intermediate vs. high-risk studies (7.09% vs. 9.62%, $p = 0.059$). This may be explained by overall growing TAVI experience because intermediate-risk studies occurred later in time. Furthermore, a lower risk profile may also be associated with less peripheral arterial disease and more accessible anatomical substrates.

Limitations

Our analysis is based on study level but not patient-level data, which prohibited performing a comprehensive multivariate regression analysis including the impact of vessel calcification, SFAR, and type of closure device. Difference in the definition of major vascular complication (i.e., VARC-1, VARC-2, and VARC-like) could lead to heterogeneity. According to the VARC-2 definitions, vascular complications may be access and non-access site related. We did not have the patient-level data to distinguish between access and non-access site-related vascular complications. We used early vs. late-phase analysis as a surrogate for operators' experience. We acknowledge that this assumption may not completely reflect the true experience, although we do believe that operators in the late-phase studies were by default more experienced than in the early phase studies, even more so because many centers (and operators) were represented in both the early and late phase studies. Still, our overall dataset is the largest reporting on VC with independent CEC adjudication.

Conclusion

The pooled rate of independently adjudicated major VCs after transfemoral TAVI was 7.71%. Experience and device profile are associated with fewer major VCs.

Table 1. Baseline and procedural characteristics of included papers.

Study	Inclusion period	Total number TF-patients	Age (years) (mean ± SD)	Male (n, %)	STS (%) (mean ± SD)	Log ES I (mean ± SD)	PAD (n, %)	CAD (n, %)	CABG (n, %)	PCI (n, %)	Myocardial infarction (n, %)	NYHA class III/IV (n, %)	LVEF(%) (mean ± SD)	Mean aortic gradient (mm Hg) (mean ± SD)	AVA (cm^2) (mean ± SD)	Valve type	VARC 1/2
Abdel-Wahab M et al. 2014 (CHOICE)[11]	Mar 2012–Dec 2013	241	80.8 ± 12.1	86/241 (35.7)	5.9 ± 3.4	21.8 ± 13.8	42/241 (17.4)	152/241 (63.1)	34/241 (14.1)	95/241 (39.4)	30/241 (12.4)	195/241 (80.9)	53.7 ± 12.9	43.2 ± 14.7	0.7 ± 0.2	ES XT (n = 121); MCV (n = 120)	VARC 1
Binder RK et al. 2015 (Swiss TAVI Registry)[12]	Feb 2011–Jun 2014	598	82.2 ± 6.6	277/598 (46.3)	8.2 ± 7.6	21.7 ± 16.0	89/598 (14.9)	328/598 (54.8)	-	-	91/598 (15.2)	393/598 (65.7)	56.4 ± 13.8	44.6 ± 18.6	0.71 ± 0.22	SAPIEN 3 (n = 153); ES XT (n = 445)	VARC 2
Vahanian A et al. 2016[13]	> Jan 2012	101	84.4 ± 3.8	46/101 (45.5)	5.2 ± 1.7	13.2 ± 3.8	16/101 (15.8)	56/101 (55.4)	11/101 (10.9)	-	11/101 (10.9)	65/101 (64.4)	57.3 ± 11.5	47.1 ± 13.3	0.7 ± 0.19	SAPIEN 3 (n = 101)	VARC 2
Manoharan G et al. 2016[14]	Dec 2011–	102	84.1 ± 4.8	3/102 (2.9)	5.6 (4.1–7.2)	15.1 (11.0–22.0)	6/102 (5.9)	48/102 (47.1)	6/102 (5.9)	19/102 (18.6)	10/102 (9.8)	81/102 (79.4)	-	45.3 ± 13.8	0.6 ± 0.2	Portico (n = 100)	VARC 1
Noble et al. 2017 (Swiss TAVI Registry)[15]	Feb 2011–Feb 2016	995	82.6 ± 6.3	371/995 (37.3)	6.2 ± 4.6	19.2 ± 13.1	126/995 (12.7)	512/995 (51.5)	-	-	121/995 (12.2)	652/995 (65.5)	55.8 ± 14.2	43.2 ± 18.5	0.69 ± 0.3	Evolut R (n = 317); MCV (n = 678)	VARC 2
Thourani VH et al. 2016[16]	Feb 2014–Sept 2014	952	-	.	-	-	-	-	-	-	-	-	-	-	-	SAPIEN 3 (n = 952)	VARC 2
Smith CR et al. 2011 (PARTNER A)[3]	11 May 2007–28 Aug 2009	244	-	.	-	-	-	-	-	-	-	-	-	-	-	ES (n = 240)	VARC-like
Schymik G et al. 2015 (SOURCE XT)[17]	Jul 2010–Nov 2011	1685	82.0 ± 6.5	600/1685 (35.6)	8.0 ± 6.8 (n = 1436)	19.8 ± 11.6 (n = 1682)	248/ 1.684 (14.7)	667/ 1.685 (39.6)	204/ 1.685 (12.1)	460/ 1.685 (27.3)	205/1.685 (12.2)	1.299/1.676 (77.5)	55.1 ± 12.5 (n = 1594)	49.2 ± 16.5 (n = 1580)	0.7 ± 0.2 (n = 1402)	ES XT (n = 1685)	VARC 1
Leon MB et al. 2016 (PARTNER 2A)[4]	Dec 2011–Nov 2013	775	81.8 ± 6.7	426/775 (55.0)	5.8 ± 2.1	-	221/775 (28.5)	531/775 (68.5)	179/775 (23.1)	202/775 (26.1)	137/775 (17.7)	601/775 (77.5)	56.3 ± 10.8	45.0 ± 13.8	0.7 ± 0.2	ES XT (n = 775)	VARC 2
Webb JG et al. 2015 (PARTNER 2B)[18]	Mar 2011–Feb 2012	560	84.3 ± 8.7	283/560 (50.5)	10.6 ± 5.5	19.9 ± 15.8	163/560 (29.1)	372/560 (66.4)	148/560 (26.4)	190/560 (33.9)	113/560 (20.2)	540/560 (96.4)	52.6 ± 13.6	45.1 ± 13.9	0.6 ± 0.2	ES (n = 270); ES XT (n = 282)	VARC 1
Leon MB et al. 2010 (PARTNER B)[1]	May 2007–March 2009	179	83.1 ± 8.6	82/179 (45.8)	11.2 ± 5.8	26.4 ± 17.2	54/178 (30.3)	121/179 (67.6)	58/155 (37,4)	47/154 (30,5)	33/177 (18,6)	165/179 (92,2)	53.9 ± 13.1	44.5 ± 15.7	0.6 ± 0.2	ES (n = 173)	VARC-like
Asgar A et al. 2017 (BRAVO-3)[19]	Oct 2012–May 2015	802	82.3 ± 6.4	411/802 (51.2)	-	17.1 ± 10.4	119/802 (14.8)	405/802 (50.5)	117/802 (14.6)	-	116/802 (14.5)	-	53.6 ± 12.6	-	-	ES (n = 445); MCV (n = 211); other (n = 126)	-
Popma JJ et al. 2014 (US Pivotal Extreme-risk)[20]	Feb 2011–Aug 2012	489	83.2 ± 8.7	234/489 (47.9)	10.3 ± 5.5	22.6 ± 17.1	171/486 (35.2)	400/489 (81.8)	193/489 (39.5)	181/489 (37.0)	151/489 (30.9)	449/489 (91.8)	54.5 ± 14.4 (48.7)	47.3 ± 14.6 (n = 481)	0.73 ± 0.23 (n = 390)	MCV (n = 486)	VARC 1
US Pivotal Extreme-risk CAS	Mar 2012–Apr 2014	1257	83.4 ± 8.1	689/1257 (54.8)	9.1 ± 5.1	24.2 ± 17.1	541/1253 (43.2)	1006/ 1257 (80)	454/1257 (36.1)	510/ 1257 (40.6)	336/1255 (26.8)	1098/1257 (87.4)	52.7 ± 14.2 (n = 1248)	46.8 ± 12.5 (n = 1255)	0.69 ± 0.36 (n = 1216)	MCV (n = 1252)	VARC 1
Adams DH et al. 2014 (US Pivotal High-risk)[21]	Feb 2011–Sept 2012	324	83.4 ± 6.9	172/324 (53.1)	7.3 ± 3.1	18.0 ± 13.2	119/321 (37.1)	245/324 (75.6)	102/324 (31.5)	105/324 (32.4)	74/324 (22.8)	282/324 (87.0)	58.15 ± 10.87 (n = 321)	48.65 ± 15.03 (n = 321)	0.72 ± 0.23 (n = 290)	MCV (n = 324)	VARC 1
US Pivotal High-risk CAS	Oct 2012–Aug 2014	963	83.8 ± 7.1	572/963 (59.4)	7.6 ± 3.3	20.2 ± 13.2	408/961 (42.5)	734/963 (76.2)	322/963 (33.4)	366/963 (38.0)	251/963 (26.1)	807/963 (83.8)	54.2 ± 13.5 (n = 961)	48.3 ± 13.5	0.67 ± 0.23 (n = 944)	MCV (n = 960)	VARC 1
Reardon MJ et al. 2017 (SURTAVI)[22]	Jul 2012–Jul 2016	808	80.0 ± 6.2	475/808 (58.8)	4.4 ± 1.5	11.8 ± 7.6	431/674 (63.9)	505/808 (62.5)	128/808 (15.8)	172/808 (21.3)	115/808 (14.2)	482/808 (59.7)	61.1 ± 9.7 (n = 807)	46.9 ± 13.7 (n = 801)	0.78 ± 0.23 (n = 739)	MCV (n = 674); Evolut R (n = 134)	VARC 2
SURTAVI CAS	Apr 2015–Jul 2017	378	78.9 ± 6.3	161/378 (42.6)	4.0 ± 1.4	9.0 ± 6.2	89/378 (23.5)	210/378 (55.6)	51/378 (13.5)	86/378 (22.8)	46/378 (12.2)	184/378 (48.7)	64.3 ± 7.9 (n = 376)	45.1 ± 12.6 (n = 369)	0.76 ± 0.21 (n = 331)	Evolut R (n = 378)	VARC 2
Popma JJ et al. 2017 (Evolut R U.S.)[23]	Sep 2014–Jul 2015	214	83.6 ± 7.0	68/214 (31.8)	7.3 ± 3.3	-	67/214 (31.3)	-	50/214 (23.4)	64/214 (29.9)	33/214 (15.4)	181/214 (84.6)	59.8 ± 12.2	47.7 ± 12.5	0.6 ± 0.2 (n = 194)	Evolut R (n = 214)	VARC 2
Grube et al. 2017 (Evolut R Forward)[24]	Jan 2016–Dec 2016	1007	81.7 ± 6.2	350/1007 (34.8)	5.5 ± 4.5	17.3 ± 11.6	214/1003 (21.3)	-	104/1000 (10.4)	276/ 1003 (27.5)	146/996 (14.7)	729/1003 (72.7)	60.5 ± 12.0 (n = 856)	41.6 ± 16.1 (n = 898)	0.8 ± 0.3 (n = 612)	Evolut R (n = 1007)	VARC 2
Naber CK et al. 2016 (DISCOVER)[25]	Mar 2013–	250	82.5 ± 5.5	153/250 (61.2)	8.2 ± 8.4 (n = 131)	18.3 ± 13.6 (n = 248)	-	165/250 (66.0)	45/250 (18.0)	112/250 (44.8)	-	175/235 (74.5)	53.7 ± 12.7 (n = 231)	48.3 ± 14.8 (n = 222)	0.72 ± 0.18 (n = 199)	Direct Flow (n = 239)	VARC 2
Meredith IT et al. 2017 (REPRISE IIE)[26]	Apr 2013–	250	84.0 ± 5.2	119/250 (47.6)	6.5 ± 4.2	-	-	-	-	-	-	193/250 (77.2)	-	45.4 ± 13.8 (n = 216)	0.68 ± 0.19 (n = 201)	Lotus (n = 249)	VARC 2

Table 2. Pooled rate of in-hospital or 30-day outcome of included studies.

Overall in-hospital or 30-day complications	Pooled rate (%)	95% CI	Test for heterogenity I^2	Cochran's Q	p-value
Major bleeding	11.58	8.86–14.62	95.56	428.08	<0.0001
Life-threatening bleeding	5.79	4.52–7.21	89.60	182.76	<0.0001
All-cause mortality	3.38	2.73–4.09	78.94	109.21	<0.0001

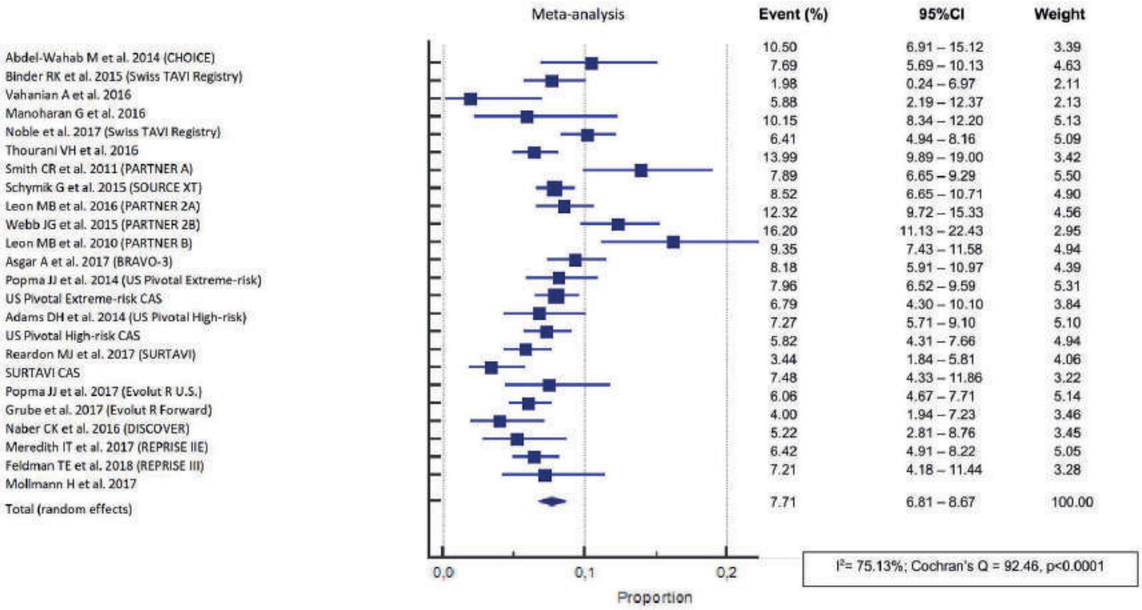


Figure 2. Forest plot for pooled estimate rate of in-hospital or 30-day major vascular complications after transfemoral TAVI.

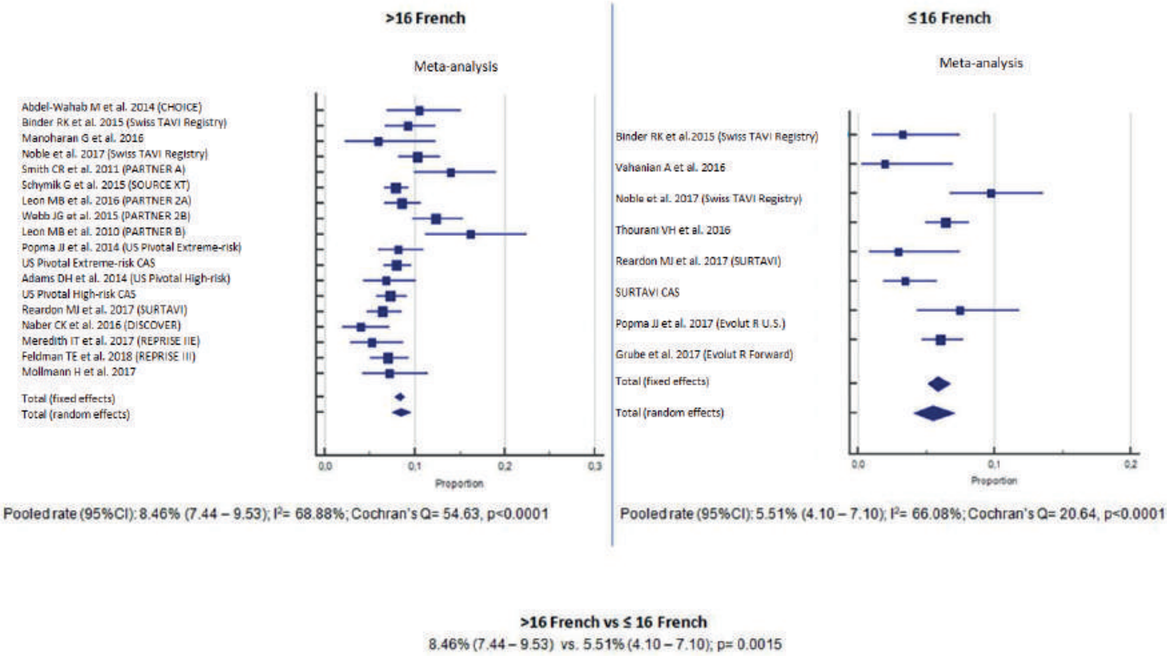


Figure 3. Comparison of major vascular complication rate in high (>16 French) versus low profile (<16 French) device studies.

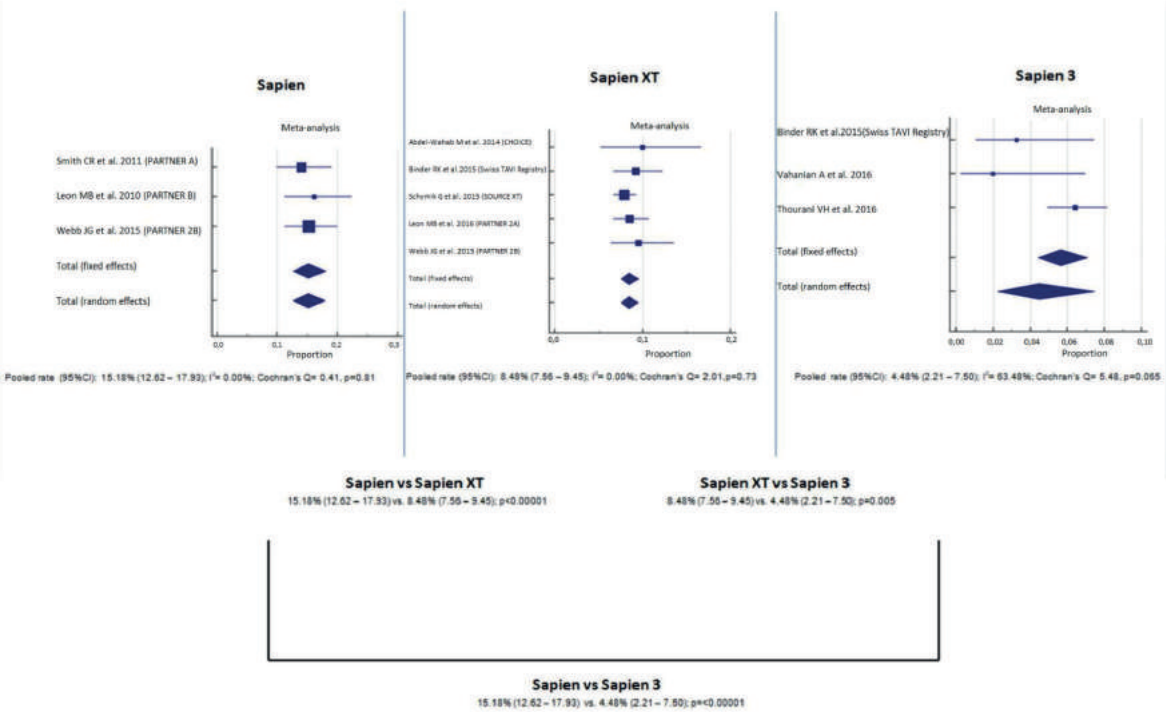
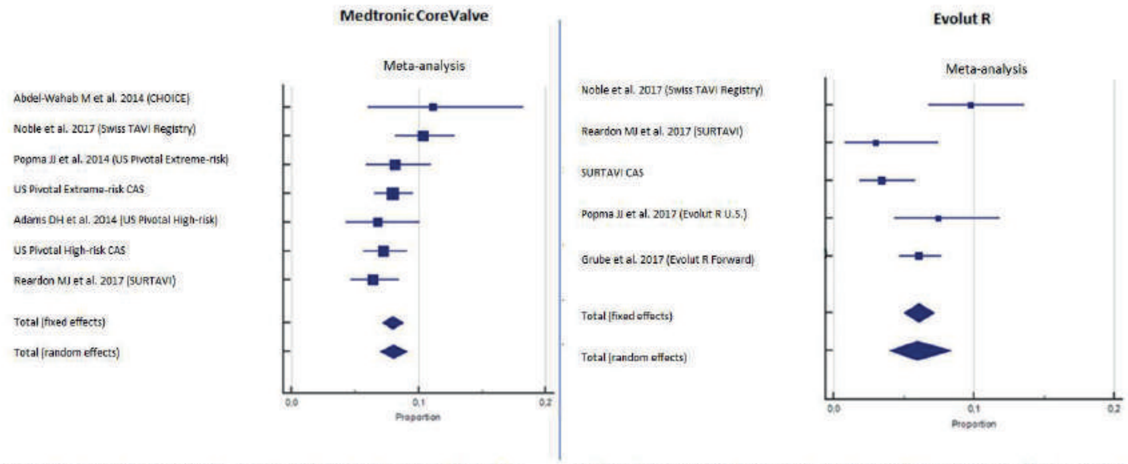


Figure 4a. Comparison of major vascular complication rate in different generation Sapien valve studies.



Pooled estimate (95%CI): 7.97% (7.20 – 8.80); I^2=39.49%; Cochran's Q= 9.92, p= 0.13

Pooled estimate (95%CI): 5.98% (3.98 – 8.36); I^2=73.22%; Cochran's Q= 14.94, p= 0.0048

Medtronic CoreValve vs. Evolut R
7.97% (7.20 – 8.80) vs. 5.98% (3.98 – 8.36); p= 0.094

Figure 4b. Comparison of major vascular complication rate in Medtronic CoreValve vs. Evolut R studies.

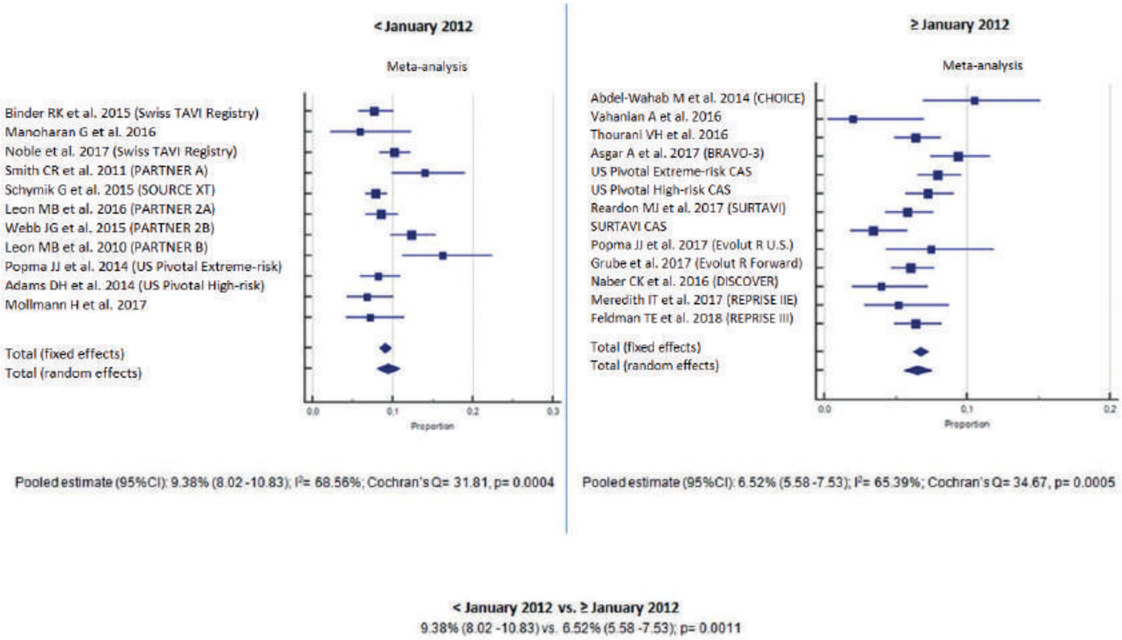


Figure 5. Comparison of major vascular complication rate in early (< January 2012) vs. late phase (≥ January 2012) studies.

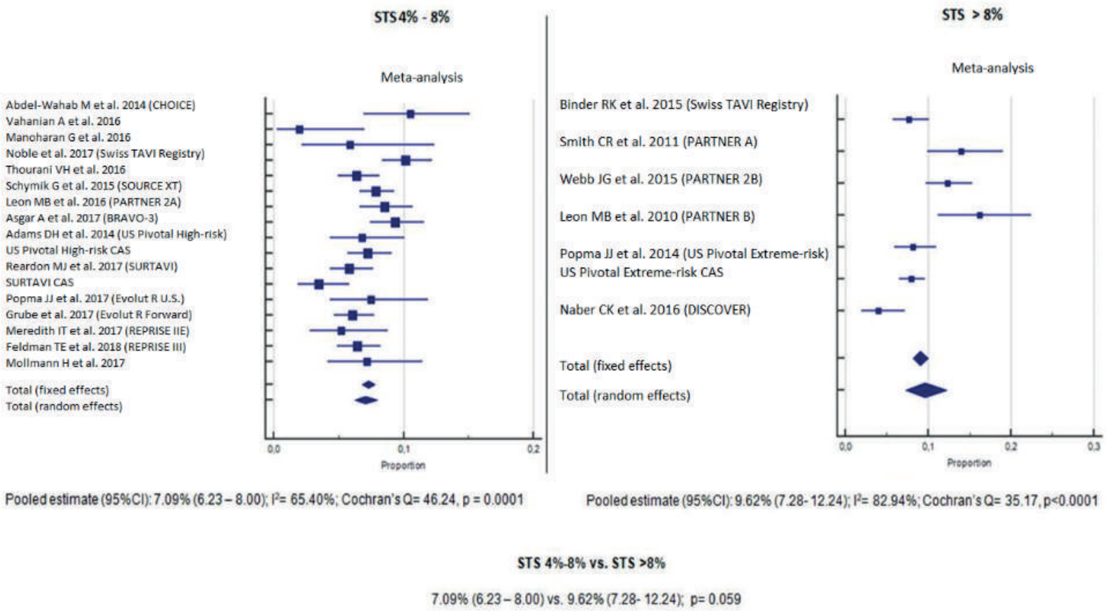


Figure 6. Comparison of major vascular complication rate in intermediate (STS 4–8%) vs. high risk (STS >8%) studies.

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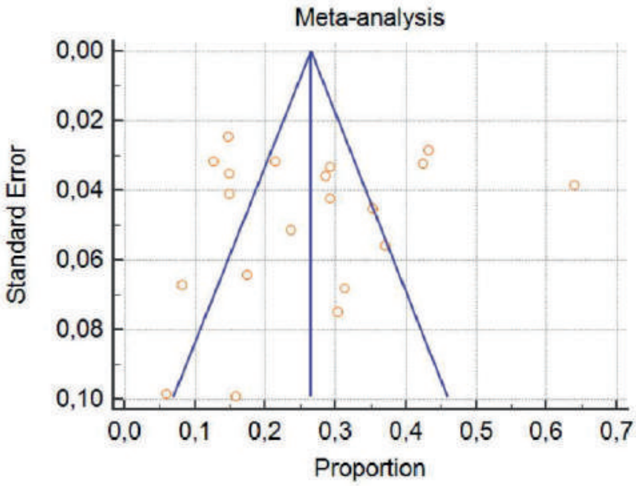
Supplementary material



Supplemental Figure 1: Funnel plot based on major vascular complication rate.

CHAPTER 4 Myocardial Injury Post Transcatheter Aortic Valve Implantation Comparing Mechanically Expanded Versus Self-Expandable Versus Balloon-Expandable Valves

Zouhair Rahhab; Quentin Labarre; Vincent J. Nijenhuis; Nahid El Faquir; Chiara de Biase; Raphael Philippart; Robin Heijmen; Isabella Kardys; Nicolas Dumonteil; Peter de Jaegere; Jan van der Heijden; Didier Tchetche; Nicolas M. Van Mieghem

Struct Heart. 2019;3(5):431–437.

ABSTRACT

Background: Myocardial injury (MI) is common with transcatheter aortic valve implantation (TAVI) and may predict poor outcome. We aim: 1) to evaluate the difference in change of high sensitivity Troponin T (hsTnT) within 24h after transfemoral-TAVI between mechanically-expanded (MEV), self-expanding (SEV) and balloon-expandable-valves (BEV); 2) to determine predictors for MI post-TAVI; and 3) to assess whether MI is associated with 30-day mortality.

Methods: This multicenter retrospective observational study included 1208 consecutively treated transfemoral-TAVI patients from three European centers. All patients treated with a MEV, SEV or BEV with available hsTnT measurements at baseline and within 24h post-TAVI were included. Significant MI was defined as an elevation of hsTnT ≥ 15x the upper reference limit.

Results: Overall, the median hsTnT rise was 741 ng/L and was lower with MEV (MEV 335 vs. SEV 901 vs. BEV 649 ng/L, $p < 0.001$). MI occurred in 925 patients (77%) and was less frequent with MEV (MEV 67%, SEV 79% and BEV 76%, $p = 0.007$). Occurrence of MI was similar after implantation of first vs. second-generation SEV (79 vs. 80%, $p = 0.72$) and BEV (77 vs. 76%, $p= 0.90$). There was no association between frequency of annulus manipulation and MI. On multivariable analysis (OR (95% CI) non-MEV (1.63 (1.06– 2.49)), mean aortic gradient (1.02 (1.01–1.03)), left ventricular ejection fraction (1.03 (1.01–1.04)), and previous myocardial infarction (1.62 (1.04–2.56)) were positively associated with MI. There was no association between MI and 30-day mortality.

Conclusion: Transcatheter valve design determines peri-procedural MI and is less frequent with MEV. MI is not associated with 30-day mortality.

Introduction

Transcatheter aortic valve implantation (TAVI) has become the treatment of choice for patients with severe aortic stenosis at elevated operative risk [1,2]. Peri-procedural myocardial injury (i.e. cardiac biomarker rise) after TAVI is frequent and may predict the outcome [3–6]. The exact patho-mechanism of myocardial injury is not clear yet, however several studies hypothesize that factors such as global myocardial ischemia due to balloon valvuloplasty, acute aortic regurgitation, rapid pacing-induced hypotension, micro-embolization of aortic valve debris in the coronary arteries, myocardial tissue compression by the expansion of the device and coronary obstruction should be considered as potential mechanisms for myocardial injury [3,7–10]. We hypothesize that prosthesis expansion mechanism may also affect the occurrence of myocardial injury.

The aims of this study are 1) to evaluate the difference in change of high sensitive Troponin T (hsTnT) within 24h after transfemoral-TAVI (TF-TAVI) between mechanically expanded (MEV), self-expanding (SEV) and balloon expand-able (BEV) transcatheter heart valves, 2) to determine predictors for myocardial injury after TAVI and 3) to assess whether myocardial injury is associated with 30-day mortality.

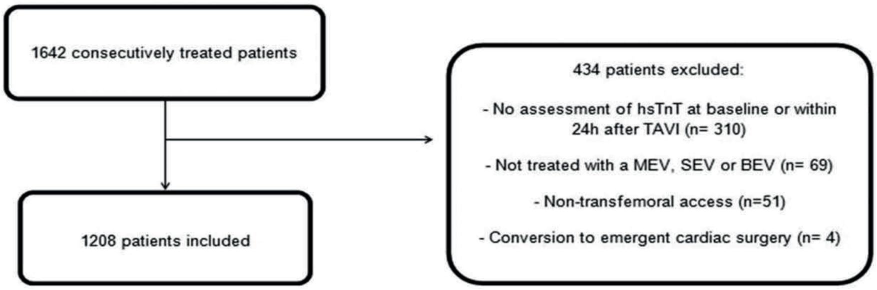
Materials and methods

This multicenter retrospective observational study included 1208 consecutively treated TF-TAVI patients from three European centers. All patients underwent coronary angiography (CAG) in preparation for TAVI and were discussed in a multi-disciplinary heart team. The decision to revascularize a coronary vessel with a significant lesion was made by the heart team. All patients treated via transfemoral access with a MEV, SEV or BEV and who had hsTnT measurements at baseline and within 24h after the index procedure were included. Patients who converted to emergent cardiac surgery were excluded (Figure 1). All patients consented for treatment.

The Lotus valve was considered as a mechanically expanded valve (MEV), Medtronic CoreValve and Evolut R as self-expandable valves (SEV) and Edwards XT and Edwards Sapien 3 as balloon-expandable valves (BEV). Peri-procedural myocardial injury was defined as an elevation of hsTnT ≥ 15x the upper reference limit (URL), within 24h after the index procedure. The highest hsTnT value within the first 24 h was used for this analysis. Tropinin elevation was defined by the following formula: hsTnT = highest troponin level within 24h post-TAVI – the baseline troponin. The URL for hsTnT was 14 ng/L. All complications were defined according to the VARC-2 [11].

Statistical analysis

Categorical variables are presented as frequencies and percentages, and compared with the Pearson Chi-Square Test or the Fisher's exact test, as appropriate. Continuous variables are presented as means (±SD) (in case of normal distribution) or medians (IQR) (in case of skewed distribution) and compared with the use of the Student's t-test, Mann–Whitney U test or Kruskal Wallis test. Normality of the distributions was assessed using the Shapiro– Wilk test. To study which patient and procedural characteristics are independently associated with myocardial injury after TAVI, logistic regression was performed. Variables were chosen based on etiological considerations. All characteristics judged to be clinically relevant or to have a pathophysiologic role in peri-procedural myocardial injury were included in the multivariable model. To investigate whether valve design is an independent predictor of periprocedural myocardial injury, baseline characteristics that were significantly different between the different valve cohorts were also included in the multivariable logistic regression model. We took into account the observed frequency of the dependent variable y (n/10). The characteristics judged to be clinically rele-vant were age, gender, previous myocardial infarction, previous PCI, previous CABG, atrial fibrillation at baseline, glomerular filtration rate (GFR), left ventricular ejection fraction (LVEF), mean aortic gradient, PCI during work-up, pre-/post balloon dilatation and valve mechanism (i.e. non-MEV and MEV). Baseline characteristics which were significantly different between the different valve cohorts were body mass index, diabetes mellitus (p= 0.004), hypertension (p= 0.036) and logistic EuroScore. A similar multivariable model was performed with further elaboration regarding valve mechanism (SEV, BEV, and MEV as reference valve mechanism). Survival after TAVI was determined with the use of Kaplan–Meier method. A log-rank test was applied to compare between-group differences. A two-sided alpha level of 0.05 was used to indicate significance. Statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, Illinois, USA).



hsTnT; high sensitive Troponin T; MEV: mechanically expanded valve ; SEV: self-expandable valve; BEV: balloon-expandable valve

Figure 1. Flowchart of the study population.

Results

Baseline-procedural characteristics and in-hospital complications

Baseline and procedural characteristics are summarized in Tables 1 and 2. Overall, 1208 patients were included with a median (IQR) age of 84 (80–87) years and 50% were female. The overall median (IQR) LVEF, mean aortic gradient and Logistic EuroScore were, respectively, 60% (45–65%), 45 (35–54) mm Hg and 17% (11–24%) (Table 1). The excluded patients were younger (83 vs. 84 years), more often had peripheral vascular disease (31% vs. 17%), a lower mean gradient (41 vs. 45 mmHg) and a higher logistic EuroScore (20% vs. 17%). During work-up for TAVI, PCI was performed in 252 patients (21%), 18% was staged and 3% concomitant with the index procedure. TAVI was performed in 12% with a MEV, in 56% with a SEV and in 32% with a BEV. Balloon pre- or post-dilatation was performed in 49% of the cases. More than mild residual aortic regurgitation (AR) was seen in 7% (Table 2).

The overall incidence of myocardial injury was 77% and was less frequent after MEV (MEV 67%, SEV 79% and BEV 76%, p= 0.007). The overall median increase of hsTnT was 741 ng/L and was lower after MEV (MEV 335 ng/L, SEV 901 ng/L and BEV 649 ng/L, p< 0.001). Patients with myocardial injury were older (85 (80–88) vs. 83 (78–85) years, p< 0.001), more often female (53% vs. 40%, p< 0.001), with a lower GFR (42 (30–56) vs. 48 (36–64), p< 0.001), a higher left ventricular ejection fraction (60% (50–65%) vs. 55% (40–60%), p< 0.001) and a higher aortic mean gradient (45 (37–55) vs. 40 (30–50) mm Hg, p< 0.001) compared to patients without myocardial injury.

The incidences of new left bundle branch block (LBBB) and new permanent pacemaker implantation (PPI) were both 15% and were higher after MEV (new LBBB: MEV 42%, SEV 14% and BEV 9%, p< 0.001; new PPI: MEV 24%, SEV 15% and BEV 11%, p= 0.001) (Table 3). The development of new LBBB was inversely associated with myocardial injury (63% vs. 80%, p< 0.001; hsTnT 327 vs. 855 ng/L, p< 0.001) while new PPI was not associated with myocardial injury (77% vs. 77%, p= 1.00; hsTnT 833 vs. 739 ng/L, p= 0.21).

First versus second-generation valves

Medtronic CoreValve versus Evolut R

The baseline characteristics of the patients treated with Medtronic CoreValve (MCV) and Evolut R were similar, except for a higher age (85 vs. 83 years, p< 0.001) and a higher Logistic Euroscore (19 vs. 16, p< 0.002) in the MCV group. From a procedural perspective, patients treated with MCV had more frequent balloon pre- or post-dilatation (62% vs. 36%, p< 0.001) and had more frequent more than mild residual AR (14% vs. 2%, p< 0.001). There was no significant difference in the occurrence of myocardial injury (MCV 79% vs. Evolut R 80%, p= 0.72) and a similar increase in hsTnT (MCV 900 vs. Evolut R 924 ng/L, p = 0.64) between the two groups.

Repositioning/retrieval data of the Evolut R was available for 127 patients (96.2%). There was no association between the frequency of annulus manipulation (i.e. repositioning/ retrieval of the valve) and myocardial injury. Also, there was no difference in the occurrence of myocardial injury between the patients treated with MCS vs. Evolut R regardless of annulus manipulation.

Edwards XT versus Sapien 3

The baseline characteristics were similar for the patients treated with Edwards XT versus Edwards Sapien 3, except for a higher frequency of NYHA class ≥3 at baseline (73% vs. 56%, p= 0.002), pulmonary hypertension (27% vs. 17%, p= 0.027), pacemaker at baseline (19% vs. 9%, p= 0.004) and a higher logistic Euroscore (20 vs. 14, p< 0.001) in the XT group. PCI during work-up for TAVI was less often performed in the XT group while balloon pre- or post-dilatation was more often performed. The occurrence of myocardial injury and increase in hsTnT were similar between the two groups (XT 77% vs. Sapien 3 76%, p= 0.90; hsTnT (XT 725 vs. Sapien 3 590 ng/L, p= 0.61).

Lotus valve

Baseline and procedural data were similar for patients with versus without annulus manipulation, except for a lower hemoglobin at baseline in the manipulation group (7.7 vs. 7.9 mmol/L, p= 0.048). The occurrence of myocardial injury was similar between the manipulation and no manipulation group (respectively, 71% vs. 60%, p= 0.38; hsTnT (269 vs. 252 ng/L, p= 0.84).

Repositionable valves

After pooling the data of all the repositionable valves (i.e. Evolut R and Lotus), the occurrence of myocardial injury was similar for the patients with versus without annulus manipulation (73% vs. 73%, p= 1.00; hsTnT (427 vs. 539 ng/L, p= 0.45). In addition, there was no association between the frequency of annulus manipulation and the occurrence of myocardial injury.

Predictors for myocardial injury

On multivariable analysis non-MEV (OR (95% CI) 1.63 (1.06 −2.49), p= 0.025), higher mean aortic gradient (OR (95% CI) 1.02 (1.01–1.03), p< 0.001), left ventricular ejection fraction (OR (95% CI) 1.03 (1.01–1.04), p< 0.001), and previous myocardial infarction (OR (95% CI) 1.62 (1.04–2.56), p= 0.032) were positively associated with myocardial injury, whereas concomitant PCI (OR (95% CI) 0.32 (0.14–0.70), p= 0.004) was inversely associated (Table 4).

A similar multivariable analysis, in which further elaboration regarding valve mechanism was performed, is shown in supplemental Table 1.

Outcome

There was no difference in 30-day all-cause and cardiovascular mortality, disabling and non-disabling stroke between the myocardial injury vs. no myocardial injury group (respectively, 3% vs. 4%, p= 0.19; 2% vs. 3%, p= 0.093; 0.2% vs. 0% and 0% vs. 0.4%, p = 0.28). In addition, Kaplan–Meier curves showed no association between myocardial injury and 30-day mortality (Figure 2a,b). Similar outcome was observed when the analysis was performed per center (Log-rank p= 0.11; Log-rank p= 0.33; Log-rank p= 0.10). There was also no association between type of prosthesis and the occurrence of myocardial injury with regard to 30-day mortality (Supplemental Figure 1A-C and 2A-C).

Discussion

This is the largest study cohort assessing peri-procedural myocardial injury (i.e. hsTnT) after TAVI including first and second generation trancatheter heart valves. Key findings:

(1) The occurrence of peri-procedural myocardial injury was 77%;
(2) Myocardial injury was less frequent after MEV;
(3) There was no difference in the occurrence of myocardial injury after implantation of first vs. second generation SEV and BEV;
(4) There were no penalties in terms of myocardial injury for additional manipulations in the annulus;
(5) Myocardial injury was not associated with the need for new PPI; and
(6) Myocardial injury was not associated with 30-day mortality.

The occurrence of peri-procedural myocardial injury after TAVI varies in the literature because different definitions and cardiac biomarkers are used. In our study, the occurrence rate was 77% and was higher than in the study of Sinning et al. (52%) [12]. This can be explained by the fact that we assessed high sensitivity tropinin T and not troponin I [13]. Despite the difference in the occurrence of myocardial injury, both studies demonstrated that the use of SEV and higher left ventricle ejection fraction (LVEF) were associated with peri-procedural myocardial injury. Patients with preserved LVEF may have more viable myocardium than patients with low ejection fraction and are therefore able to release higher troponin levels. Also, SEV typically requires more oversizing, which might lead to greater myocardial tissue compression and trauma and thus more myocardial injury [12].

Kahlert et al. suggested that myocardial injury is more related to hypoperfusion-induced ischemia than to peri-procedural microembolization [8]. In our study, there was less myocardial injury after the use of MEV than with the other valve mechanisms. We can only hypothesize that there might be more hemodynamic stability during the implantation of a MEV since there is early valve function and no need for rapid pacing. Conversely, a small cardiac magnetic resonance (CMR) study identified myocardial injury in 18% of patients and suggested a coronary embolic pathophysiologic mechanism because of the multifocal distribution and small lesion size [9]. Multiple randomized trials on filter-based cerebral embolic protection confirmed cerebral embolization of debris in almost all patients [14,15]. Conceivably, embolization is not restricted to the brain but also affects the coronary (micro) circulation. Of note in the US SENTINEL trial, number and overall volume of new brain lesions by DW-MRI was higher with SEV than with BEV suggesting more embolization after the use of SEV [16]. In addition, we have shown that a higher aortic valve mean gradient is an independent predictor for peri-procedural myocardial injury. Patients with more severe aortic stenosis (i.e. higher mean gradient) may have more degenerative calcifications that may dislodge and embolize into the coronary vasculature. Also, they may have a larger myocardial muscle mass, which may result in higher troponin release.

First versus second-generation transcatheter heart valves

Second generation THV aim to address the limitations of the first generation THV, introducing repositioning/retrievable features and sealing fabric to reduce paravalvular leaks. Our study showed no difference in peri-procedural myocardial injury between first vs. second generation SEV and BEV. In addition, there were no penalties in terms of myocardial injury for manipulating (i.e. repositioning/retrieval of the valve) in the aortic annulus.

New LBBB and new PPI

The incidence of new LBBB and PPI in our study was higher after MEV, and echoes other registries/studies [17–19]. Conduction disorders may occur as a result of myocardial ischemia [20]. However, we have shown that development of new LBBB post-TAVI was inversely associated with myocardial injury and that PPI was not associated with myocardial injury. The higher rate of new LBBB and PPI after MEV might be explained by the higher radial force during frame expansion which can damage the conduction tissue. Another potential explanation is the extensive contact of the Lotus frame with the left ventricular outflow tract during the implantation process (i.e. Lotus foreshortening and locking), which could damage the conduction system even more [21].

Thirty-day mortality

Similar to the study of Sinning et al. we have shown that there is no association between myocardial injury and 30-day mortality [12]. Studies with longer follow-up are needed to assess whether the myocardial injury is associated with long-term survival.

Limitations

We acknowledge the fact that patients were not randomly allocated to a specific valve mechanism and that the groups were not equal in size. Although we did capture patient's history of prior coronary artery disease, information on the completeness of revascularization prior to TAVI was lacking. However, incomplete revascularization did not affect myocardial injury after TAVI in an earlier study [3]. The "true" occurrence rate of peri-procedural myocardial injury might be higher since in our study troponin rise was limited to 24h post TAVI while the VARC-2 recommends assessing troponin rise up to 72h. Indeed, troponin levels might further increase over time and meet the definition of myocardial injury after 24h post-TAVI. However, current trends for early discharge would preclude troponin assessments up to 72h after TAVI. In addition, several studies have shown a peak of cardiac troponin within 24h after TAVI [3,12].

There are several studies to show that new pacemaker implantation, as well as myocardial injury, are associated with worse outcome [3–6,22]. In our study, there was no association between myocardial injury and 30-day mortality. One can only speculate on how the finding of less myocardial injury would compare to the higher incidence of new conduction disorders in terms of long-term survival. Further comparative studies should shed further light on the significance of these findings.

Generalizability of our findings should be put in perspective of 1) the cardiac biomarkers used (hsTnT vs. troponin I, CK-MB, etc.), 2) definition of periprocedural myocardial infarction, 3) specific patient population (i.e. risk profile) and 4) access approach (proportion of apical access).

Conclusion

Transcatheter valve design determines peri-procedural myocardial injury, which is less frequent with MEV.

Table 1. Baseline characteristics of the total patient population and per valve mechanism.

	Total population	Mechanically expanded valve	Self-expandable valve	Balloon-expandable valve	P-value
	n= 1208	n= 144	n= 678	n= 386	
Age (yrs), median (IQR)	84 (80-87)	82 (76-86)	85 (81-88)	84 (79-87)	<0.001
Female, n (%)	604 (50)	76 (53)	399 (59)	129 (33)	<0.001
Height (cm), median (IQR)	165 (158-170)	167 (159-172)	162 (155-168)	168 (160-172)	<0.001
Weight (kg), median (IQR)	70 (60-80)	75 (65-86)	68 (58-78)	74 (64-82)	<0.001
Body mass index (kg/m2), median (IQR)	25.6 (23.1-29.0)	26.6 (23.8-30.7)	25.3 (22.9-28.5)	25.8 (23.6-29.3)	0.001
New York Heart Association class ≥ III, n (%)	801 (66)	101 (70)	459 (68)	241 (62)	0.089
Previous myocardial infarction, n (%)	246 (20)	25 (17)	123 (18)	98 (25)	0.012
Previous coronary artery bypass graft surgery, n (%)	151 (13)	22 (15)	76 (11)	53 (14)	0.29
Previous percutaneous coronary intervention, n (%)	408 (34)	41 (29)	231 (34)	135 (35)	0.33
Diabetes mellitus, n (%)	329 (27)	56 (39)	173 (26)	100 (26)	0.004
Hypertension, n (%)	935 (77)	123 (85)	512 (76)	300 (78)	0.036
Peripheral vascular disease, n (%)	202 (17)	29 (20)	107 (16)	66 (17)	0.43
Pulmonary Hypertension, n (%)	243 (20)	21 (15)	142 (21)	80 (21)	0.21
Chronic obstructive pulmonary disease, n (%)	284 (24)	40 (28)	157 (23)	87 (23)	0.43
Atrial fibrillation, n (%)	262 (22)	40 (28)	136 (20)	86 (22)	0.12
Permanent pacemaker, n (%)	157 (13)	22 (15)	86 (13)	49 (13)	0.70
Laboratory results					
Creatinine (umol/L), median (IQR)	102 (83-133)	104 (81-128)	101 (81-133)	103 (85-134)	0.25
GFR (ml/min), median (IQR)	43 (32-58)	47 (36-67)	41 (29-54)	46 (33-62)	<0.001
Hemoglobin (mmol/L), median (IQR)	7.8 (7.1-8.4)	7.8 (7.1-8.4)	7.8 (7.1-8.4)	7.8 (7.1-8.6)	0.23
Echocardiography					
Left ventricular ejection fraction, median (IQR)	60 (45-65)	60 (49-65)	60 (46-65)	55 (43-63)	0.004
Mean gradient, median (IQR)	45 (35-54)	43 (35-52)	45 (36-55)	45 (34-53)	0.32
Logistic Euroscore, median (IQR)	17 (11-24)	13 (9-19)	18 (12-25)	16 (10-24)	<0.001

Table 2. Procedural characteristics of the total patient population and per valve mechanism.

	Total population n = 1208	Mechanically expanded valve n= 144	Self-expandable valve n= 678	Balloon-expandable valve n= 386	P-value
PCI work-up					0.009
Staged, n(%)	222 (18)	16 (12)	124 (19)	82 (22)	0.031
Concomittant PCI, n (%)	30 (3)	7 (6)	11 (2)	12 (4)	0.051
Pre- implantation balloon dilation, n (%)	424 (35)	48 (33)	248 (37)	128 (33)	0.49
Post implantation balloon dilation, n (%)	234 (19)	0 (0)	192 (28)	42 (11)	<0.001
Pre-or post balloon dilatation, n (%)	586 (49)	48 (33)	386 (57)	152 (39)	<0.001
Valve in Valve, n (%)	42 (4)	0 (0)	39 (6)	3 (1)	<0.001
Residual Aortic regurgitation (Sellers) ≥ grade 2, n (%)	89 (7)	2 (1)	79 (12)	8 (2)	<0.001

Table 3. In-hospital complications of the total patient population and divided per valve mechanism.

	Total population n = 1208	Mechanically expanded valve n= 144	Self-expandable valve n= 678	Balloon-expandable valve n= 386	P-value
Myocardial infarction, n (%)	15 (1)	0 (0)	10 (1)	5 (1)	0.42
Cardiac tamponade, n (%)	12 (1)	3 (2)	6 (1)	3 (1)	0.33
Coronary obstruction, n (%)	3 (0.2)	0 (0)	2 (0.3)	1 (0.3)	1.00
Myocardial injury, n (%)	925 (77)	96 (67)	535 (79)	294 (76)	0.007
Difference hsTnT, (median (IQR)	741 (228-1780)	335 (175-1167)	901 (274-1888)	649 (222-1671)	<0.001
<u>Vascular complications</u>					0.99
Major, n (%)	47 (4)	6 (4)	25 (4)	16 (4)	
Minor, n (%)	123 (10)	13 (9)	70 (10)	40 (10)	
<u>Bleeding complications</u>					0.67
Life-threatening, n (%)	34 (3)	5 (4)	20 (3)	9 (2)	
Major, n (%)	39 (3)	7 (5)	23 (3)	9 (2)	
Minor, n (%)	111 (9)	13 (9)	66 (10)	32 (8)	
<u>Conduction disorders</u>					
New LBBB, n (%)	187 (15)	60 (42)	92 (14)	35 (9)	<0.001
New PPI, n (%)	177 (15)	35 (24)	99 (15)	43 (11)	0.001

hsTnT; high sensitive Troponin T, LBBB; left bundle branch block, PPI; permanent pacemaker implantation

Table 4. Multivariate logistic regression for the determination of peri-procedural myocardial injury

Determinants	OR (95% CI)	p-value
Age (years)	1.02 (0.99-1.04)	0.22
Female	0.85 (0.62-1.16)	0.31
BMI	1.00 (0.99-1.01)	0.96
Previous myocardial infarction	1.62 (1.04-2.56)	0.032
Previous PCI	0.90 (0.64-1.27)	0.56
Previous CABG	0.69 (0.44-1.10)	0.12
Atrial fibrillation at baseline	0.99 (0.69-1.41)	0.95
Diabetes mellitus	0.80 (0.58-1.10)	0.17
Hypertension	1.24 (0.88-1.74)	0.22
GFR (ml/min)	1.00 (0.99-1.00)	0.083
LVEF (%)	1.03 (1.01-1.04)	<0.001
Mean aortic gradient (mm Hg)	1.02 (1.01-1.03)	<0.001
Logistic EuroScore (%)	1.02 (1.00-1.03)	0.072
PCI work-up		0.004
Staged PCI	1.36 (0.88-2.10)	0.16
Concomitant PCI	0.32 (0.14-0.70)	0.004
Pre/or post balloon dilatation	0.76 (0.56-1.03)	0.074
non-MEV	1.63 (1.06-2.49)	0.025
residual AR (Sellers) ≥ grade 2	0.72 (0.42-1.24)	0.24

BMI: body mass index; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; MEV: mechanically expanded valve; AR: aortic regurgitation

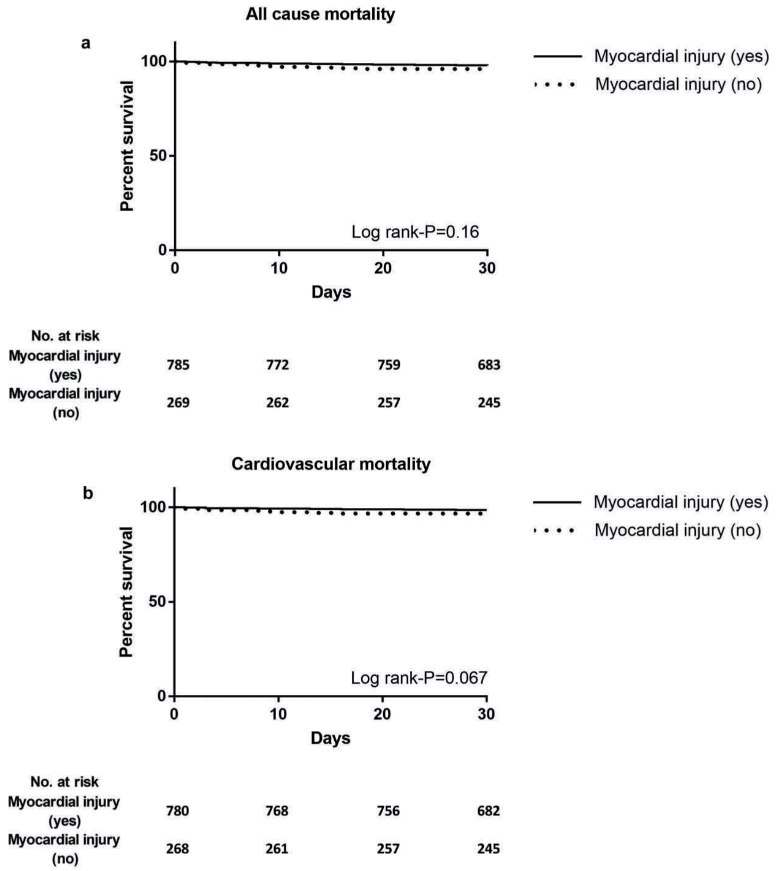


Figure 2. Kaplan–Meier curves for 30-day (a) all-cause and (b) cardiovascular mortality in the myocardial injury vs. no myocardial injury group.

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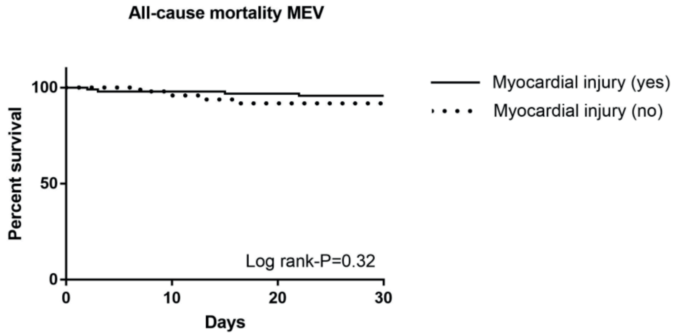
Supplementary material

Supplemental Table 1. Multivariate logistic regression for the determination of per-procedural myocardial injury with MEV as reference valve mechanism.

Determinants	OR (95% CI)	p-value
Age (years)	1.01 (0.99-1.04)	0.24
Female	0.88 (0.64-1.21)	0.43
BMI	1.00 (0.99-1.01)	0.96
Previous myocardial infarction	1.65 (1.05-2.60)	0.029
Previous PCI	0.90 (0.64-1.26)	0.54
Previous CABG	0.69 (0.44-1.10)	0.12
Atrial fibrillation at baseline	0.99 (0.70-1.42)	0.97
Diabetes mellitus	0.79 (0.58-1.10)	0.16
Hypertension	1.25 (0.89-1.76)	0.21
GFR (ml/min)	1.00 (0.99-1.00)	0.080
LVEF (%)	1.03 (1.01-1.04)	<0.001
Mean aortic gradient (mm Hg)	1.02 (1.010-1.03)	<0.001
Logistic EuroScore (%)	1.01 (1.00-1.03)	0.083
PCI work-up		0.003
Staged PCI	1.37 (0.88-2.11)	0.16
Concomitant PCI	0.32 (0.15-0.71)	0.005
Pre/or post balloon dilatation	0.74 (0.54-1.01)	0.054
Valve mechanism (MEV as reference)		0.049
Self-expandable valve	1.76 (1.12-2.77)	0.014
Balloon-expandable valve	1.47 (0.92-2.34)	0.10
residual AR (Sellers) ≥ grade 2	0.69 (0.40-1.19)	0.18

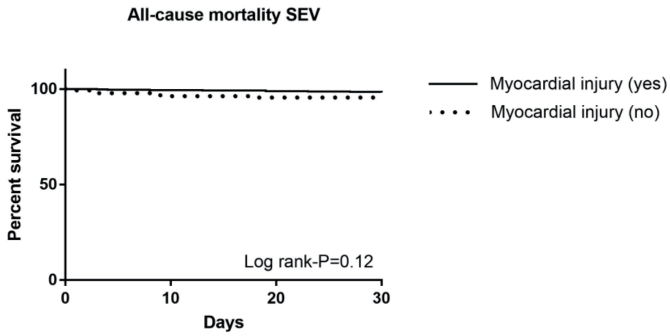
BMI: body mass index; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; MEV: mechanically expanded valve; AR: aortic regurgitation

A



No. at risk				
Myocardial injury (yes)	94	92	91	87
Myocardial injury (no)	48	47	44	44

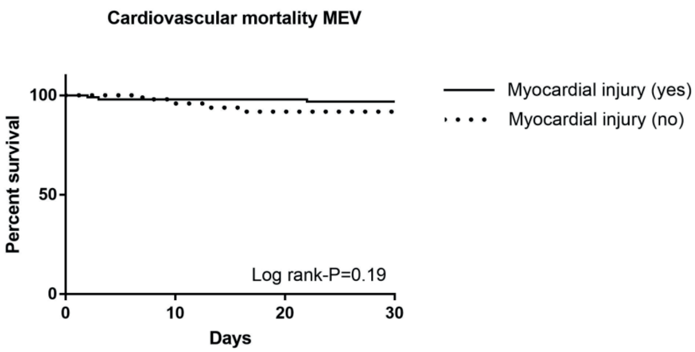
B



No. at risk				
Myocardial injury (yes)	443	438	431	378
Myocardial injury (no)	133	128	126	119

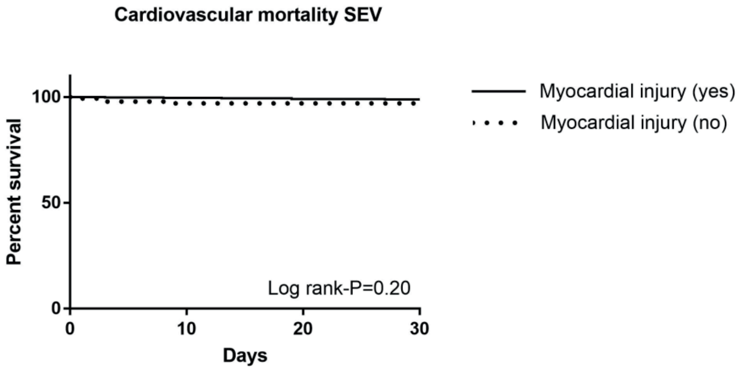
Supplemental Fig. 1 Kaplan-Meier curves for 30-day all-cause mortality in the myocardial injury vs. no myocardial injury group stratified per valve mechanism (A) mechanically expanded (MEV) and (B) self-expandable (SEV) group

A



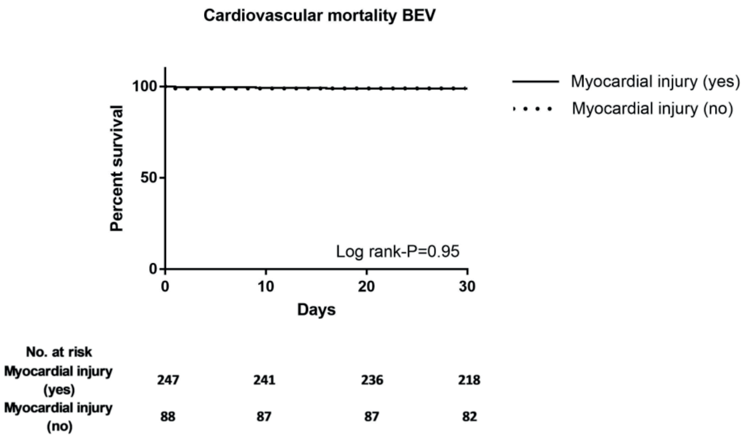
No. at risk				
Myocardial injury (yes)	93	91	91	87
Myocardial injury (no)	48	47	44	44

B



No. at risk				
Myocardial injury (yes)	440	436	429	377
Myocardial injury (no)	132	127	126	119

C



Supplemental Fig. 2 Kaplan-Meier curves for 30-day cardiovascular mortality in the myocardial injury vs. no myocardial injury group stratified per valve mechanism (A) mechanically expanded (MEV) (B) self-expandable (SEV) and (C) balloon-expandable (BEV) group

CHAPTER 5 Expanding the indications for transcatheter aortic valve implantation

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of symptomatic severe aortic valve stenosis. Current guidelines recommend TAVI in patients at increased operative risk of death. Advanced imaging planning, new transcatheter valve platforms, procedure streamlining and growing operator experience have improved procedural safety and bioprosthetic valve performance. As a result, TAVI has been explored for other indications. Two randomized trials published in 2019 to assess TAVI in patients with symptomatic severe aortic stenosis at low operative risk have set the stage for a new wave of indications. In younger and low-risk patients, TAVI had an early safety benefit over surgical aortic valve replacement and was associated with faster discharge from hospital and recovery and fewer rehospitalizations. In patients with symptomatic severe aortic stenosis, TAVI has now been explored across the entire spectrum of operative risk, from inoperable to low-risk populations, in properly designed, randomized clinical trials, although data on the long-term durability of these valves are lacking. The use of TAVI in severe bicuspid aortic valve stenosis, asymptomatic severe aortic stenosis, moderate aortic stenosis in combination with heart failure with reduced ejection fraction, and isolated pure aortic regurgitation is now under investigation in clinical trials. In this review, we provide our perspective on these evolving indications for TAVI, discuss relevant available data from clinical trials, and highlight procedural implications and caveats of new and future indications.

Key points

(1) Transcatheter aortic valve implantation (TAVI) is an accepted treatment option for elderly patients with symptomatic severe degenerative tricuspid aortic valve stenosis across the entire spectrum of operative risk.
(2) Long-term durability of transcatheter valves is unknown and requires further research.
(3) The use of TAVI with new-generation devices seems attractive for bicuspid aortic valve stenosis, but sizing algorithms might need to be modified.
(4) Timing to proceed with TAVI and procedural safety are crucial in truly asymptomatic patients with severe calcified aortic stenosis.
(5) TAVI might complement afterload reduction with medical therapy in patients with heart failure and moderate aortic stenosis.
(6) Treatment for pure aortic regurgitation might demand dedicated transcatheter valve designs to secure device anchoring in noncalcified aortic roots.

Introduction

Randomized clinical trials have established transcatheter aortic valve implantation (TAVI) as the best option for treating patients with symptomatic severe aortic stenosis who are considered to be at intermediate or high operative risk of death or who are deemed inoperable [1–7]. Consequently, contemporary European and US guidelines have formulated strong recommendations for TAVI in patients with symptomatic severe aortic stenosis at increased operative risk [8,9]. Advanced imaging planning, growing operator experience and the intro- duction of new transcatheter valve platforms including, for example, sealing fabric, a lower profile and repositioning and/or recapturable features, have improved procedural safety and bioprosthetic valve performance [3,4,10,11]. For femoral arterial access, a direct correlation exists between the ratio of arterial dimensions to device profile and sheath size and the frequency of access site complications and clinically significant bleeding. A lower device profile is associated with fewer complications [12].

Self-expanding valve designs introduced repositioning and recapturing capacities to correct suboptimal device deployment that could otherwise result in device migration, clinically significant paravalvular leakage or conduction abnormalities [3,4,10,11]. Sealing fabric is typically added to the outside of transcatheter valves to further mitigate paravalvular leakage [3,4,10,11].

Two randomized clinical trials published in 2019 to assess TAVI in patients with severe aortic stenosis at a low surgical risk have set the stage for a new wave of TAVI indications. In these trials, TAVI had a clear early safety benefit over surgical aortic valve replacement (SAVR) in young and low-risk patients and was associated with faster discharge from hospital, faster recovery and fewer rehospitalizations [13,14] . The use of TAVI has now been explored in patients with symptomatic severe tricuspid aortic valve stenosis across the entire spectrum of operative risk — from inoperable to low-risk patient populations — with properly designed, randomized clinical trials (Fig. 1), although data on the long-term durability of these valves are so far lacking. Ongoing trials are pushing these boundaries by exploring the use of TAVI in patients with asymptomatic severe aortic stenosis, patients with heart failure (HF) with reduced ejection fraction with moderate aortic stenosis and patients with severe bicuspid aortic valve stenosis. In this review, we give an overview of these evolving indications for TAVI, discuss relevant published data from clinical trials, and highlight procedural implications and caveats.

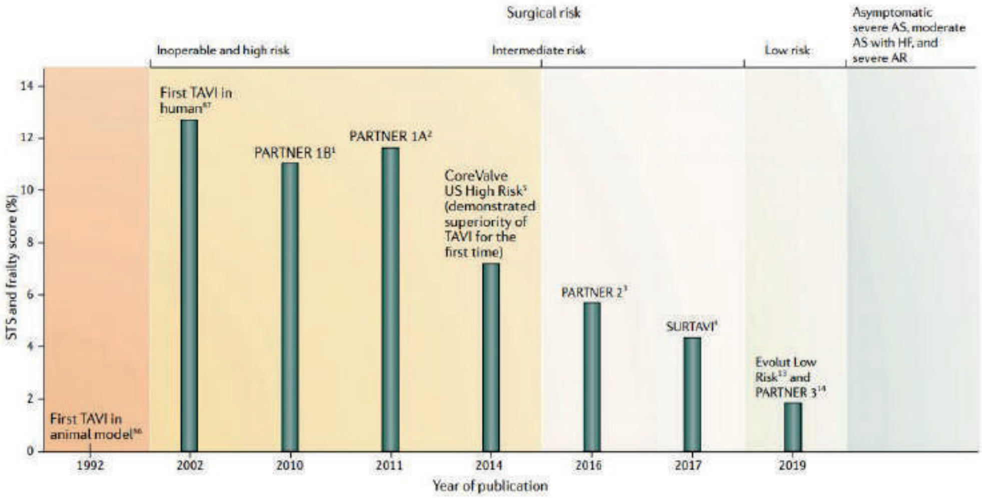

Fig. 1 | **Evolution of TAVI indications.** Over time, the indications for transcatheter aortic valve implantation (TAVI) have expanded to include patients at a lower operative risk (that is, a lower Society of Thoracic Surgeons (STS) score) and with less frailty. Several ongoing studies are exploring the indications for TAVI in asymptomatic severe aortic stenosis (AS), moderate AS with heart failure (HF), and severe aortic regurgitation (AR). The graph shows the STS and frailty score and the surgical risk classification of the patient cohort in each study plotted according to the year of study publication [86,87]

TAVI transition to low-risk patients

TAVI was first introduced as a treatment strategy in patients with severe aortic valve stenosis who were deemed to be at a prohibitive or high operative risk and subsequently emerged as a viable option for patients at intermediate surgical risk [1–4,15]. In the PARTNER 2 trial [3], 2,032 patients with severe aortic stenosis at intermediate surgical risk were assigned to TAVI with a balloon-expandable valve or to SAVR. The rate of the primary end point of all-cause death or disabling stroke at 2 years was similar with TAVI and SAVR (19.3% for TAVI versus 21.1% for SAVR; P = 0.25) and a potential superiority of TAVI over SAVR was observed in the cohort receiving transfemoral TAVI (HR 0.79, 95% CI 0.62–1.00, P=0.05) [3]. In the SURTAVI trial [4], 1,746 patients with severe aortic stenosis at intermediate surgical risk were randomly assigned to either TAVI with a self- expandable valve or SAVR. At 2 years, the estimated incidence of the primary end point (all-cause death or disabling stroke) was 12.4% in the TAVI group and 14.0% in the SAVR group (95% credible interval (as calculated by Bayesian analysis) for difference, –5.2 to 2.3%; posterior probability of noninferiority >0.999) [4].

Both trials confirmed favourable clinical outcomes with TAVI compared with SAVR in patients considered to be at intermediate operative risk [3,4]. In addition to at least equal safety, patients consistently showed faster recovery and improvements in quality of life after transfemoral TAVI than after SAVR throughout the spectrum of surgical risk [16,17].

The NOTION trial [18,19] was positioned as a so-called all-comers trial and enrolled 280 patients with severe aortic stenosis with a mean (±s.d.) Society of Thoracic Surgeons (STS) risk score of 3.0 ± 1.7%, which is indicative of a low risk, who were randomly assigned to receive TAVI with a first-generation self-expanding valve or SAVR [18,19]. No differences in mortality or in the composite endpoint of all-cause mortality, stroke or myocardial infarction were observed between the two cohorts at 5 years of follow-up, particularly in patients with a low operative risk on the basis of the STS score [20]. Remarkably, although clinically relevant bioprosthetic valve failure was rare with either treatment strategies, structural valve degeneration (defined by a mean gradient ≥20 mmHg, an increase in mean gradient ≥10 mmHg, or new or worsening intraprosthetic aortic regurgitation relative to the reference at 3 months after the procedure) was significantly more frequent with SAVR than with TAVI (24.0% versus 4.8%; $P < 0.001$) [21].

In the STACCATO trial [22], elderly patients with severe aortic stenosis and no operative risk restriction were randomly allocated to either transapical TAVI (STS score 3.1 ± 1.5%) or SAVR. The trial was terminated prematurely due to an excessive event rate (including death and stroke) in the transapical TAVI group [22]. In a propensity-matched substudy of the PARTNER trial, patients receiving transapical TAVI had more adverse procedural events, had a significantly longer hospital stay (5 days versus 8 days; $P < 0.0001$), a slower recovery (NYHA class I at 30 days, 31% versus 38%; $P = 0.0003$) and a higher mortality at 6 months (19% versus 12%; $P = 0.01$) than patients receiving transfemoral TAVI [23]. These findings show that transfemoral access is essential for optimal short-term and long-term outcomes [24,25]. The transfemoral approach indeed enables a minimalist approach under local anaesthesia or minimal sedation and accelerates patient recovery and ambulation [26,27].

A meta-analysis of randomized trials and propensity-matched studies including a total of 9,851 patients with severe aortic stenosis at low to intermediate surgical risk showed that TAVI was associated with a significantly lower risk of acute kidney injury and new-onset atrial fibrillation but with more vascular complications, the need for permanent pacemaker implan- tation and paravalvular leakage compared with SAVR ($P < 0.05$) [28].

In 2019, the 1-year outcomes of two trials in low-risk populations of patients with severe aortic stenosis were reported [13,14]. Local heart teams confirmed the low operative risk, with a mean STS predicted risk of mortality of <2% and a mean age of <75 years in both trials. Patients with bicuspid aortic valve stenosis were excluded. Of note, clinically significant coronary artery disease was uncommon, and patients had preserved systolic left ventricular function. In the Medtronic Evolut Low Risk study [13,29], 1,468 patients with severe aortic stenosis and at low surgical risk were randomly allocated (1:1) to either TAVI with a self-expanding valve or SAVR. A predefined interim Bayesian analysis after 850 patients reached 1 year of follow-up confirmed non- inferiority of TAVI versus SAVR for the primary composite end point of all-cause death or disabling stroke at 24 months (5.3% versus 6.7%; difference –1.4%, 95% Bayesian credible- interval for difference –4.9 to 2.1; posterior probability of noninferiority >0.999). The group who received TAVI had fewer disabling strokes (0.5% versus 1.7%) but needed more implantations of pacemakers (17.4% versus 6.1%) at 30 days than the SAVR group. In terms of bioprosthetic valve performance, TAVI was associated with lower transprosthetic gradients (8.6 mmHg versus 11.2 mmHg), higher valve area (2.3 cm2 versus 2.0 cm2) and less prosthesis–patient mismatch, but more mild and moderate paravalvular leakage, than occurred with SAVR [13].

In the PARTNER 3 trial [30], 1,000 patients with severe aortic stenosis and low surgical risk were randomly assigned 1:1 to transfemoral TAVI with the balloon-expandable valve SAPIEN 3 (Edwards Lifesciences) or to SAVR. TAVI was superior to SAVR for the primary composite end point of death, stroke or rehospitalization at 1 year (8.5% versus 15.1%; absolute difference –6.6%, 95% CI –10.8 to –2.5, P <0.001 for noninferiority; HR 0.54, 95% CI 0.37–0.79, P = 0.001 for superiority) [14]. TAVI with the

balloon-expandable valve was associated with a lower incidence of disabling stroke at 30 days than SAVR, and no significant differences were observed in the need for pacemaker implantation and no more than mild paravalvular leakage occurred. Interestingly, SAVR was associated with slightly lower transprosthetic gradients (11.2 mmHg versus 12.8 mmHg), a larger valve area (1.8 cm2 versus 1.7 cm2) and a lower incidence of mild paravalvular leakage than TAVI. Taken together, both trials in patients at low surgical risk offer compelling evidence for an early safety benefit (lower rates of disabling stroke, acute kidney injury, life-threatening bleeding and new-onset atrial fibrillation and a trend towards lower mortality), a significantly shorter stay in hospital, faster recovery and fewer rehospitalizations with TAVI than with SAVR. These favourable data justify that patients who are scheduled for aortic valve replacement with a bioprosthesis in 2019 should at least be informed about the option of TAVI to achieve adequate shared decision-making.
The randomized NOTION 2 trial [31] is currently enrolling younger (aged <75 years) patients with severe aortic stenosis and low surgical risk (STS score <4%) to be randomly assigned to either transfemoral TAVI or SAVR. Any CE mark-approved transcatheter valve platform is allowed. The primary end point at 1 year is the composite of all-cause mortality, myocardial infarction and stroke. The DEDICATE trial [32] aims to enrol in Germany 1,600 patients with severe aortic stenosis and low to intermediate surgical risk (STS score 2–6%) to compare TAVI with a CE-marked device versus SAVR. The aim is to investigate whether TAVI is noninferior to SAVR with regard to short-term and long-term mortality (at 1 year and 5 years).

Challenges. So far, adoption of TAVI has been restricted to a predominantly elderly patient population, and the reduction in operative risk is driven by fewer comorbidities rather than a younger age (Fig. 2; Table 1). More data will be needed to support the use of TAVI in younger patients (aged <70 years). Also, TAVI in patients at low surgical risk but with challenging iliofemoral arterial trajectories and, particularly, the effect of nontransfemoral access need to be clarified in further studies. Of note, the randomized trials in low surgical risk populations discussed above excluded bicuspid aortic valve disease (except NOTION 2, which allows bicuspid aortic valve stenosis if the ascending aorta is ≤45 mm). By default, this criterion affects the generalizability of the findings from these trials because the prevalence of bicuspid aortic valve disease is substantially higher in younger patients (see below). Importantly, the lingering controversy on valve durability will require extended follow-up in the prospective trials in low-risk populations that include younger patients with a longer life expectancy to generate meaningful echocardiography data at 10 years of follow-up. The definition of durability should extend beyond the need for reoperation, as was often applied in previous surgical literature.

Therefore, a consensus statement published in 2017 suggested a definition of durability that is based on maximum and changing transprosthetic gradients over time and the aggravation or occurrence of new regurgitation [33]. Further debate remains concerning the clinical effect of mild paravalvular leaks, which are consistently more prevalent after TAVI than SAVR. Coronary artery disease is more frequent in combination with severe aortic stenosis than reported in the recent low-risk TAVI trials. Coronary artery disease requires specific attention in terms of procedural planning (staged or concomitant percutaneous coronary intervention), and younger patients will conceivably have coronary events later in life and, therefore, require coronary interventions after TAVI. Coronary accessibility after TAVI varies according to the transcatheter heart valve design because the metal frame might hinder selective engagement of the coro- nary ostia. The majority of current transcatheter heart valve designs, notably the self-expanding systems, seem to be associated with higher rates of new conduction abnormalities and the need for permanent implantation of a pacemaker compared with SAVR [34]. The effect of new bundle branch blocks or a new pacemaker on long-term clinical outcomes is debated, but monitoring whether the need for pacemakers is different in (younger) patients at low operative risk with a longer life expectancy from that in the elderly patients at increased risk who are candidates for TAVI according to current guidelines will be important [8,9].

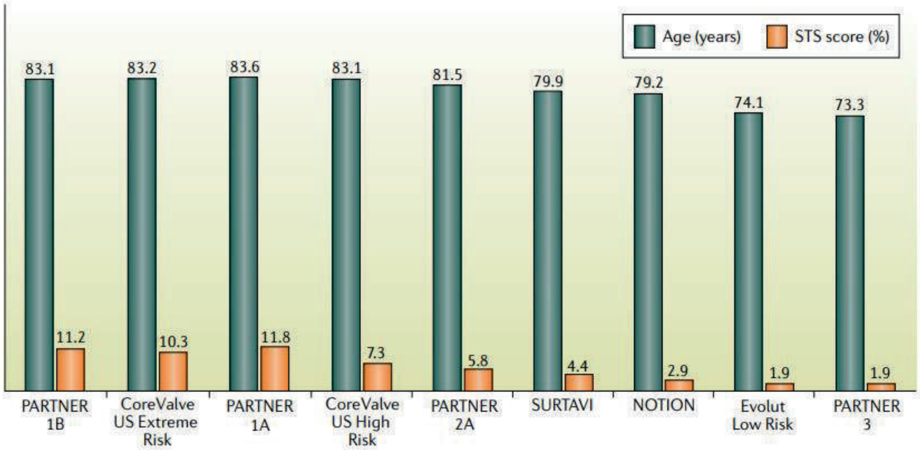

Fig. 2 | **Studies on TAVI versus SAVR in patients at different surgical risk and of similar age.** As shown in the graph, the decrease in the surgical risk of death, as assessed by the Society of Thoracic Surgeons (STS) risk score, in the successive trials on transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) is driven by fewer comorbidities in the study cohort rather than by younger age.

Table 1 | Trials on TAVI versus SAVR in patients with severe aortic stenosis with different surgical risks

Trial (study years)	Design	*n*	Age, mean ± s.d. (years)[a]	STS score, mean ± s.d.(%)[a]	Main outcomes at 1 year *			
					All-cause death (%)	Stroke (%)	Repeat hospitalization (%)	Ref
PARTNER 1B (2007-2009)	Randomized, controlled	358	83.1 ± 8.6	11.2 ± 5.8	30.7	10.6	22.3	1
CoreValve US Extreme Risk (2011-2012)	Non-randomized, single arm	489	83.2 ± 8.7	10.3 ± 5.5	24.3	7.0	NR	6
PARTNER 1A (2007-2009)	Randomized, controlled	699	83.6 ± 6.8	11.8 ± 3.3	24.2	8.3	18.2	2
CoreValve US High Risk (2011-2012)	Randomized, controlled	747	83.1 ± 7.1	7.3 ± 3.0	14.2	8.8	NR	5
PARTNER 2A (2011-2013)	Randomized, controlled	2032	81.5 ± 6.7	5.8 ± 2.1	12.3	8.0	14.8	3
SURTAVI (2012-2016)	Randomized, controlled	1660	79.9 ± 6.2	4.4 ± 1.5	6.7	5.4	8.5[b]	4
NOTION (2009-2013)	Randomized, controlled	280	79.2 ± 4.9	2.9 ± 1.6	4.9	2.9	NR	19
Evolut Low Risk (2016-2018)	Randomized, controlled	1403	74.1 ± 5.8	1.9 ± 0.7	2.4	4.1	3.2[c]	13
PARTNER 3 (2016-2017)	Randomized, controlled	950	73.3 ± 5.8	1.9 ± 0.7	1.0	1.2	7.3	14

NR, not reported; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation. a TAVI population. bFor aortic valve-related disease. cFor heart failure.

Severe bicuspid aortic valve stenosis

Bicuspid aortic valve disease is the most common congenital valve abnormality, occurring in 0.5–2.0% of the general population, and is associated with accelerated valve degeneration and concomitant aortopathy, such as dilated ascending aorta and coarctation [35]. Bicuspid aortic valve and severe aortic stenosis is more prevalent in young patients, although a study demonstrated that one-fifth of octogenarian patients undergoing SAVR for severe aortic stenosis had congenital bicuspid aortic valves [36]. The presence of a bicuspid aortic valve has so far been an exclusion criterion in all randomized trials of TAVI, and data on TAVI in bicuspid aortic valve disease are scarce.

The use of TAVI in patients with a bicuspid aortic valve might result in uneven bioprosthetic valve frame expansion and suboptimal function because the bicuspid aortic valve tends to have a higher degree of root calcification than the tricuspid aortic valve (Agatston score 1,262.7 ± 396.0 versus 556.4 ± 461.9; $P < 0.01$), which might increase the risk of procedural complications such as paravalvular leakage and aortic root injury [37,38]. In patients with bicuspid aortic valve treated with first-generation transcatheter heart valves, paravalvular leakage grade ≥2 occurred in 28.4% of patients, and 3.6% needed more than one transcatheter heart valve implantation [39] (Table 2). However, the use of pre-procedural, multislice CT for annular sizing improved outcomes in this patient population, decreasing the rate of paravalvular leakage grade ≥2 to 17.4% [39]. Later-generation transcatheter heart valves with sealing fabric (to mitigate paravalvular leakage), repositioning features and smaller delivery profiles were associated with improved outcomes in patients with bicuspid aortic valves compared with first-generation devices [40–43]. Among patients with aortic stenosis, those with a bicuspid aortic valve had procedural complications more frequently than patients with a tricuspid aortic valve when treated with early-generation devices, with rates of moderate or severe paravalvular leakage of 15.9% versus 10.3% ($P = 0.03$), second valve implantation of 7.2% versus 2.2% ($P = 0.003$), conversion to surgery of 2.5% versus 0.3% ($P = 0.02$) and device failure of 21.6% versus 3.1% ($P = 0.005$) [42] (Table 2). Conversely, procedural complication rates were similar between patients with bicuspid aortic valve stenosis and patients with tricuspid aortic valve stenosis with newer-generation transcatheter valve platforms [42]. A systematic review and meta-analysis including 13 observational studies on TAVI and a total of 758 patients with bicuspid aortic valve reported a 95% (95% CI 90.2–98.5%) device success rate and an early safety event in 16.9% (95% CI 12.2–22.0%) of patients [44] (Table 2).

In terms of 30-day outcomes, all-cause mortality occurred in 3.7% (95% CI 2.1–5.5%) of patients, and a new pacemaker was permanently implanted in 17.9% (95% CI 14.1–21.9%) of patients, without significant heterogeneity between the studies [44].

Annular CT measurement is the gold standard for transcatheter heart valve size selection. However, sizing can vary between a tricuspid aortic valve and a bicuspid aortic valve. In the bicuspid aortic valve, excessive calcification is often located above the virtual annular plane at the intercommissural level whereas, in the tricuspid aortic valve, calcification is located at the virtual annular level. Whether device sizing based on intercommissural dimensions might affect TAVI outcomes in patients with a bicuspid aortic valve is a matter of ongoing debate. In a study using a balloon-sizing strategy that relied on the 'waist sign' to determine transcatheter heart valve size in 12 patients with severe bicuspid aortic valve stenosis, procedural success was 100%, and the waist sign suggested a smaller device size in 91.7% of the patients [45].

Several trials are ongoing to study the long-term outcomes after TAVI in patients with a bicuspid aortic valve, with an emphasis on patients at intermediate surgical risk and on optimal sizing strategies [46–49]. The START trial [48] is a randomized study to compare the clinical outcome of different sizing strategies (that is, downsizing versus standard sizing) in patients with type 0 bicuspid aortic valve. The Bivolut X trial [49] is a prospective, multicentre registry that plans to enrol 150 consecutive patients with bicuspid aortic valve (aortic stenosis or mixed aortic stenosis–aortic regurgitation). The aim of the study is to evaluate the clinical outcomes with a latest-generation, self-expanding transcatheter heart valve in patients with bicuspid aortic valve and to obtain insights into various sizing algorithms (annular-based sizing, intercommissural -based sizing or combined sizing) with the use of an independent core laboratory assessment of echocardiography and multislice CT. In addition, the PARTNER 3 trial [30] had an imbedded registry of 100 patients with bicuspid aortic valve stenosis, which is followed by a continued access registry to assess latest-generation, balloon-expandable transcatheter heart valves in patients with bicuspid aortic valve stenosis.

Challenges. Compared with tricuspid aortic valves, the annulus in a bicuspid aortic valve tends to be more elliptical and has more annular calcification with irregular distribution that can affect transcatheter valve frame expansion (for example, resulting in a more elliptical final configuration) and that can increase the risk of procedural complications, such as paravalvular leakage (owing to uneven frame expansion and suboptimal function of the transcatheter heart valve) and aortic root injury (owing to a higher degree of aortic root calcification and connective tissue abnormalities in the aortic wall) [50]. In addition, concomitant thoracic aorta pathology, such as a dilated ascending aorta, aneurysm or coarctation, commonly accompanies bicuspid aortic valve anatomy and might require treatment. Current transcatheter heart valve devices were not designed to address concomitant aorta pathologies, and TAVI should therefore be limited to patients with isolated aortic valve disease. Another concern is the unknown durability of the transcatheter heart valve in this younger patient population in particular because contemporary transcatheter valves were designed for the treatment of degenerated native tricuspid valves.

Table 2 | Overview of complications in different studies of TAVI in bicuspid aortic valve disease

Study (year)	THV Generation	Device success	AR ≥ grade 2	Need for second THV	Aortic root rupture/injury	Conversion to SAVR	New pacemaker implantation	Refs
Myelotte et al. (2014)	First	89.9	28.4	3.6	0.7	2.2	23.2	19
Yoon et al. (2017)	First and second	85.3	10.4	4.8	1.6	2.0	15.4	42
	First	78.4	15.9	7.2	NR	2.5	14.7	
	Second	95.1	2.7	1.3	NR	1.3	16.4	
Reddy et al. (2018); meta-analysis, adjusted rate	First and second	95.0	12.2	1.5	0	NR	17.9	44

AR, aortic regurgitation; NR, not reported; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve

Asymptomatic severe aortic stenosis

Up to 50% of patients with severe aortic stenosis report no symptoms at the time of diagnosis [51]. The annual risk of sudden death in these asymptomatic patients is approximately 1.5% [52]. Given that the majority of elderly patients have a sedentary lifestyle, symptoms might be latent or be ascribed to advanced age and comorbidities. Therefore, stress testing (such as exercise and pharmacological testing) is recommended to unmask symptoms and to assess the haemodynamic response (that is, the decrease in blood pressure) [8,9]. However, in clinical practice, stress tests are not routinely performed in elderly patients with extensive comorbidities and limited exercise capacities.

Increased left ventricular afterload imposed by aortic stenosis causes compensatory left ventricular hypertrophy and myocardial fibrosis [53,54]. The presence of myocardial fibrosis (diagnosed by either cardiac MRI or endomyocardial biopsy) might mitigate the effect of aortic valve replacement [55–57]. Therefore, earlier aortic valve replacement might prevent myocardial fibrosis. However, the management of asymptomatic patients with severe aortic stenosis remains controversial. Current guidelines recommend SAVR for selected patients with asymptomatic severe aortic stenosis [8,9] (Table 3). Otherwise, a watchful waiting strategy is recommended [8,9].

Several studies have suggested a benefit of aortic valve replacement in asymptomatic patients with severe aortic stenosis [52,58,59]. A 2016 meta-analysis has shown that asymptomatic patients with severe aortic stenosis who were treated conservatively with the strategy of watchful waiting had a ~3.5-fold higher rate of all-cause death at 4 years compared with those who received early aortic valve replacement [58]. Similarly, a propensity-matched analysis showed that asymptomatic patients with severe aortic stenosis who received aortic valve replacement had a lower risk of all-cause death and hospitalization for HF than patients treated with the conservative strategy of watchful waiting [52]. Another report showed better survival and fewer hospitalizations for HF after aortic valve replacement in asymptomatic patients with severe aortic stenosis than in symptomatic patients, suggesting that earlier aortic valve replacement might be recommended in selected asymptomatic patients with severe aortic stenosis at low operative risk [59].

The EARLY TAVR study [60] is an ongoing, randomized controlled trial to compare (1:1) TAVI with clinical surveillance in truly asymptomatic patients with severe aortic stenosis (confirmed by treadmill stress test) (Fig. 3). The primary outcome is a composite of all-cause death, all strokes and unplanned hospitalization for cardiovascular causes.

Challenges. The timing to proceed with TAVI and procedural safety seem to be of the essence in truly asymptomatic patients with severe aortic stenosis. If performed too early, the procedural risk would not counterbalance the low annual risk of cardiovascular death. However, if performed too late, the procedure might be futile because irreversible myocardial fibrosis might have already occurred, thereby precluding myocardial recovery and reducing the effect of TAVI in decreasing the risk of sudden death associated with severe aortic stenosis (predicted annual risk is 1.5% in patients managed conservatively) [52]. The decision to intervene for asymptomatic severe aortic stenosis should also consider coexisting comorbidities and the expected life expectancy of the patient.

Table 3 | Current indications for SAVR in patients with asymptomatic severe aortic stenosis

Recommendation	ACC/AHA[9] Class/ level of evidence	ESC [8] Class/ level of evidence
SAVR is indicated in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <50%) not due to another cause	I/B	I/ C
SAVR is indicated in asymptomatic patients with severe aortic stenosis and an abnormal exercise test showing symptoms on exercise clearly related to aortic stenosis.	IIa/B	I/ C
SAVR should be considered in asymptomatic patients with severe aortic stenosis and an abnormal exercise test showing a decrease in blood pressure below baseline	IIa/B	IIa/C
SAVR should be considered in asymptomatic patients with normal ejection fraction and none of the above-mentioned exercise test abnormalities if the surgical risk is low and one of the following findings is present:		
• Very severe aortic stenosis defined by a Vmax >5.5 m/s (≥5.0m/s ACC/AHA)	IIa/B	IIa/C
• Severe valve calcification and a rate of Vmax progression >_0.3 m/s/year	IIb/C	IIa/C
• Markedly elevated BNP levels (>threefold age- and sex-corrected normal range) confirmed by repeated measurements without other explanations	-	IIa/C
• Severe pulmonary hypertension (systolic pulmonary artery pressure at rest >60 mmHg confirmed by invasive measurement) without other explanation.	-	IIa/C

SAVR, surgical aortic valve replacement; Vmax, peak transvalvular velocity

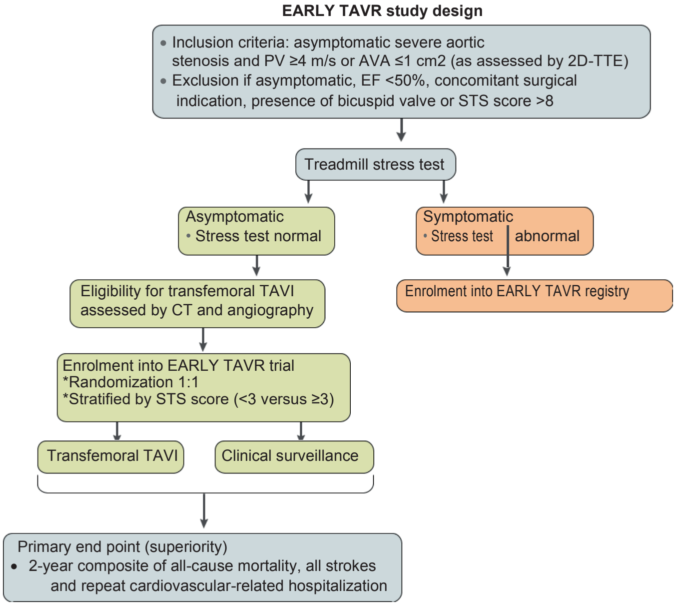

Fig. 3 | Flowchart of the design of the EARLY TAVR study. The EARLY TAVR study is an ongoing, randomized (1:1) controlled trial to compare transcatheter aortic valve implantation (TAVI) with clinical surveillance in patients with truly asymptomatic severe aortic stenosis, as confirmed by treadmill stress test.
AVA, aortic valve area; EF, ejection fraction; PV, peak velocity; STS, Society of Thoracic Surgeons; TTE, transthoracic echocardiography.

HF and moderate aortic stenosis

In people aged >70 years, >10% have HF and a poor prognosis, with 1-year and 5-year mortality of 20% and 50%, respectively [8,61,62]. The cornerstone of HF treatment is pharmacological treatment with neurohormonal antagonists (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, mineralocorticoid receptor antagonists and β-blockers) to reduce afterload. Degenerative aortic stenosis also increases with age and affects 5% of patients aged >65 years [63,64]. Therefore, moderate aortic stenosis and HF often coexist [65]. A multi-centre analysis demonstrated a 60% composite event rate, including all-cause death, aortic valve replacement or hospitalization for HF over a 4-year period, in patients with moderate aortic stenosis and reduced left ventricular function (as defined by left ventricular ejection fraction (LVEF) 20–50%) [66].

According to European and US guidelines, SAVR could be considered or is reasonable in patients with moderate aortic stenosis who are undergoing cardiac surgery for other indications, such as CABG surgery or concomitant severe valvulopathy (class IIa, level of evidence C in both the ESC and ACC/AHA guidelines) [8,9]. SAVR is not indicated in patients with isolated moderate aortic stenosis [8,9]. Indirect evidence suggests that aortic valve replacement for moderate aortic stenosis could benefit patients with depressed left ventricular function.

A retrospective analysis of the Duke Echocardiography Corelab database showed that SAVR in patients with moderate aortic stenosis (mean gradient 25–39 mmHg) and reduced LVEF (≤50%) was associated with a significantly decreased risk of death (HR 0.59, 95% CI 0.44–0.78, *P* = 0.0002) compared with medical treatment [65]. Similarly, in a single-centre, Canadian retrospective analysis, moderate prosthesis–patient mismatch (defined by an indexed aortic valve area 0.65–0.85 cm2/m2) after SAVR, which would correspond to moderate aortic stenosis, was associated with increased mortality only in patients with depressed left ventricular function [67]. The global load to the left ventricle is determined by a valvular (that is, aortic stenosis) and arterial (that is, arterial resistance) component. Pharmacological reduction of afterload with neurohormonal antagonists would only target the arterial load to the left ventricle. However, increased arterial stiffness in elderly patients can result in a fixed arterial afterload and no, or minimal, response to vasodilators. Therefore, in the case of (moderate) aortic stenosis, aortic valve replacement might provide additional afterload reduction and therefore complement HF therapy [68]. This hypothesis was the premise for the TAVR UNLOAD trial [69]. The investigators of TAVR UNLOAD are currently randomizing (1:1) 300 patients with HF and with moderate aortic stenosis to optimal HF therapy versus optimal HF therapy plus transfemoral TAVI with the balloon-expandable Edwards SAPIEN 3 valve (Fig. 4). The primary outcomes are all-cause death, disabling stroke, hospitalizations related to HF, symptomatic aortic valve disease or nondisabling stroke and change in Kansas City Cardiomyopathy Questionnaire from baseline.

Challenges. Patients with moderate aortic stenosis can have a lower valve calcium burden than patients with severe aortic stenosis [70]. Importantly, less aortic root calcification seems to be an independent predictor of prosthetic valve dislodgement [71]. A less calcified aortic root might offer inferior grip and less seating in the native valve, which can lead to prosthetic valve dislodgement. Multislice CT planning should, therefore, confirm the presence of sufficient calcium in the aortic root to secure transcatheter valve anchoring. Minor device oversizing should reduce the risk of prosthetic valve dislodgement, albeit at the expense of aortic root injury. Furthermore, and particularly with small annuli, optimal transcatheter heart valve expansion and circularity can be crucial to achieving a sufficient increase in aortic valve area in the setting of moderate aortic stenosis [72,73] (Table 4).

Finally, conduction abnormalities after TAVI might require permanent implantation of a pacemaker [74]. Cardiac resynchronization therapy should be considered in these patients because current HF management guidelines recommend cardiac resynchronization therapy in patients with LVEF ≤35% and a QRS complex duration ≥130 ms [75].

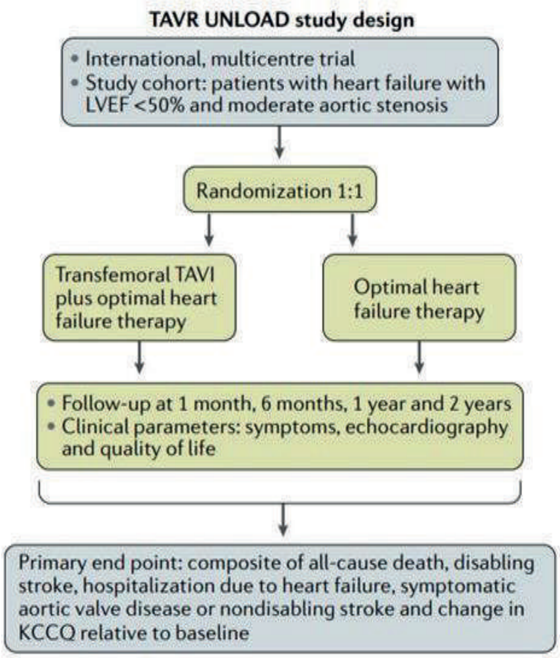

Fig. 4 | Design of the TAVR UNLOAD trial. TAVR UNLOAD is an ongoing trial in patients with heart failure with moderate aortic stenosis who will be randomly assigned 1:1 to optimal heart failure therapy plus transfemoral transcatheter aortic valve implantation (TAVI) with the balloon-expandable valve SAPIEN 3 (Edwards Lifesciences) or to optimal heart failure therapy alone. *KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction*

Table 4. Effective orifice area of different prosthetic valves

EOA ± SD (cm2)	CoreValve (72)	Evolut R (72)	Sapien (72)	Sapien XT (72)	Sapien 3 (72)	Lotus (73)
Valve size						
20					1.22 ± 0.22 (n= 47)	
23	1.12 ± 0.36 (n= 19)	1.09 ± 0.26 (n=3)	1.56 ± 0.43 (n= 1212)	1.41 ± 0.30 (n= 545)	1.45 ± 0.26 (n= 471)	1.62 ± 0.40 (n= 26)
25						1.78 ± 0.35 (n= 29)
26	1.74 ± 0.49 (n=289)	1.69 ± 0.40 (n=71)	1.84 ± 0.52 (n= 1130)	1.74 ± 0.42 (n= 675)	1.74 ± 0.35 (n=626)	
27						2.14 ± 0.52 (n= 24)
29	1.97 ± 0.53 (n= 446)	1.97 ± 0.54 (n= 129)		2.06 ± 0.52 (n= 251)	1.89 ± 0.37 (n= 326)	
31	2.15 ± 0.72 (n= 81)					
34		2.60 ± 0.75 (n= 52)				

Data are presented as effective orifice area ± SD (cm^2) and number of patients.

Severe aortic valve regurgitation

SAVR is the treatment of choice for patients with severe native aortic valve regurgitation who have symptoms, impaired LVEF (≤50%) or left ventricular enlargement [8,76]. According to data from the Euro Heart Survey, among patients with severe native aortic regurgitation only 21.8% with LVEF 30–50% and 2.7% with LVEF <30% were referred for SAVR [77]. Advanced age and comorbidities were often given as reasons not to offer SAVR [77]. The annual mortality of untreated patients with severe aortic regurgitation is 10–20% [8,78]. Pure native aortic regurgitation has been an exclusion criterion in all randomized controlled trials on TAVI because the specific anatomical features can preclude adequate valve implantation. Small, retrospective studies with off-label use of TAVI for aortic regurgitation with first-generation devices pointed towards high rates of clinically significant paravalvular leakage and device embolization or migration requiring more than one transcatheter heart valve intervention [79]. The improved features in later-generation transcatheter heart valves have dramatically reduced the frequency of moderate to severe paravalvular leakage compared with early-generation transcatheter heart valves (3% versus 27%) and the need for more than one transcatheter heart valve implantation (10% versus 24%) [79]. A systematic review and meta-analysis on the use of TAVI for pure native aortic

regurgitation using a self-expandable valve in 79% and a balloon-expandable valve in 21% of patients reported device success in 74–100% of the patients [80]. The implantation of a second valve was required in 7% of patients, and conversion to surgery occurred in 2.5% of patients [80]. The estimated rate of 30-day all-cause death and moderate to severe postprocedural aortic regurgitation were 7% (95% CI 3–13%; $I2$ = 37%) and 9% (95% CI 0–28%; $I2$ = 90%), respectively [80].
Transcatheter heart valve designs that have been proposed for approval for native aortic regurgitation leverage the native leaflets for additional anchoring. The JenaValve (JenaValve Technology) was the only CE mark-approved transcatheter heart valve system for the treatment of patients with severe native aortic regurgitation who were deemed inoperable or at high surgical risk, but this valve is no longer commercially available because the conversion to a transfemoral access version proved challenging. The JenaValve relied on a clip fixation mechanism to anchor the transcatheter heart valve on the native aortic valve leaflets rather than in the annulus [81]. A redesigned transfemoral JenaValve concept is now under clinical evaluation in the international JenaValve Pericardial TAVR Aortic Regurgitation Study [82], with early safety data forecast to be reported in 2019. The J-Valve system (JC Medical) is a two-piece transcatheter heart valve design that contains a nitinol anchor ring to be seated in the aortic sinuses and a nitinol stented valve with bovine pericardial leaflets to be deployed within the ring, clasping and anchoring onto the native valve leaflets. After initial reports with the transapical access version in a small number of patients in China, a first-in-human, single-case study with a transfemoral access design has been reported [83,84]. In the same spirit, the Helio transcatheter aortic dock (Edwards Lifesciences) is a self-expandable nitinol stent to be deployed in the nadir of the aortic sinuses to assist annular fixation of a balloon-expandable transcatheter heart valve by entrapping the native leaflets between the dock and the transcatheter heart valve [85]. As of today, no further device iterations of this Helio transcatheter aortic dock concept have been presented.

Challenges. A larger aortic annulus size and the absence of, or insufficient, valvular calcification can hamper the adequate anchoring and sealing of the transcatheter heart valve, which might increase the risk of transcatheter heart valve embolization and migration and paravalvular leakage. In addition, the currently available transcatheter heart valve sizes might not fit the larger aortic annuli observed in many patients with severe pure aortic regurgitation. Different sizing algorithms, including excessive oversizing, might be required to secure valve anchoring, obtain proper sealing and avoid transcatheter heart valve migration.

Current no-go indications for TAVI

Careful expansion of TAVI for new indications requires appropriate scrutiny and carefully designed, prospective (preferably randomized) trials. Notwithstanding the spectacular uptake of TAVI in clinical practice and its expanding indications, several clinical areas remain the domain of conventional SAVR. For example, active endocarditis mandates surgical excision or removal of the infected tissue and, therefore, precludes the use of TAVI. Furthermore, TAVI should not be considered for younger patients [8,9], who would fare better with a mechanical prosthesis. Finally, in patients who need CABG surgery or other valve or aortic surgery, SAVR in principle should remain the preferred treatment for moderate or severe aortic stenosis.

Conclusions

The success of TAVI for the treatment of severe tricuspid aortic valve stenosis and the introduction of improved device features and optimized imaging algorithms have paved the way for the exploration of TAVI in different clinical and anatomical phenotypes. Ongoing trials will establish whether TAVI truly is a viable strategy beyond severe aortic stenosis in patients at higher operative risk. The favourable results published in 2019 from the trials in patients at low surgical risk underpin the rationale for the use of TAVI in elderly patients, regardless of the operative risk. However, confirmation of long-term transcatheter valve durability warrants further study. The maturation of the TAVI technology has paved the way for its expansion into the unchartered territories of asymptomatic severe aortic stenosis, moderate aortic stenosis in combination with HF and left ventricular dysfunction, bicuspid aortic valve stenosis and pure native aortic regurgitation.

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Part II Mitral Valve

CHAPTER 6 Current MitraClip experience, safety and feasibility in the Netherlands

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Abstract

Purpose: Data on MitraClip procedural safety and efficacy in the Netherlands are scarce. We aim to provide an overview of the Dutch MitraClip experience.

Methods: We pooled anonymised demographic and procedural data of 1151 consecutive MitraClip patients, from 13 Dutch hospitals. Data was collected by product specialists in collaboration with local operators. Effect on mitral regurgitation was intra-procedurally assessed by trans-oesophageal echocardiography. Technical success and device success were defined according to modified definitions of the Mitral Valve Academic Research Consortium (MVARC).

Results: Median age was 76 (interquartile range 69–82) years and 59% were males. Patients presented with ≥ moderate mitral regurgitation and a predominance of functional mitral regurgitation (72%). Overall, 611 (53%) patients were treated with one Clip, 486 (42%) with ≥2 Clips and 54 (5%) received no Clip. The number of patients with ≥2 Clips increased from 22% in 2009 to 52% in 2016. Device success and technical success were 91 and 95%, respectively, and were consistent over the years. Significant reduction of mitral regurgitation by MitraClip was achieved in 94% of patients and was observed more often in patients with functional mitral regurgitation (95% vs. 91%, p= 0.025). Device time declined from 145 min in 2009 to 55 min in 2016.

Conclusion: MitraClip experience in the Netherlands is growing with excellent technical success and device success. Over the years, device time decreased and more pa-tients were treated with ≥2 Clips.

Keywords Valvular heart disease · Mitral valve · Mitral valve therapies

Introduction

Mitral regurgitation (MR) has a 2% prevalence in the general population and is more frequent in the elderly [1, 2]. Surgical treatment is considered the 'gold standard' for patients with symptomatic severe mitral regurgitation [3]. However, a significant proportion (49%) of eligible patients are denied for surgery because of age, comorbidities or poor left ventricular function [4].

The MitraClip (Abbott Vascular, Menlo Park, CA) offers a completely percutaneous mitral valve edge-to-edge repair. The efficacy and safety of the MitraClip device have been demonstrated in the EVEREST I (Endovascular Valve Edge-to-Edge Repair Study) trial [5]. Subsequently, the EVEREST II randomised controlled trial compared conventional surgery with MitraClip in operable patients with moderate-to-severe or severe, predominantly degenerative MR [6]. MitraClip was associated with superior safety and similar improvements in clinical outcomes. However, it was less effective in reducing MR [6]. Based on these results, the Food and Drug Administration approved MitraClip for high-risk patients with symptomatic degenerative MR. In European practice, the majority of patients treated with MitraClip have functional MR [7,8]. In this clinical setting, MitraClip may improve survival and hospital readmissions [9].

Data on the Dutch MitraClip experience are scarce. We therefore aim to provide an informative overview of the current MitraClip procedural safety and efficacy in the Netherlands.

Methods

This multicentre observational retrospective study collected all patients (n= 1151) from 13 Dutch hospitals treated with MitraClip between January 2009 and June 2016. All patients were discussed in local multi-disciplinary heart teams including interventional cardiologists, imaging specialist and cardiac surgeons, and were considered symptomatic and at high operative risk. All patients provided written informed consent for the MitraClip procedure.

Procedural data were prospectively and anonymously collected by product specialists in collaboration with local operators and, after approval of the participating centres, retrospectively analysed. Effect on MR was intra-procedurally (onsite) assessed by transoesophageal echocardiography. The Medical Ethics Committee of the Erasmus Medical Center reviewed the study protocol and waived the need for additional informed consent because of the non-interventional character of this retrospective study (MEC-2016-423) using anonymous data collection. The investigation conforms to the principles outlined in the Declaration of Helsinki.

MitraClip procedure

The MitraClip device is a 4 mm wide, polyester-covered cobalt chromium V-shaped clip with two movable arms and grippers (Fig. 1a). All procedures are performed under general anaesthesia, using fluoroscopic and transoesophageal echocardiographic guidance. A 24-French guide catheter is introduced in a femoral vein and delivered into the left atrium after transseptal puncture (Fig. 1b). The clip delivery system is advanced through the guide catheter into the left atrium and positioned above the origin of the regurgitation jet, perpendicular to the mitral coaptation line (Fig. 1c). The arms of the Clip are opened and advanced into the left ventricle. The Clip is then gradually pulled back towards the left atrium in order to grasp both mitral valve leaflets (Fig. 1d). The grippers are lowered, the clip is closed (Fig. 1e) and the leaflets are approximated resulting in a double mitral orifice (Fig. 1f). Before releasing the Clip, the severity of MR is assessed and the transmitral gradient is measured. If the result is satisfactory, the Clip can be released. In case of inadequate MR reduction or a high transmitral gradient, the Clip can be opened and repositioned or removed. More than 1 Clip may be necessary for significant MR reduction.

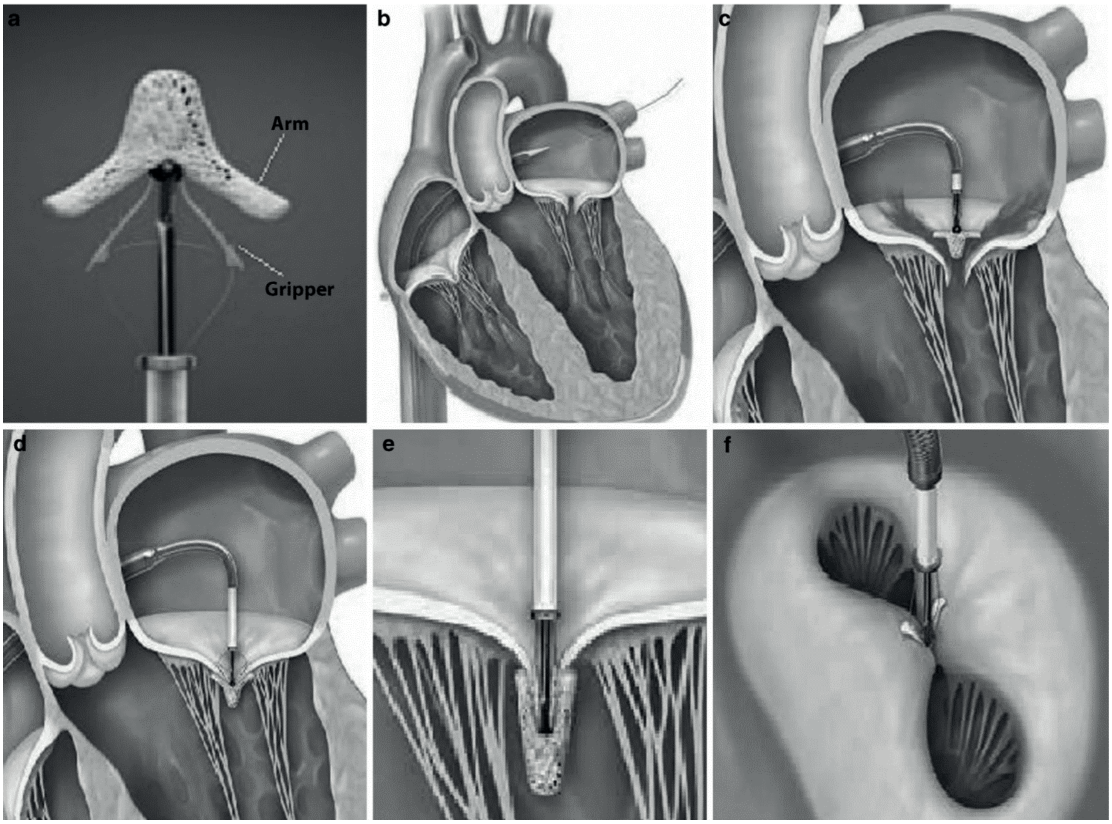

Fig. 1 a MitraClip device with two movable arms and grippers; b Guide catheter advanced into the left atrium after transseptal puncture; c Posi-tioning of the MitraClip above the regurgitation jet perpendicular to mitral coaptation line; d The MitraClip is pulled back in order to capture both leaflets; e The grippers are lowered and the arms are closed approximating the leaflets; and f creating a double mitral orifice. Image courtesy of Abbott

Study endpoints and definitions

The primary endpoints were procedural safety expressed in 'technical success' and procedural efficacy expressed in 'device success', both were modified from the Mitral Valve Research Consortium (MVARC) criteria [10].

- Technical success is defined as successful deployment of the device with absence of procedural mortality and freedom from emergency surgery.

- Device success is defined as proper placement of the device without procedural mortality and with reduction in post-procedural MR by ≥1 grade from baseline and to an absolute level of ≤moderate MR.

- Significant MR reduction: reduction in post-procedural MR by ≥1 grade from baseline.

Device time is defined as the time from guide catheter insertion to guide catheter removal

Statistical analysis

Categorical variables are presented as frequencies and percentages, and compared with the use of the Pearson Chi Square Test or the Fisher's exact test, as appropriate. Continuous variables are presented as means (± standard deviation – SD), in case of normal distribution, or medians (interquartile range – IQR), in case of skewed distribution, and compared with the use of the Student's t-test or the Mann-Whitney U test. Normality of the distributions was assessed using the Shapiro-Wilk test. We used a two-sided alpha level of 0.05 to indicate significance. Statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 1151 patients underwent percutaneous mitral valve edge to-edge repair with the MitraClip device. Relative contributions of the participating centres are summarised in Fig. 2a. The overall cohort had a median age of 76 (IQR 69–82) years and 59% were males. All patients presented with ≥moderate MR at baseline, with a clear dominance of functional MR (72%) (Table 1). Overall, 611 (53%) patients were treated with one Clip, 486 (42%) with ≥2 Clips and 54 (5%) received no Clip (Table 2). The number of patients treated with ≥2 Clips increased from 22% in 2009 to 52% in 2016 (Fig. 2). Significant MR reduction (≥1 grade) was achieved in 94% of patients.

The overall device and technical success were 91% and 95%, respectively, and were consistent over the years (Fig. 2b). Intra-procedural death and need for emergency surgery occurred in 3 (0.3%) and 6 (0.5%) patients, respectively (Table 2). The median device time declined from 145 (IQR 108–177) minutes in 2009 to 55 (IQR 34–86) minutes in 2016 (Fig. 2b).

Degenerative vs. functional MR

Patients with degenerative MR were older (median age 82 [IQR 76–85] vs. 74 [IQR 67–79] years, $p< 0.001$), had more often severe MR at baseline (73% vs. 61%, $p< 0.001$) and were more often treated with ≥2 Clips (50% vs. 39%, $p= 0.001$) when compared to patients with functional MR. Patients in the latter group had more often significant MR reduction (95% vs. 91%, $p= 0.025$) (Fig. 3) and a shorter device time (62 [IQR 40–99] minutes vs. 75 [IQR 49–110] minutes, $p< 0.001$).

One vs. ≥ two MitraClips

Patients treated with ≥2 Clips were more often males (68% vs. 53%, $p< 0.001$) with degenerative MR (33% vs. 23%, $p< 0.001$) and severe MR at baseline (81% vs. 53%, $p< 0.001$). Significant MR reduction was similar in both groups (98% vs. 98%, $p= 0.59$) (Fig. 4) while median device time was higher in ≥2 Clips group (86 [IQR 58–120] vs. 51 [IQR 35–75] minutes, $p < 0.001$).

Table 1 Baseline characteristics of patients undergoing MitraClip implantation

	Total population 2009–2016 (*n* = 1151)
Male, *n* (%)	684 (59)
Age, median (IQR)	76 (69–82)
Etiology MR	
Degenerative, *n* (%)	198 (17)
Functional, *n* (%)	832 (72)
Mixed, *n* (%)	118 (10)
Unknown, *n* (%)	3 (0.3)
Severity of MR at baseline	
Moderate, *n* (%)	19 (2)
Moderate-to-severe, *n* (%)	388 (34)
Severe, *n* (%)	744 (65)
LVEF <30%, *n* (%)	500 (43)

IQR interquartile range, *MR* mitral regurgitation, *LVEF* left ventricular ejection fraction

Table 2 Procedural characteristics of patients undergoing MitraClip implantation

	Total population 2009–2016 (*n* = 1151)
Clips	
0 Clips, *n* (%)	54 (5)
1 Clip, *n* (%)	611 (53)
≥2 Clips, *n* (%)	486 (42)
Device Time (min)[a], median (IQR)	66 (42–103)
MR reduction	
0, *n* (%)	75 (7)
1, *n* (%)	108 (9)
2, *n* (%)	587 (51)
3, *n* (%)	381 (33)
≥1, *n* (%)	1076 (94)
Device success[b], *n* (%)	1049 (91)
Technical success[c], *n* (%)	1097 (95)
Intra-procedural death, *n* (%)	3 (0.3)
Emergency surgery, *n* (%)	6 (0.5)

IQR interquartile range, *MR* mitral regurgitation

[a]Device time: defined as the time from delivery system insertion to clip delivery system removal

[b]Device success: defined as proper placement of the device without procedural mortality and with reduction in post-procedural MR by ≥1 grade from baseline and to an absolute level of moderate MR

[c]Technical success: defined as successful deployment of the device with absence of procedural mortality and freedom from emergency surgery

Discussion

To date, more than 1250 patients have undergone MitraClip treatment in the Netherlands. We present the largest Dutch multi-centre MitraClip study including 1151 patients. Key findings are: 1) MitraClip was predominantly used to treat functional MR; 2) MitraClip was successful in reducing MR in 94% of patients; 3) MitraClip was slightly more effective in patients with functional MR; 4) Over the years, implantation of ≥2 Clips became more frequent; 5) With growing experience, procedure time decreased with preserved device success and technical success. Patient demographics in our study were comparable with large European registries (i. e. ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe (ACCESS-EU) and German Transcatheter Mitral Valve Interventions Registry [TRAMI]) but different from the EVEREST-II trial. The EVEREST trial was conducted

in the USA and included younger patients (67.3 ± 12.8 years) with preserved left ventricular ejection fraction (60 ± 10.1). In Europe, MitraClip is more often applied in functional MR, which contrasts with the clear dominance (73%) of degenerative MR in the USA (Table 3) [6–8].
In our study, MitraClip seemed slightly more effective in functional MR than in degenerative MR (95% vs. 91%, p= 0.025). Intra-procedural death and moderate MR after Clip implantation were comparable with the ACCESS-EU and TRAMI registry (0.3% vs. 0% vs. 0% and 92% vs. 91% vs. 97%, respectively), confirming the safety and efficacy of MitraClip (Table 3).

Over the years, practice changed with a higher frequency of implanting ≥2 Clips. Patients treated with ≥2 Clips were more often males with degenerative MR and severe MR at baseline. Patients with degenerative MR may have thicker and more mobile leaflets and had (in our cohort) more often severe MR at baseline, which may explain why these patients in particular are treated with ≥2 Clips. A previous study identified anterior leaflet thickness (OR 1.7 per mm [95% CI; 1.16–2.57], $p = 0.007$) and a greater regurgitation volume at baseline (OR 1.21 per 10 ml [95% CI; 1.0–1.3], $p = 0.01$) as echocardiographic predictors for the need for more than 1 Clip [11]. Another study showed that the vena contracta (jet width) predicted need for >1 Clip (OR 2.5 [95% CI; 1.2–5.3], $p= 0.013$) with 83% sensitivity and 90% specificity for a cut-off value of ≥7.5 mm [12]. The increased device time in degenerative MR may also be explained by thicker and more mobile leaflets since this may aggravate the grasping process. Another reason is simply because of implantation of more Clips.

According to the latest European guidelines on valvular heart disease, MitraClip may be considered in patients with symptomatic severe primary and secondary MR, despite optimal medical therapy, including cardiac resynchronization therapy, who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a heart team, and have a life expectancy greater than 1 year (recommendation Class IIb, level of evidence C) [3]. The American guidelines consider transcatheter mitral valve repair only for severely symptomatic patients with chronic severe primary MR who have favourable anatomy for the repair procedure and a reasonable life expectancy, but who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal guideline-directed medical therapy for heart failure (recommendation Class IIb, level of evidence B) [13]. Yet, a wealth of recent clinical data underscores procedural safety and efficacy of MitraClip and a favourable longer-term outcome in selected patients. MitraClip seems an excellent treatment strategy in patients who are deemed at very high or prohibitive operative risk by heart team consensus. Several studies have shown significant MR reduction in the vast majority of high-risk patients, resulting in positive left ventricular remodelling and improvement of functional capacity [14, 15].

Also, heart failure patients who do not respond effectively to cardiac resynchronisation therapy and have at least moderate MR can improve with MitraClip. Auricchio et al. showed that 73% of cardiac resynchronization therapy non-responders (with functional MR) improved in functional class, and had increased left ventricular ejection fraction and reduced ventricular volumes after MitraClip treatment [16].

Ongoing randomised trials further elaborate on the value of MitraClip in functional MR. The MATTERHORN (Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHaemic ORigiN) trial, is comparing MitraClip with reconstructive mitral valve surgery in high-risk patients with moderate-to-severe functional MR. The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial is investigating the safety and efficacy of MitraClip versus optimal medical treatment (OMT) in patients with moderate-to-severe or severe functional MR who have been assessed as not eligible for mitral valve surgery.

The Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) is comparing the safety, efficacy and the cost-effectiveness of OMT versus OMT plus MitraClip in patients with severe secondary mitral regurgitation.

Expectedly, focused guidelines on valvular heart disease will be updated in the foreseeable future and include stronger recommendations for MitraClip. For now, our study demonstrated substantial MitraClip experience in the Netherlands with excellent procedural safety and efficacy.

Limitations

Given the retrospective observational character of this study and the onsite assessment of MR (i. e. absence of echo core lab), potential self-reporting bias may be introduced. Specific echocardiographic (quantitative) parameters such as regurgitation volume and jet width were not available. In addition, data were limited to procedural outcome. Follow-up data are needed to evaluate the durability of device success.

Long-term efficacy may reveal recurrence of MR (grade 3 or 4) as shown by the EVEREST-II trial and ACCESS-EU study with more than moderate MR recurrence rates of 21% at 12 months in both studies. Furthermore, we also acknowledge that complications such as stroke, bleeding and vascular complications, although rare, may occur during follow-up.

Conclusion

MitraClip experience in the Netherlands is growing with excellent technical success and device success. Over the years, the device time decreased and more patients were treated with ≥2 Clips.

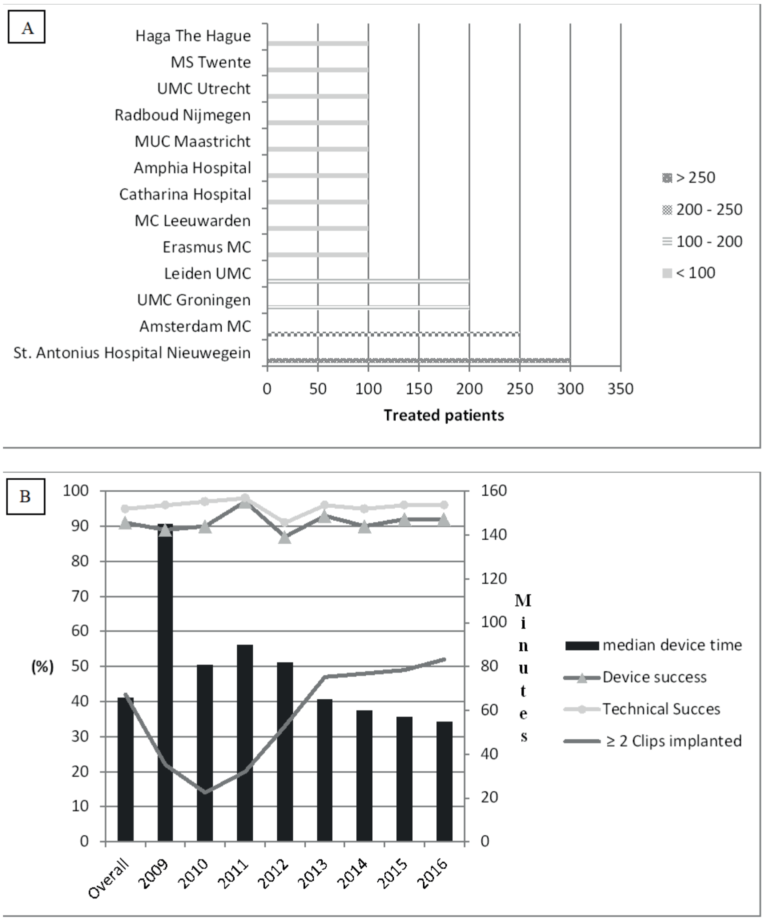

Fig. 2 Overview of A the relative contributions of the participating centres and B procedural characteristics and the primary endpoints over the years

Table 3 Baseline and procedural characteristics of patients undergoing MitraClip implantation in different cohorts

	MitraClip Netherlands (*n* = 1151)	ACCESS-EU Phase I (*n* = 567)	German TRAMI Registry *n* = 1064	EVEREST-II *n* = 184
Male, *n* (%)	684 (59)	362 (64)	658 (62)	115 (63)
Age (years)	76 (69–82)	73.7 ± 9.6	75 (70–81)	67.3 ± 12.8
Etiology MR				
Degenerative, *n* (%)	198 (17)	117 (23)	246 (29)	135 (73)
Functional, *n* (%)	832 (72)	393 (77)	590 (71)	49 (27)
Mixed, *n* (%)	118 (10)	–	–	–
Unknown, *n* (%)	3 (0.3)	–	–	–
Severity of MR at baseline				
Moderate, *n* (%)	19 (2)	13 (2)	42 (5)	8 (4)
Moderate-to-severe, *n* (%)	388 (34)	230 (41)	–	130 (71)
Severe, *n* (%)	744 (65)	324 (57)	827 (95)	46 (25)
LVEF <30%, *n* (%)	500 (43)	193 (34)	294 (33)	N. A.
LVEF, mean ± SD	N. A.	N. A.	N. A.	60 ± 10.1
Procedural				
0 Clips, *n* (%)	54 (5)	2 (0.4)	N. A.	N. A.
1 Clip, *n* (%)	611 (53)	(60)	N. A.	N. A.
≥2 Clips	486 (42)	(40)	N. A.	N. A.
Severity of MR after Clip				
Moderate, *n* (%)	1057 (92)	475 (91)	417 (97)	(77)
Moderate-to-severe, *n* (%)	57 (5)	39 (8)	–	41 (23)
Severe, *n* (%)	37 (3)	7 (1)	17 (3)	–
Device success[a], *n* (%)	1049 (91)	N. A.	N. A.	N. A.
Technical success[b], *n* (%)	1097 (95)	N. A.	N. A.	N. A.
Intra-procedural death, *n* (%)	3 (0.3)	0 (0)	0 (0)	N. A.
Emergency surgery, *n* (%)	6 (0.5)	N. A.	N. A.	N. A.

MR mitral regurgitation, *LVEF* left ventricular ejection fraction, *SD* standard deviation

[a]Device success: defined as proper placement of the device without procedural mortality and with reduction in post-procedural MR by ≥1 grade from baseline and to an absolute level of ≤ moderate MR

[b]Technical success: defined as successful deployment of the device with absence of procedural mortality and freedom from emergency surgery

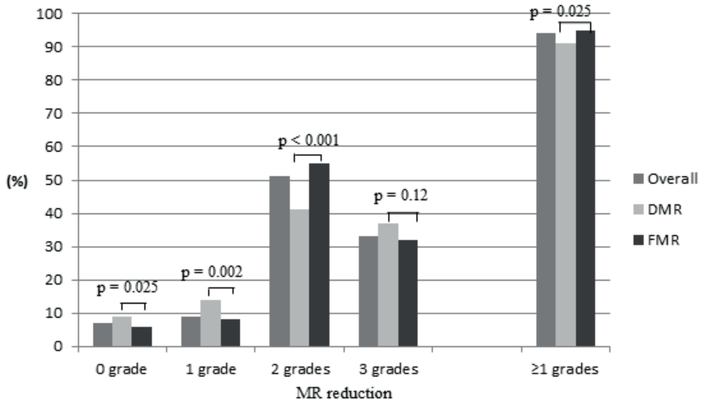

Fig.3 Comparison of reduction of mitral regurgitation in patients with degenerative mitral regurgitation versus functional mitral regurgitation.
MR mitral regurgitation, *DMR* degenerative mitral regurgitation, *FMR* functional mitral regurgitation

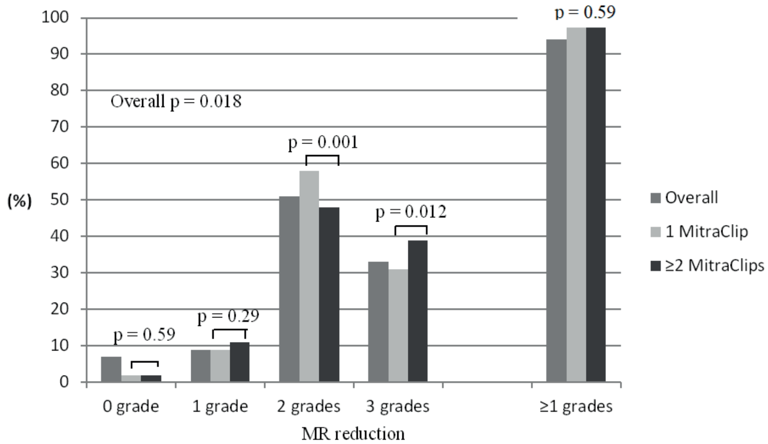

Fig.4 Comparison of mitral regurgitation reduction in patients treated with 1 versus ≥ MitraClips.
MR mitral regurgitation

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CHAPTER 7 MitraClip After Failed Surgical Mitral Valve Repair - An International Multicenter Study

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ABSTRACT

Background: Recurrence of mitral regurgitation (MR) after surgical mitral valve repair (SMVR) varies and may require reoperation. Redo mitral valve surgery can be technically challenging and is associated with increased risk of mortality and morbidity. We aimed to assess the feasibility and safety of MitraClip as a treatment strategy after failed SMVR and identify procedure modifications to overcome technical challenges.

Methods and results: This international multicenter observational retrospective study collected information for all patients from 16 high-volume hospitals who were treated with MitraClip after failed SMVR from October 29, 2009, until August 1, 2017. Data were anonymously collected. Technical and device success were recorded per modified Mitral Valve Academic Research Consortium criteria. Overall, 104 consecutive patients were included. Median Society of Thoracic Surgeons score was 4.5% and median age was 73 years. At baseline, the majority of patients (82%) were in New York Heart Association class ≥III and MR was moderate or higher in 86% of patients. The cause of MR pre-SMVR was degenerative in 50%, functional in 35%, mixed in 8%, and missing/unknown in 8% of patients. The median time between SMVR and MitraClip was 5.3 (1.9–-9.7) years. Technical and device success were 90% and 89%, respectively. Additional/modified imaging was applied in 21% of cases. An MR reduction of ≥1 grade was achieved in 94% of patients and residual MR was moderate or less in 90% of patients. In-hospital all-cause mortality was 2%, and 86% of patients were in New York Heart Association class ≤II.

Conclusions: MitraClip is a safe and less invasive treatment option for patients with recurrent MR after failed SMVR. Additional/ modified imaging may help overcome technical challenges during leaflet grasping.

CLINICAL PERSPECTIVE

What is new?

- MitraClip after failed surgical mitral valve repair is feasible and safe in selected patients, with a technical and device success rate of 90% and 89%, respectively.
- Procedure modifications may be required to overcome technical challenges related to prior mitral surgery.

What are the clinical implications?

- For selected patients with recurrent mitral regurgitation after failed surgical mitral valve repair, MitraClip is a safe and less invasive treatment option.
- Additional/modified imaging may help overcome technical challenges during leaflet grasping.

Nonstandard Abbreviations and Acronyms

CTSN	Cardiothoracic Surgical Trials Network
EVEREST II	Endovascular Valve Edge-to-Edge Repair Study II
MR	mitral regurgitation
MVARC	Mitral Valve Academic Research Consortium
SMVR	surgical mitral valve repair
STS	Society of Thoracic Surgeons

Introduction

Mitral valve surgery is the treatment of choice for symptomatic patients with severe degenerative mitral regurgitation (MR) and left ventricular (LV) ejection fraction >30% [1,2]. In functional MR, surgery is indicated in patients with severe MR undergoing coronary artery bypass grafting and LV ejection fraction >30% [2]. Recurrence of MR after surgical repair varies and may require reoperation [3-5]. Compared with primary mitral surgery, redo mitral valve surgery can be technically challenging and is associated with a higher operative mortality, higher complication rate, and increased length of stay [6]. Alternatively, transcatheter mitral valve replacement and percutaneous mitral valve edge-to-edge repair with MitraClip can be performed in selected patients after failed surgical mitral valve repair (SMVR) [7-11]. The aim of this study was to assess the feasibility and safety of MitraClip after failed SMVR and identify procedure modifications to overcome technical challenges related to the prior mitral surgery.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.
This international multicenter observational retrospective study collected information from all consecutive patients, from 16 high-volume hospitals, who were treated with MitraClip after failed SMVR from October 29, 2009, until August 1, 2017. Selection of patients and assessment of eligibility was left at the discretion of the local multidisciplinary heart teams, which included interventional cardiologists, imaging specialists, and cardiac surgeons. Data were anonymously collected.
The medical ethics committee of the Erasmus Medical Center reviewed the study protocol and waived the need for additional informed consent because of the noninterventional design of this retrospective study (MEC-2017-1021) using anonymous data collection. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Study Endpoints and Definitions

The primary end points were procedural safety expressed as "technical success" and procedural efficacy expressed as "device success," both were modified from Mitral Valve Academic Research Consortium (MVARC) criteria [12].

1. Technical success is defined as successful deployment of the device with absence of procedural mortality and freedom from emergency surgery.
2. Device success is defined as proper placement of the device without procedural mortality and with reduction in postprocedural MR by ≥1 grade from baseline and to an absolute level of moderate or less MR.
3. Significant MR reduction is defined as reduction in postprocedural MR by ≥1 grade from baseline.
4. Device time is defined as the time from guide catheter insertion to guide catheter removal.

Statistical analysis

Categorical variables are presented as frequencies and percentages and compared using Pearson chi-square test or Fisher exact test, as appropriate. Continuous variables are presented as means (±SD) (in case of normal distribution) or medians (interquartile range) (in case of skewed distribution) and compared with using Student *t* test or Mann Whitney *U* test. Normality of the distributions was assessed using the Shapiro-Wilk test. A 2-sided α level of 0.05 was used to indicate significance. Statistical analyses were performed using SPSS software version 21.0 (IBM).

Results

Baseline Characteristics

Overall, 104 consecutive patients were included with a median age of 73 years, 70% were men, 82% were in New York Heart Association class ≥III, and the median Society of Thoracic Surgeons (STS) score was 4.5% (Table 1). The median LV ejection fraction was 50% (30%–60%), mean LV end-diastolic diameter was 60 ± 11 mm, and transmitral gradient was 3.0 mm Hg (interquartile range, 2.2–4.0 mm Hg) (Table 1). The cause of MR pre-SMVR was degenerative in 50%, functional in 35%, mixed in 8%, and missing/unknown in 8%, and further specified in Table 2. The cause of MR pre-MitraClip was degenerative in 44%, functional in 39%, mixed in 10%, ring rupture/detachment/dehiscence in 7%, and systolic anterior motion in 3% (Table 2 and Figure 1A)). The median time between surgery and MitraClip was 5.3 years (Table 2).

Table 1. Baseline characteristics

	Total population n=104
Age (yrs), median (IQR)	73.0 (67.0 - 80.0)
Male, n (%)	73 (70)
Height (cm), mean ± SD	171 ± 10
Weight (kg), median (IQR)	75.0 (65.0 - 85.0)
Body mass index (kg/m2), median (IQR)	24.9 (22.7 - 28.0)
New York Heart Association class ≥ III, n (%)	85 (82)
STS score (%), median (IQR)	4.5 (2.2 - 6.6)
<u>Cardiomyopathy</u>	
Ischemic, n (%)	32 (36)
Non-ischemic, n (%)	12 (13)
Hypertrophic, n (%)	1 (1)
<u>Implantable device</u>	
Permanent pacemaker, n (%)	9 (9)
ICD, n (%)	16 (15)
CRT, n (%)	11 (11)
<u>Atrial fibrillation</u>	
Paroxysmal, n (%)	30 (29)
Permanent, n (%)	30 (29)
Previous myocardial infarction, n (%)	27 (27)
Previous coronary artery bypass graft surgery, n (%)	38 (37)
Previous percutaneous coronary intervention, n (%)	20 (19)
Previous cerebrovascular event, n (%)	7 (7)
Diabetes mellitus, n (%)	24 (23)
Hypertension, n (%)	82 (79)
Peripheral vascular disease, n (%)	13 (13)
Pulmonary hypertension, n (%)	65 (63)
Chronic obstructive pulmonary disease, n (%)	20 (19)
<u>Laboratory results</u>	
GFR (ml/min), mean ± SD	56 ± 21
Hemoglobin (mmol/L), median (IQR)	6.6 (7.9 - 8.6)
<u>Echocardiography</u>	
Left ventricular ejection fraction (%), median (IQR)	50 (30 - 60)
Left ventricular end diastolic diameter (mm), mean ± SD	60 ± 11
Left ventricular end systolic diameter (mm), mean ± SD	45 ± 13
Mean transmitral gradient (mmHg), median (IQR)	3.0 (2.2 - 4.0)

Severity mitral regurgitation	
Mild- moderate, n (%)	3 (3)
Moderate, n (%)	12 (12)
Moderate- severe, n (%)	37 (36)
Severe, n (%)	52 (50)

BMI indicates body mass index; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; ICD, implantable cardioverter--defibrillator; IQR, interquartile range; LV, left ventricular; NYHA, New York Heart Association; and STS, Society of Thoracic Surgeons.

Table 2. Mitral valve regurgitation cause, treatment, and mode of failure

	Total population n= 104
Etiology MR before surgical repair	
DMR, n (%)	52 (50)
Prolapse, n (%)	32 (62)
Chordal rupture, n (%)	7 (14)
Other, n (%)	6 (12)
FMR, n (%)	36 (35)
Annular dilatation, n (%)	11 (31)
Leaflet tethering, n (%)	13 (36)
Both, n (%)	9 (25)
Mixed, n (%)	8 (8)
Missing/unknown, n (%)	8 (8)
Type of surgical mitral valve repair	
Ring, n (%)	90 (87)
Chordal repair, n (%)	13 (13)
Partial leaflet resection, n (%)	16 (15)
Other, n (%)	8 (8)
Combined (ring/chordal repair/resection), n (%)	28 (27)
Type of ring	
Complete ring, n (%)	65 (70)
Incomplete ring, n (%)	25 (28)
Ring size	
25mm - 30mm	37 (41)
31mm – 35mm	26 (29)
36mm – 40mm	11 (12)
Etiology pre-MitraClip	
Degenerative, n (%)	46 (44)
Functional, n (%)	41 (39)
Mixed, n (%)	10 (10)
Ring rupture/detachment, n (%)	7 (7)
Systolic anterior motion, n (%)	3 (3)
Median time (years (IQR)) between surgery and MitraClip	5.3 (1.9 - 9.7)

IQR indicates interquartile range; and MR, mitral regurgitation.

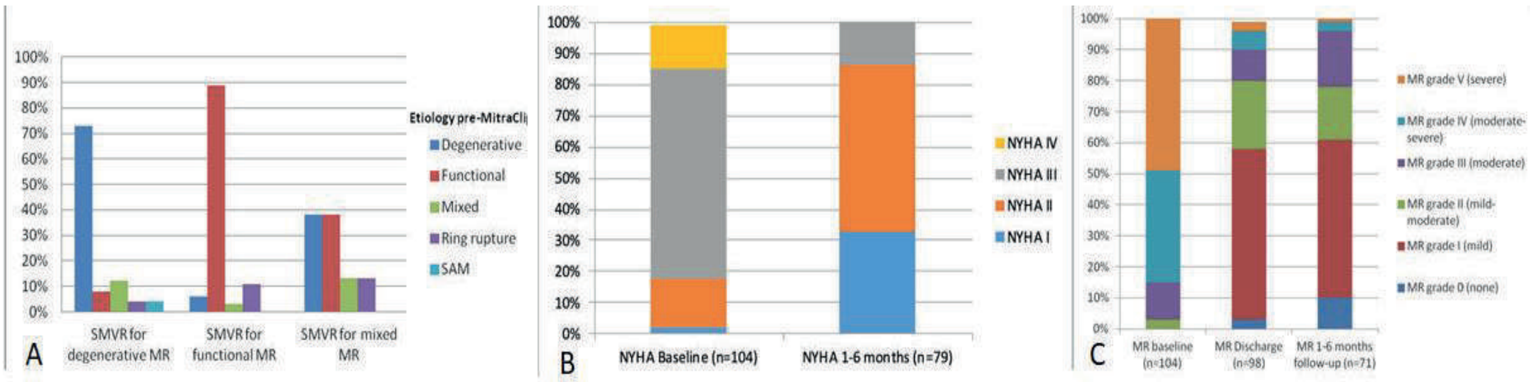

Figure 1. Baseline characteristics (eg, mitral regurgitation [MR] etiology) and follow-up of New York Heart Association (NYHA) class and MR.

A, Overview of MR etiologies before surgical mitral valve repair (SMVR) and before MitraClip procedure. B, NYHA at baseline and at 1 to 6 months of follow-up. C, MR at baseline, at discharge, and at 1 to 6 months of follow-up. *SAM indicates systolic anterior motion*.

Procedural characteristics

MitraClip implantation was feasible in 92% of patients. In the unfeasible cases (8%), reasons for not clipping were development of inacceptable mitral valve gradients in 5 cases, persistent MR in combination with inacceptable mitral valve gradient in 1 case, and inability to grasp both leaflets because of a severely tethered and short posterior leaflet in combination with poor image quality in 2 cases. Seven of the 8 patients (the unfeasible cases) had a surgical annuloplasty ring, 2 patients had a 28-mm size ring, 3 patients had a 30-mm size ring, 1 patient had a 32-mm size ring, and the ring size was missing in 1 patient. Overall, 64% of patients were treated with 1 clip, 23% with 2 clips, and 5% with 3 clips. Significant MR reduction (MR reduction ≥1 grade) and technical and device success were achieved in 94%, 90%, and 89%, respectively. There was no difference in technical and device success between patients treated with degenerative versus functional MR pre-SMVR (89% versus 97% [*P*= 0.23] and 88% versus 94% [*P*= 0.46], respectively) (Table 3).

In 79% of the patients, standard transesophageal echocardiography (TEE) views (ie, LV outflow tract and intercommisural view) were used during the grasping process, in 16% of the patients transesophageal echocardiography views were used with modified angles, and in 5% of the patients standard transesophageal echocardiography views were used in combination with adjunctive intracardiac echocardiography.

The median device time was 70 minutes and appeared shorter with additional/modified imaging versus standard LV outflow tract/intercommissural view (39 minutes [21–67 minutes] versus 79 minutes [56–116 minutes], *P*< 0.001). However, there was no difference between the 2 groups (standard views versus additional/modified imaging) with regards to technical success (89% versus 95%, *P*= 0.68) and device success (87% versus 95%, *P*= 0.45).

Table 3. Procedural characteristics and in-hospital complications

	Total population n= 104
Imaging during grasping proces	
Standard LVOT and intercommissural view	80 (79)
LVOT/intercommissural view with modified angles	15 (15)
LVOT/intercommissural view with ICE	6 (6)
Clips	
0 clips, n (%)	8 (8)
1 clip, n (%)	67 (64)
2 clips, n (%)	24 (23)
3 clips, n (%)	5 (5)
MR reduction	
0, n (%)	6 (6)
1, n (%)	10 (10)
2, n (%)	18 (18)
3, n (%)	37 (38)
4, n (%)	27 (28)
≥1, n (%)	92 (94)
Left ventricular ejection fraction (%), median (IQR)	45 (28 – 56)
Mean transmitral gradient (mmHg) post-clip, median (IQR)	4.7 (3.0 - 6.0)
Concommitant mitral therapy	
Plug/occluder implantation, n (%)	2 (2)
Other, n (%)	1 (1)
Device Time * (min), median (IQR)	70 (41 - 113)
Technical success**, n (%)	94 (90)
Device success ***, n (%)	88 (89)
Conversion to mitral valve surgery, n (%)	0 (0)
Bleeding	
Minor, n (%)	3 (3)
Major, n (%)	2 (2)
Extensive, n (%)	0 (0)
Life-threatening, n (%)	0 (0)
Fatal	0 (0)
Vascular complication	
Minor, n (%)	2 (2)
Major, n (%)	0 (0)
Stroke	
Disabling, n (%)	0 (0)
Non-disabling, n (%)	1 (1)
Myocardial infarction, n (%)	1 (1)
In-hospital mortality, n (%)	2 (2)
Length of stay (days), median (IQR)	3 (2-6)

ICE: intracardiac echocardiography; IQR, interquartile range; LV, left ventricular; and LVOT, left ventricular outflow tract.

*Device time is defined as the time from guide catheter insertion to guide catheter removal.

**Technical success is defined as successful deployment of the device with absence of procedural mortality and freedom from emergency surgery.

***Device success is defined as proper placement of the device without procedural mortality and with reduction in post-procedural MR by ≥1 grade from baseline and to an absolute level of ≤ moderate MR.

In-hospital complications and follow-up

The in-hospital mortality rate was 2% and a similar percentage was seen for major bleeding and minor vascular complication. Minor bleeding occurred in 3% of patients. The median length of stay was 3 days. New York Heart Association class and MR at 1 month to 6 months are shown in Figure 1B and 1C. Mortality rates at 6 months and 1 year were 6% and 9%, respectively.

Discussion

We report the largest series of patients treated with MitraClip after failed SMVR. The findings indicate that: (1) MitraClip was feasible and safe after failed SMVR in selected patients with technical and device success rates of 90% and 89%, respectively; (2) the median time between SMVR and MitraClip was 5.3 years; and (3) additional/modified imaging techniques may facilitate leaflet grasping and shorten device time by dealing with technical challenges caused by shadowing from the annuloplasty ring (Figure 2).

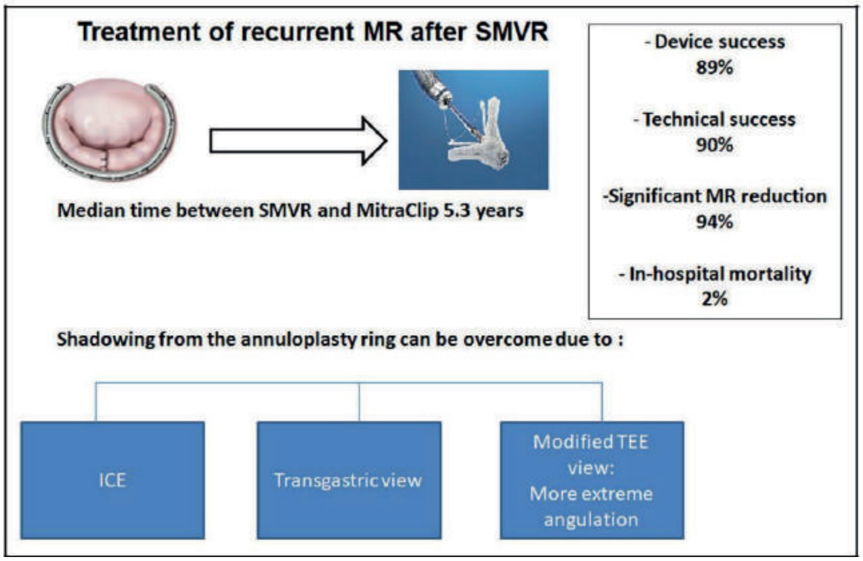

Figure 2. Overview of the main outcomes of this study.
ICE indicates intracardiac echocardiography; MR, mitral regurgitation; SMVR, surgical mitral valve repair; and TEE, transesophagal echocardiography.

Recurrence of MR after SMVR is not uncommon and is associated with an increased risk of mortality [13-14]. Petrus et al [13] demonstrated that the cumulative incidence of recurrent MR (grade ≥2) after SMVR for functional ischemic MR is 27.6% (at 10 years of follow-up). One of the randomized CTSN (Cardiothoracic Surgical Trials Network) initiatives compared mitral repair with mitral valve replacement for severe functional MR and reported MR recurrence rates of 32.6% at 1 year and 58.8% at 2 years of follow-up including mortality rates of 14.3% at 1 year and 19% at 2 years of follow-up after mitral repair [3,15]. Another CTSN trial reported an 11.2% MR recurrence 2 years after mitral repair in patients with at least moderate ischemic MR who underwent SMVR in combination with coronary artery bypass grafting [16]. EVEREST II (Endovascular Valve Edge-to-Edge Repair Study II), which was predominantly composed of degenerative causes, compared MitraClip with mitral surgery (86% surgical repair), and ≈11% of the surgical arm had moderate to severe or severe MR at 5-year follow-up [17]. Suri et al [18] showed a 15-year overall incidence rate of recurrent MR after SMVR for degenerative MR of 13.3%, while the 15-year incidence rate of mitral reoperation was 6.9%, suggesting that a substantial proportion (6.4%) of patients did not undergo redo mitral valve surgery. Compared with primary mitral surgery, redo mitral valve surgery is associated with higher operative mortality (11.1% versus 6.5%, $P< 0.0001$), higher complication rates (such as prolonged ventilation [28.1% versus 19.7%, $P< 0.0001$], renal failure [9.4% versus 7.0%, $P= 0.004$], reoperation [14.7% versus 10.3%, $P< 0.0001$], stroke [2.8% versus 1.9%, $P= 0.042$], cardiopulmonary bypass time [165 versus 148 minutes, $P< 0.0001$], and intensive care unit stay [88 versus 68 hours, $P< 0.0001$]), and increased length of stay (9 versus 7 days, $P< 0.0001$) [6]. In our study, using the MitraClip to treat failed SMVR was associated with a 2% in-hospital mortality rate and a short length of stay (3 days).

Our study confirms the feasibility and safety of MitraClip in patients with recurrent MR after SMVR. A previous report including 57 patients undergoing MitraClip after prior SMVR showed a procedural success rate of 84% (compared with 89% in our series) [7]. In that study, patients had a higher STS score of 6.0%, a 52% functional MR pre-SMVR, and 79% of patients with original repair including a ring annuloplasty (as compared with STS 4.5%, 35% functional MR, and 87% with prior annuloplasty ring in our series) [7]. However, device success in our study is still lower than what is achieved in MitraClip for native MR studies (ie, functional and/or degenerative), which varies between 91% and 96% [19-23].

Additional/modified imaging and procedure modifications

In our study, additional/modified imaging techniques had favorable effects on device time and similar technical and device success rates. A nondehisced annuloplasty ring approximates the leaflets, minimizes the coaptation gap, and increases coaptation length, which may facilitate the grasping maneuver. Conversely, shadowing from the annuloplasty ring may obscure the echocardiographic window for posterior leaflet grasping and also limit the orifice dimensions through which the clip needs to enter the left ventricle from the left atrium. Conventional clip passing is recommended in an ≈180° open configuration to help maintain and monitor the clip orientation as the clip is positioned perpendicular to the coaptation plane before leaflet grasping. In the case of a prior surgical ring, there is a reduction in the mitral orifice such that it can sometimes be impossible to enter the left ventricle in this 180° open position, and the clip should be formally oriented in the left atrium, closed, then advanced into the left ventricle in the partially or totally closed position and reopened under the mitral plane with confirmation of the maintained correct orientation (Figure 3). The leaflets will be typically grasped well below the surgical ring and more towards the left ventricle (and more often so in secondary MR). At times, the presence of the surgical ring and the open MitraClip in the left ventricle may further impede leaflet visualization because of shadowing of the posterior leaflet by the annuloplasty ring. In cases of ring dehiscence, the ring may conflict with the delivery system, create shadowing, and sometimes impede passing of the clip into the left ventricle. A transgastric short-axis view may then offer improved visualization of both leaflets to assist proper and controlled leaflet grasping (Figure 4). In some cases, the surgical ring could induce an inflow gradient, which may further increase after leaflet grasping leading to mitral stenosis. Consequently, operators may decide not to release the clip. Postprocedural mitral stenosis (ie, transvalvular mitral gradient measured invasively >5 mm Hg or echocardiographically >4.4 mm Hg) after MitraClip has been shown to have a negative impact on long-term outcome [24]. Invasive transmitral pressure monitoring may further guide MitraClip implantation in this setting [25].

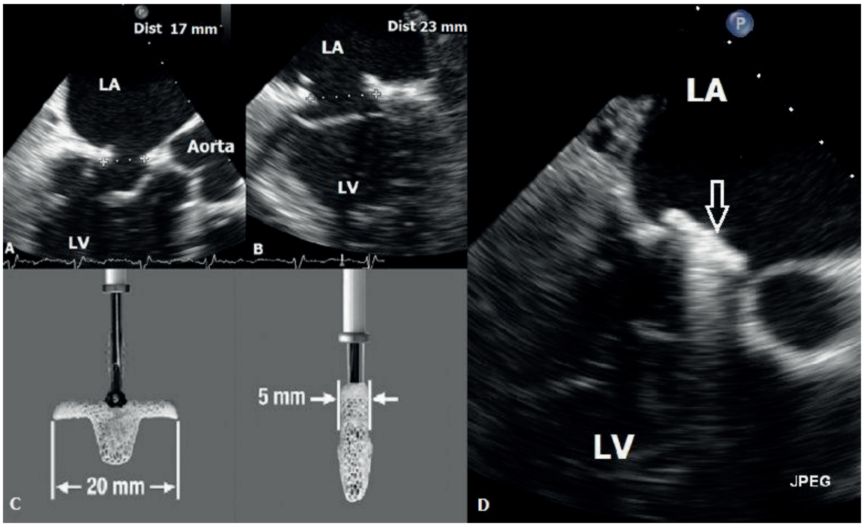

Figure 3. Case example in which the mitral annuloplasy ring precluded crossing of the MitraClip in an open configuration.
A and B, The dimensions of the mitral annuloplasty ring measured with transesophageal echocardiography. (A) The anterior--posterior diameter and (B) the medial--lateral diameter. C, The length of the MitraClip with open and closed arms. D, MitraClip in open configuration was not able to cross the surgical mitral ring. Arrow indicates MitraClip; LA, left atrium; and LV, left ventricle.

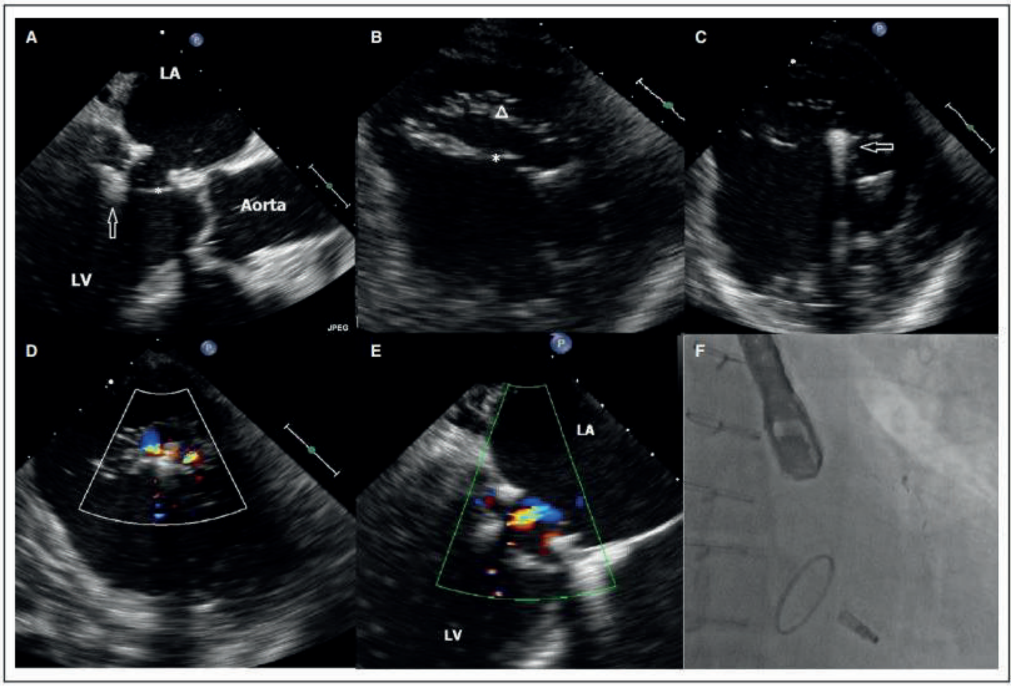

Figure 4. Additional value of the transgastric view during MitraClip grasping.
A, Poor visualization of the posterior leaflet in the long--axis view. B, Excellent visualization of both mitral valve leaflets in the transgastric view. C, The transgastric view was used during the grasping process and (D and E) resulted in significant mitral regurgitation reduction (F) after the implantation of a MitraClip.
*Arrow indicates MitraClip; LA, left atrium; and LV, left ventricle. *Anterior mitral valve leaflet; Δ posterior mitral valve leaflet.*

Poor visualization of the posterior leaflet caused by shadowing from the annuloplasty ring can often be addressed by manipulation of the transesophageal echocardiography probe to move the imaging element relatively more left lateral within the esophagus (Figure 5). This maneuver will often reposition the image of the posterior mitral leaflet so that it does not fall within the surgical ring shadow. In general, atypical multiplanar angles or adjustment wheel manipulation may be necessary to view the complete leaflet grasping zone. Alternatively, the MitraClip may be deployed without complete visualization of the posterior leaflet but with the knowledge that the leaflet is often vertically oriented and under chordal restriction, which limits the concern for leaflet curling within the device closure zone.

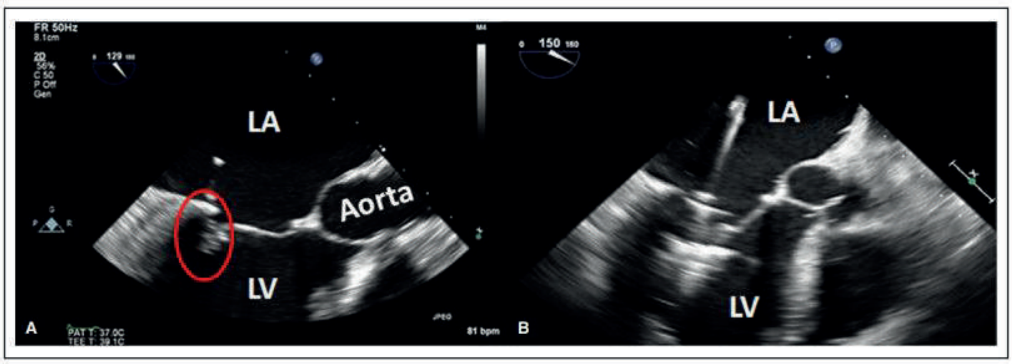

Figure 5. Case example in which more extreme transesophageal echocardiography angulation optimized visualization of the posterior leaflet.
A, Poor visualization of the posterior leaflet with the standard transesophageal echocardiography view (indicated by the red circle). B, More extreme angulation offered better visualization of the posterior leaflet.
LA indicates left atrium; and LV, left ventricle.

In selected cases in which confirmation of the insertion of the posterior leaflet into the MitraClip could not be achieved by standard or modified imaging planes of the transesophageal probe, some investigators have used adjunctive intracardiac echocardiography (Figure 6 and Video S1). Both venous and arterial approaches have been used to position the intracardiac echocardiography catheter in order to obtain a clear view of the anterior and posterior leaflet and visualize grasping and clipping maneuvers. Conceivably, further intracardiac echocardiography iterations (eg, 4-dimensional technology) may enhance mitral valve imaging in the near future.

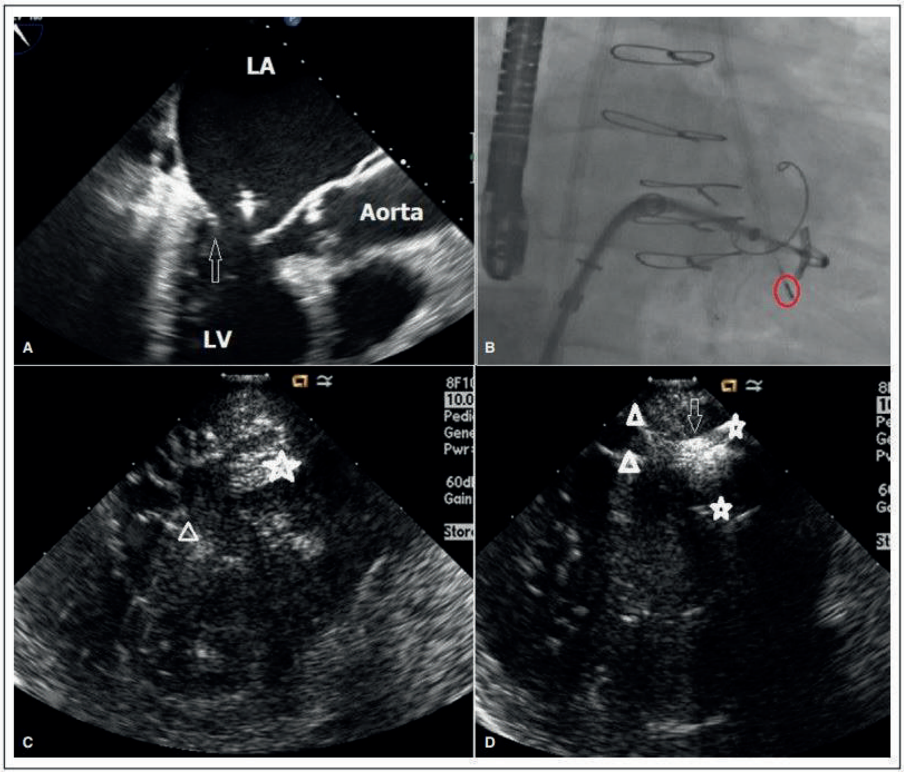

Figure 6. Additional value of intracardiac echocardiography in the visualization of both mitral valve leaflets.
A, Transesophageal echocardiographic image showing shadowing of the posterior leaflet (indicated by the arrow). B, Intracardiac echocardiographic catheter in the left ventricle (LV; indicated by the red circle). C and D, Short-axis LV visualization including both mitral valve leaflets (*anterior mitral valve leaflet; Δ posterior mitral valve leaflet; arrow MitraClip). LA indicates left atrium.

In our study, patients were treated with the MitraClip NT device (Abbott Vascular). Additional device sizes are emerging and may generate a more individualized/patient tailored approach.
Another minimally invasive alternative for redo surgery in the setting of prior surgical mitral repair is transcatheter mitral valve replacement. Device success and 30-day all-cause mortality with transcatheter mitral valve replacement in prior surgical ring are 69.5% and 9.9%, respectively [11].
An important and potentially fatal complication is LV obstruction. Small LV cavity, septal hypertrophy, length of the anterior mitral valve leaflet, and aorto-mitral angle <120° are important risk factors for LV outflow tract obstruction [11,26-28]. Therefore, these anatomic characteristics favor MitraClip treatment.

Limitations

The retrospective nature of our research is susceptible to selection bias. There was no echo-core laboratory or clinical event committee for completely independent data analysis. The modest patient population, limited follow-up, and the lack of a standardized echocardiography protocol should be acknowledged. Furthermore, the overall recurrence rate of MR after failed SMVR was missing in this study. Still, this is the largest cohort to date confirming the safety and efficacy of MitraClip treatment in patients with prior SMVR. Larger trials with longer follow-up data are needed to assess long-term efficacy.

Conclusions

MitraClip is a safe and minimally invasive treatment option for patients with recurrent MR after failed SMVR. Additional/modified imaging may help overcome technical challenges during leaflet grasping.

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Part III. Creative solutions to complex interventions

CHAPTER 8 How should I treat a patient with a symptomatic and severe low-flow low-gradient aortic stenosis and an incidental abdominal aortic aneurysm?

Zouhair Rahhab; Sander ten Raa; Nathalie van der Ploeg; Nicolas M. Van Mieghem; Hence Verhagen; Peter P.T. de Jaegere

EuroIntervention. 2017 Jul 20;13(4):491-494.

CASE SUMMARY

Background: An 88-year-old male with a symptomatic severe low-flow low-gradient aortic stenosis was referred for catheter-based treatment (STS 7.7%).

Investigation: Transthoracic echocardiography showed a severe low-flow low-gradient aortic stenosis (peak velocity of 2.9 m/s, AVA 0.6 cm², LVEF 30%). CT during work-up revealed an unexpected finding of a large fusiform infrarenal AAA with a diameter of 59 mm, a mural thrombus and dissection.

Diagnosis: Severe low-flow low-gradient aortic stenosis and a large fusiform infrarenal AAA with mural thrombus and dissection.

Management: The strategy was to treat both conditions in the same setting ("one-stop shop") using a complete percutaneous approach under local anaesthesia. Immediately after transfemoral implantation of an Edwards S3 29 mm, a Medtronic Endurant II endograft was implanted in the abdominal aorta.

KEYWORDS: abdominal aortic aneurysm, aortic stenosis, incidentaloma, multislice computed tomography, transcatheter aortic valve implantation

Presentation of the case

An 88-year-old male (173 cm, 78 kg) with progressive symptoms of dyspnoea (NYHA Class III) was referred for catheter-based treatment of aortic stenosis. Except for mild chronic kidney disease (GFR 58 ml/min) there were no antecedents. Physical examination showed him to be a vital, independently living, elderly patient (ADL 0/6, IADL 2/14, MMSE 30/30). There were no signs of cardiac failure. The ECG revealed a sinus rhythm (93 bpm) with non-specific repolarisation disturbances. Cardiac enzymes were normal, NT-proBNP was 1,027 pmol/L. Transthoracic echocardiography showed a severely calcified tricuspid aortic valve (Figure 1A), with a peak velocity of 2.9 m/sec over the aortic valve (valve area 0.6 cm²) in the presence of an impaired LV function (LVEF 30%) and grade 1 mitral regurgitation. On coronary angiography, one-vessel disease (stenosis in the proximal and mid segments of the right coronary artery) was seen.

First, the patient was discussed by the Heart Team before performing MSCT. A decision was taken first to perform PCI that did not affect the patient's symptoms. A decision was then taken to perform MSCT in preparation for TAVR. This confirmed the presence of a severely calcified aortic valve (Figure 1B) with an annulus area of 590 mm², perimeter of 88 mm and diameter of 27.4 mm. The diameter of both common femoral arteries was 8 mm, without significant calcification or tortuosity. However, there was a large fusiform infrarenal abdominal aortic aneurysm (AAA) with a diameter of 59 mm, a mural thrombus and dissection (Figure 2).

The patient was rejected for surgical aortic valve replacement (SAVR) because of age, risk (STS score 7.7) and the unexpected finding of the abdominal aneurysm on MSCT. Transfemoral TAVR was technically feasible but not preferred given the need for crossing the aneurysms with wires and catheters. A subclavian approach was considered but was not possible since the annulus required the implantation of a SAPIEN 3, 29 mm valve (Edwards Lifesciences, Irvine, CA, USA), the sheath size of which exceeded the diameter of the subclavian artery. A transapical TAVR was possible but not considered ideal given the impaired LV function. In addition, there was the aortic aneurysm with mural thrombus that would also determine the prognosis. What would the recommendation be for planning and executing an invasive treatment, including the anaesthesiologic management of this elderly but otherwise vital and independently living patient?

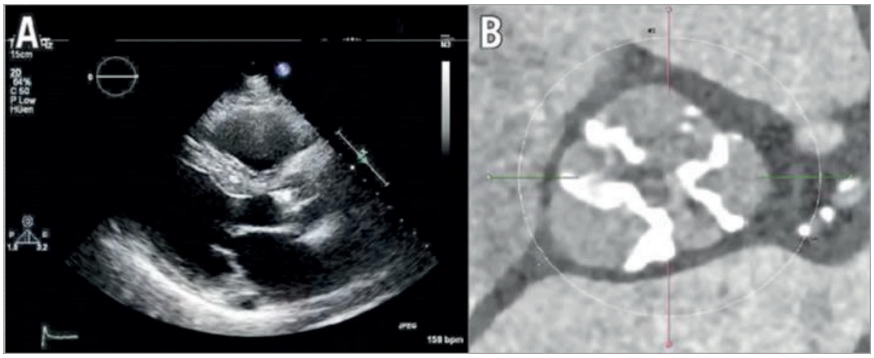

Figure 1. Imaging during work-up. A) Transthoracic echocardiography showing a severely calcified aortic valve. B) Severely calcified aortic valve on multislice computed tomography.

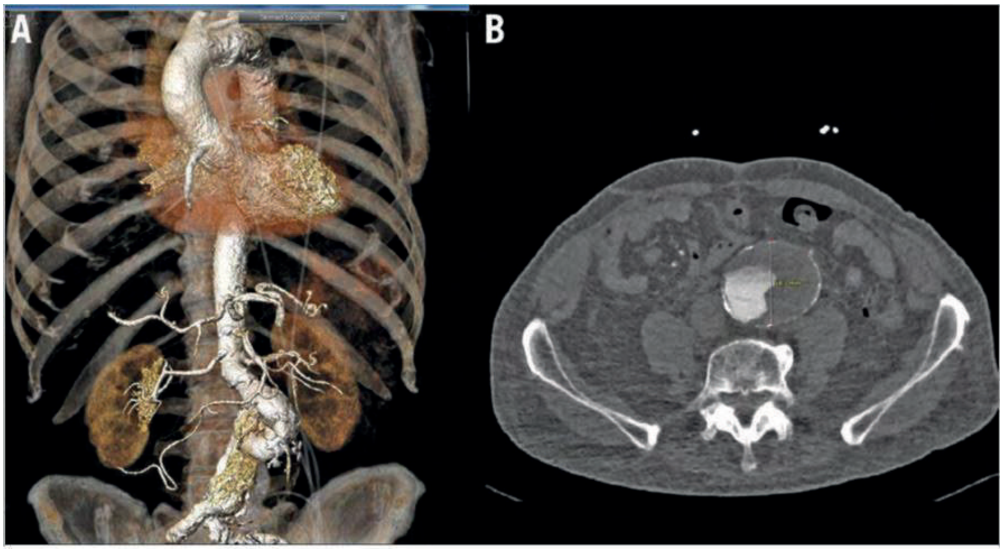

Figure 2. Imaging during work-up. A) A three-dimensional CT reconstruction of the fusiform infrarenal abdominal aortic aneurysm. B) Axial view of the fusiform abdominal aortic aneurysm.

How would I treat?

The invited experts' opinion

Mani Arsalan, MD; Won Kim, MD; Thomas Walther*, MD, PhD

The present case is challenging for several reasons: an 88-year-old patient with severe symptomatic aortic stenosis, a high procedural risk (STS score 7.7) and impaired left ventricular function (LVEF 30%) at first sight seems to be a straightforward TAVR candidate. However, in the presence of a low-flow low-gradient aortic stenosis (LFLG-AS) and an incidental abdominal aortic aneurysm (AAA), decision making becomes more complex. Co-existing one-vessel coronary artery disease is considered to be haemodynamically irrelevant, and other potential causes of the symptoms have been ruled out. Given the complexity and various possible strategies, we would discuss this case in the Heart Team with cardiologists, cardiac and vascular surgeons, and anaesthetists regarding the following issues:

1. LFLG-AS is quite common with almost 12% of all patients undergoing TAVR suffering from LFLG-AS and even more from paradoxical LFLG-AS [1]. In order to evaluate whether the patient has true severe AS and to assess left ventricular flow reserve, a low-dose dobutamine stress echocardiography is recommended [2,3]. In our opinion, the present patient's symptoms and clinical findings (including the MSCT) indicate a true AS. Consequently, the patient should benefit from AVR. Considering the patient's age and risk, TAVR is the procedure of choice.
2. Due to the large diameter of the AAA (59 mm) and according to guidelines, there is an indication for thoracic endovascular aortic repair (TEVAR) as well [4]. One might argue whether treatment of AAA should be performed prior to, simultaneously with or after TAVR. There are several reports of successful, simultaneous TAVR and TEVAR, but in this very aged patient a staged procedure may be favoured with respect to the patient's convalescence.
3. Regarding the TAVR access, the authors are sceptical about crossing the AAA with wires and catheters during transfemoral TAVR. However, in our opinion this should be feasible without significantly increased procedural

risk. Nevertheless, as we would opt for a staged procedure, we would favour transapical TAVR, thus minimising crossing of the AAA and performing TEVAR as a second step. The authors' concerns regarding transapical access in patients with reduced EF are quite common, but recent studies suggest that there is no impact of the apical approach on global LV function [5]. An alternative option would be transfemoral TAVR, which would have the advantage of the procedure being able to be performed without general anaesthesia and TEVAR being performed simultaneously in case of uneventful TAVR. Of note, patients with reduced LVEF tolerate new-onset aortic regurgitation (AR) quite badly, thus preoperative planning, including sizing and valve selection, as well as the procedure itself should be optimised to reduce paravalvular leaks.

4. The only remaining concern for this patient is the known unfavourable midterm outcome for patients with LFLG-AS undergoing TAVR. However, this specific vital and independently living patient with symptomatic AS needs treatment to retain his quality of life.

How would I treat?

Didier Tchétché, MD

The combination of a severe symptomatic aortic stenosis (AS) and a significant aneurysm of the abdominal aorta (AAA) is not rare in daily practice. Based on the patient's age and comorbidities, a percutaneous approach was logically selected by the local Heart Team. The patient's symptoms are mainly related to the aortic stenosis but TAVI cannot be performed alone. In my opinion, both AAA and AS must be treated during the same procedure. Indeed, given the large diameter of the AAA, any post-procedural increase in systolic blood pressure after TAVI could apply excessive strain within the aortic wall and potentialise the risk of rupture. However, we must anticipate several risks inherent to a combined approach: cholesterol embolisation, stroke and contrast-induced nephropathy. Among commercially available transfemoral TAVI devices, the Edwards SAPIEN 3 (S3) 29 mm is the only one suitable given the patient's aortic annulus diameter (27.4 mm). The Medtronic Evolut™ R (Medtronic, Dublin, Ireland) 34 mm, recently approved by the Food and Drug Administration in the USA, is not yet available in Europe. As the S3 must be relocated onto the carrier balloon within the abdominal aorta, the manoeuvre is likely to be performed within the aneurysm, increasing the risk of stroke or even aortic perforation. The S3 should therefore be protected, during its course across the abdominal aorta, by an external conduit. The anatomy of the AA appears suitable for a percutaneous procedure owing to the presence of a well-defined infrarenal collar and preserved integrity of the common iliac arteries. A large thrombus burden is easily identifiable on MSCT.

My strategy would be first to proceed with the placement of a Claret Sentinel™, cerebral protection device (Claret Medical, Santa Rosa, CA, USA) via the right radial artery, to limit the risk of stroke. Heparin should be provided beforehand aiming at an ACT above 250 sec. The second step would be to perform the endovascular treatment of the AAA. Finally, across the AAA endograft, a 16 Fr eSheath™ (Edwards Lifesciences) or a 22 Fr re-collapsible SoloPath™ sheath (Terumo Corp., Tokyo, Japan) could then be advanced easily and the transfemoral TAVI procedure carried out in a conventional way. If needed, at the end of the procedure, the AAA endograft collar and legs could be re-expanded using appropriate post-dilatation balloons. As an identified risk, contrast-induced nephropathy should be prevented by preprocedural proper hydration and keeping the contrast total volume below fourfold the creatinine clearance (232 ml) during the procedure [6].

Several reports have illustrated the feasibility and safety of a concomitant percutaneous treatment of AS and AAA. This could be the default strategy in such scenarios [7].

How did I treat?

Actual treatment and management of the case

This patient has a severe low-flow low-gradient aortic stenosis and a fusiform infrarenal AAA (59 mm) that determine the prognosis when left untreated. Given the patient's vital status and age, a decision was taken to treat them both in the same setting using a complete percutaneous approach, although a sequential treatment consisting of TAVI followed by (percutaneous or surgical) AAA correction was considered but rejected given the preference to offer a "one-stop shop" to minimise the number of hospitalisations.

In addition, sequential treatment exposes the patient to an increased risk of AAA rupture in case one would first treat the aortic stenosis due to the eventual increase in systolic blood pressure after TAVI, acknowledging that a fusiform aneurysm is less prone to rupture than a saccular aneurysm [8-10]. Vice versa, if one were first to correct the AAA, the patient would be exposed to a five-fold increase in perioperative mortality and non-fatal myocardial infarction [11].

In order also to minimise the length of stay, we chose local anaesthesia since this has been shown to be associated with shorter hospital stay [12]. Since 2006 we have had a default strategy of echographically guided vascular access during TAVI [13]. This technique was used for the infiltration of the region of the common femoral arteries using 2x20 ml of a combination of lidocaine 2 mg/kg and bupivacaine 1 mg/kg. A 16 Fr eSheath (Edwards Lifesciences) was then introduced into the right femoral artery and a 9 Fr sheath into the left femoral artery after the application of two Proglide® devices (Abbott Vascular, Santa Clara, CA, USA) at each site. An Edwards S3 29 mm was implanted under fluoroscopic guidance using rapid pacing at 180 bpm for 20 seconds. The valve was well deployed (Figure 3). There was minimal (grade 0-1) residual aortic regurgitation, and absence of a gradient and conduction disorders. Immediately after TAVI, the vascular surgeons implanted a Medtronic Endurant II endograft under fluoroscopic guidance (ETBF 2516C166EE right side and ETLW 1616C82EE and ETLW 1620C124EE left side). Angiography confirmed the correct position and deployment of the prosthesis just below the ostium of the renal arteries and no type 1a or 1b endoleak (Figure 4A). Complete haemostasis was achieved with the Proglide closure devices. Transthoracic echocardiography before discharge revealed a peak velocity of 1 m/sec (peak gradient 4 mmHg) and a grade 0-1 aortic regurgitation. CTA before discharge showed that the prosthesis was well positioned (Figure 4B); however, there was a type 2 endoleak with unchanged diameter of the aneurysm sac. The patient was discharged 10 days after the procedure.

Several reports have described similar cases in which simultaneous or sequenced transfemoral TAVI and EVAR were performed, but so far this is the only case report in which both procedures have been simultaneously performed under loco regional anaesthesia.

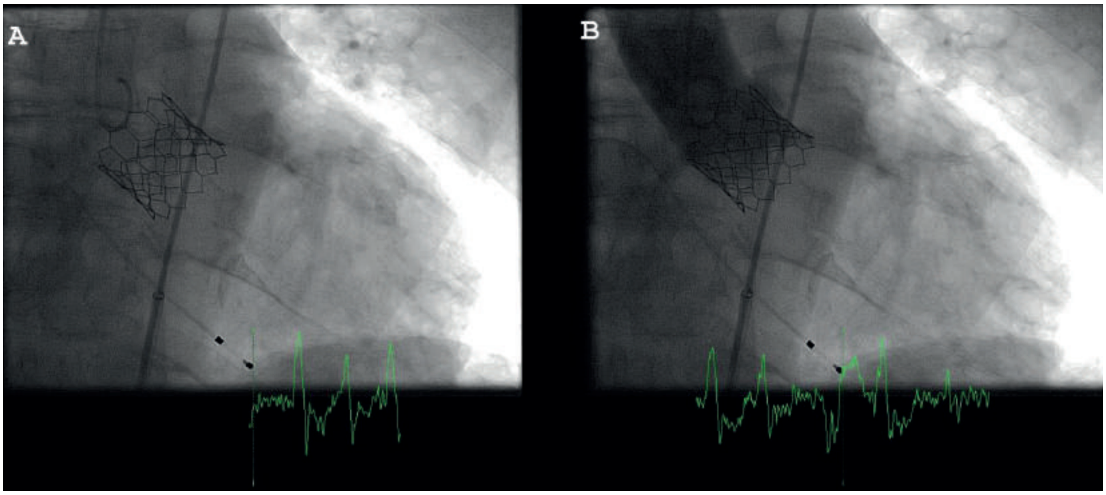

Figure 3. Intraprocedural imaging. Angiography without (A) and with (B) contrast immediately after implantation of an S3 29 mm valve.

Figure 4. Intraprocedural and post-procedural imaging. Abdominal angiography immediately after the implantation of the aortic prosthesis just below the origin of the renal arteries (A) and three-dimensional CT reconstruction post EVAR (B).

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CHAPTER 9 Mitral valve injury after MitraClip implantation

Zouhair Rahhab; Ben Ren; Frans Oei; Peter P.T. de Jaegere; Nicolas M. Van Mieghem

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A 68-year-old wheelchair-dependent female with diabetes and end-stage kidney failure presented with symptomatic severe functional mitral regurgitation (MR) (Figure 1A) and a left ventricular ejection fraction of 37%. The multidisciplinary heart team reached consensus for MitraClip (Abbott Vascular, Santa Clara, California, implantation because of high operative risk (Society of Thoracic Surgeons 8.5) and frailty.

The MitraClip procedure was performed under general anesthesia and 2-dimensional and 3-dimensional transesophageal echocardiography guidance. After multiple attempts of leaflet grasping and clipping along the mitral coaptation plane, 2 MitraClips were released at the level of A2-P2 and A1-P1. A third clip toward the posteromedial commissures was attempted because of persistent severe MR (Figure 1B to 1C) and markedly reduced the MR, albeit at the expense of an unacceptably high transmitral mean gradient up to 9 mm Hg. Intraprocedural transesophageal echocardiography revealed ruptured chordae and a perforation in the posterior leaflet (Figure 1D to 1F). The third clip was therefore not released and the patient was sent for high-risk mitral valve surgery. Perioperatively, the mitral valve seemed to be injured severely with partial clip dehiscence at the level of A2-P2, including a tear in the posterior mitral leaflet, several chordal ruptures, and leaflet damage at the level of P3 (Figure 1G to 1I). The mitral valve was replaced with a 29-mm St. Jude mechanoprothesis with excellent final results (no MR, no significant gradient).

This case report illustrates that leaflet grasping and clipping attempts during a MitraClip procedure may not be trivial and may significantly damage the mitral apparatus requiring surgical bailout. A multidisciplinary approach is essential in terms of MitraClip patient selection, procedure execution and problem solving.

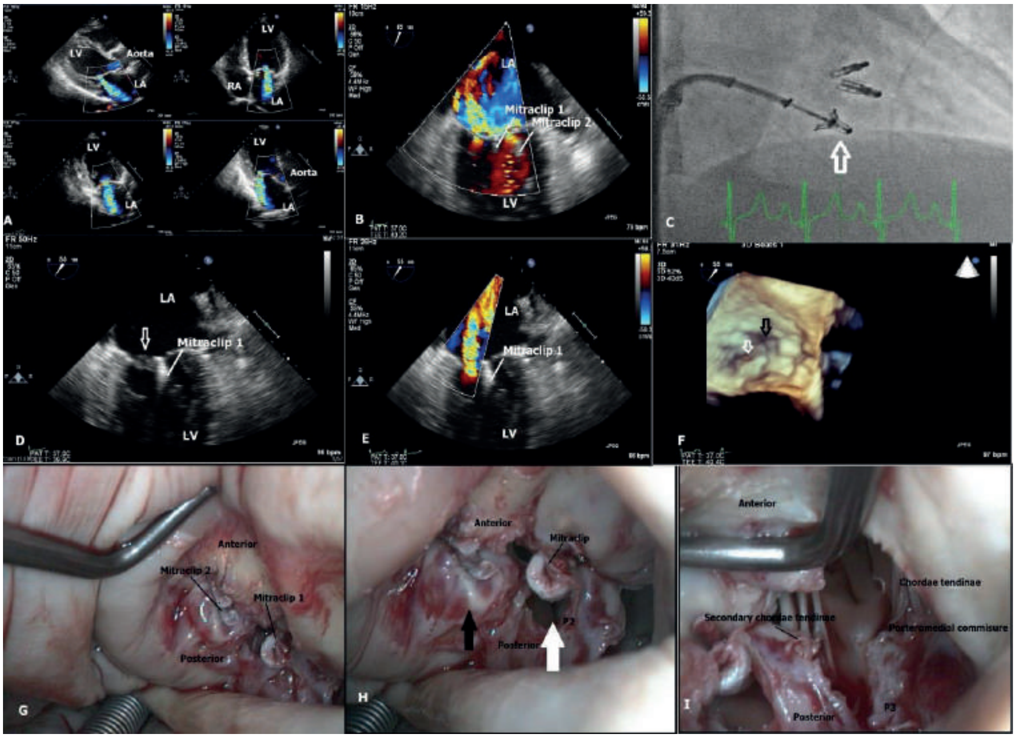


Figure 1 Baseline and Procedure

(A) Severe mitral regurgitation (MR) confirmed with different transthoracic echocardiographic views.
(B) Transesophageal echocardiography (TEE) showing severe MR after implantation of 2 MitraClips.
(C) Angiographic view of three MitraClips, MitraClip 3 (arrow) was attempted more medially.
(D) TEE reveals perforation of the posterior leaflet (arrow) medial to MitraClip 1 and (E) severe MR localized at the perforation site. (F) Three-dimensional view of ruptured chordae tendinae (white arrow) and perforation (black arrow).
(G) Surgical view of the mitral valve with (H) thickening of the posterior leaflet due to hematoma (black arrow) with a tear at the level of P2 (white arrow) and (I) laceration of P3 with ruptured secondary chordae tendinae. *LA= left atrium; LV= left ventricle; RA= right atrium.*

CHAPTER 10 Transcatheter Lotus Valve Implantation in a Stenotic Mitral Valve

Ben Ren; Zouhair Rahhab*; Jan von der Thüsen; Joost Daemen; Marcel L. Geleijnse; Peter P.T. de Jaegere; Arie Pieter Kappetein; Nicolas M. Van Mieghem*
**equally contributed*

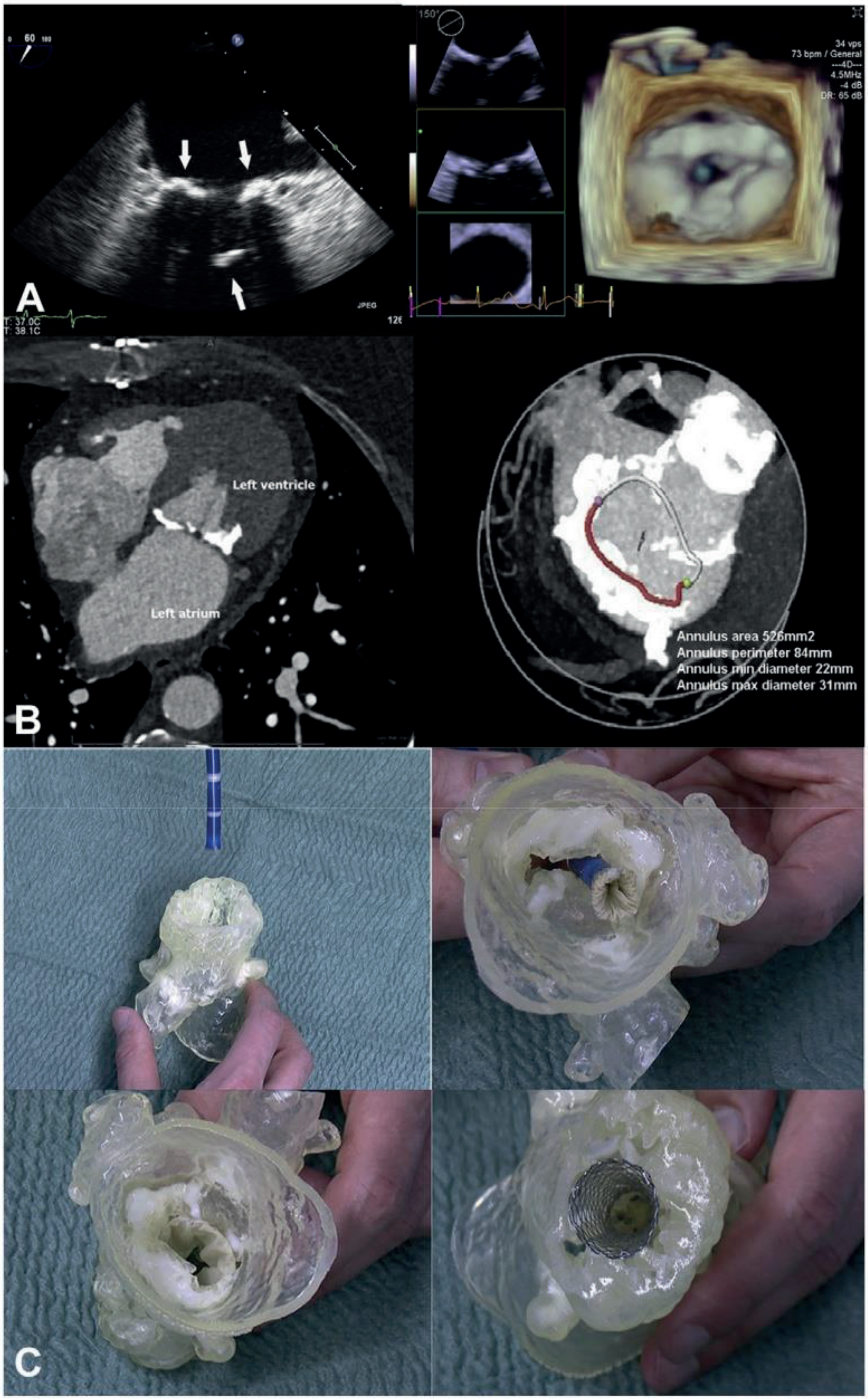
JACC Cardiovasc Interv. 2016 Nov 14;9(21):e215-e217.

A 75-year-old woman with degenerative mitral stenosis and a prior aortic bioprosthesis was referred for potential valvular intervention. She had been symptomatic (New York Heart Association functional classes III to IV), with a history of syncope, chronic obstructive pulmonary disease, latent tuberculosis, and thrombocytopenia. She was considered inoperable because of excessive comorbidities (Society of Thoracic Surgeons score 9.5%) by the heart team consensus.

Transthoracic echocardiography revealed a severely calcified mitral annulus with a transvalvular mean pressure gradient of 13 mmHg. Transesophageal echocardiography confirmed a heavily calcified mitral apparatus, including the chordae tendineae, with an immobile posterior leaflet (Figure 1A, Online Video 1). The mitral orifice area was 0.9 cm^2 by 3-dimensional planimetry. The Wilkins score was 10, ruling out safe percutaneous balloon mitral valvuloplasty [1]. Extensively calcified mitral annulus and leaflets were also seen on multi-slice computed tomography. The mitral annular area was 526 mm^2, and the perimeter was 84 mm, with a minimum diameter of 22 mm and a maximal diameter of 31 mm (Figure 1B). On the basis of the findings of multislice computed tomography, an in vitro valve implantation was conducted in a reconstructed 3-dimensional printed model (Figure 1C, Online Videos 2 and 3), which confirmed the suitability of transapical transcatheter mitral valve implantation with a 27-mm Lotus valve (Boston Scientific, Natick, Massachusetts).

The procedure was performed under general anesthesia, supported with fluoroscopy and transesophageal echocardiography. A cerebral embolic protection device was deployed in the brachiocephalic trunk and left common carotid artery prior to the valve implantation to collect potential debris released during the procedure (Figure 1D). A coronary guidewire in the left circumflex coronary artery served as a fluoroscopic landmark for Lotus valve positioning (Figure 1E). Through a left lateral minithoracotomy, the Lotus valve was smoothly delivered into the mitral annulus and gradually deployed (Online Video 4). After 1 position adjustment, the valve was released somewhat higher above the mitral annulus (Figure 1F) to avoid interference with the left ventricular outflow tract and aortic bioprosthesis. The transvalvular mean pressure gradient was 2 mmHg, with mild paravalvular leakage (Figure 1G). Debris was captured in the embolic protection device (Figure 1H) and consisted of platelet aggregates, endothelium, fragments of connective tissue, myxoid stroma, and myocardium (Figure 1I).

As previously reported, transcatheter mitral valve implantation in a native calcified mitral valve and degenerated bioprosthesis is feasible with balloon-expandable valves [2-3]. In our case, considering the sizing and repositionable and retrievable characteristics of the prosthesis, the mechanically expanded Lotus valve was chosen, also avoiding the fast pacing required in balloon-expandable valve implantation.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B
Left ventricle
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C

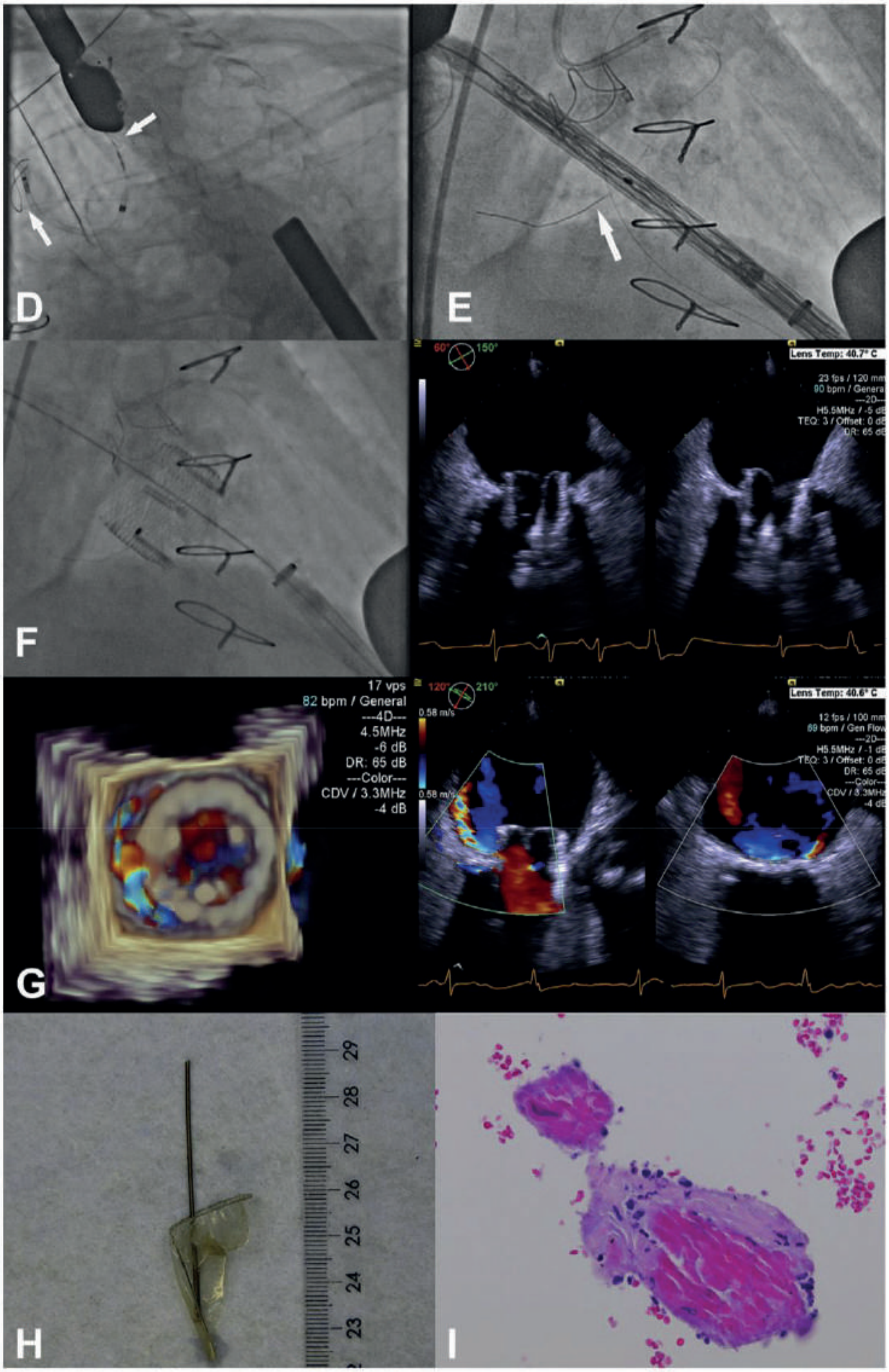
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Figure 1 Multi-Imaging modality in pre-procedural work up and intraprocedural monitoring and assessment

(A) 2-dimensional (2D) transesophageal echocardiography (TEE) showing a heavily calcified mitral apparatus, including the chordae tendineae (arrows point to the calcification) (left); 3-dimensional (3D) TEE showing calcified mitral annulus (MA) and leaflets, with a severely stenotic orifice opening in diastole (right). See Online Video 1. (B) Multislice computed tomography showing severely calcified MA (left) with its dimensions (right). (C) In vitro Lotus valve implantation in a reconstructed 3D printed model based on multislice computed tomographic measurements. See Online Videos 2 and 3. (D) A Sentinel cerebral embolic protection device was placed in the brachiocephalic artery (proximal) and left common carotid artery (distal) (arrows point to the filters implanted). (E) The circumflex coronary artery was visualized with a wire on fluoroscopy (arrow) and used as a landmark for valve positioning. (F) Final release of the Lotus valve shown on fluoroscopy (left); the valve was intentionally released a little higher than the mitral annulus, as shown with TEE (right) to avoid interference to the left ventricular outflow tract and aortic bioprosthesis. See Online Video 4. (G) 3D (left) and 2D (right) color TEE showing mild eccentric paravalvular leakage. (H) Cerebral embolic protection device after retrieval and (I) histopathologic coupe of fragments of myocardium captured.

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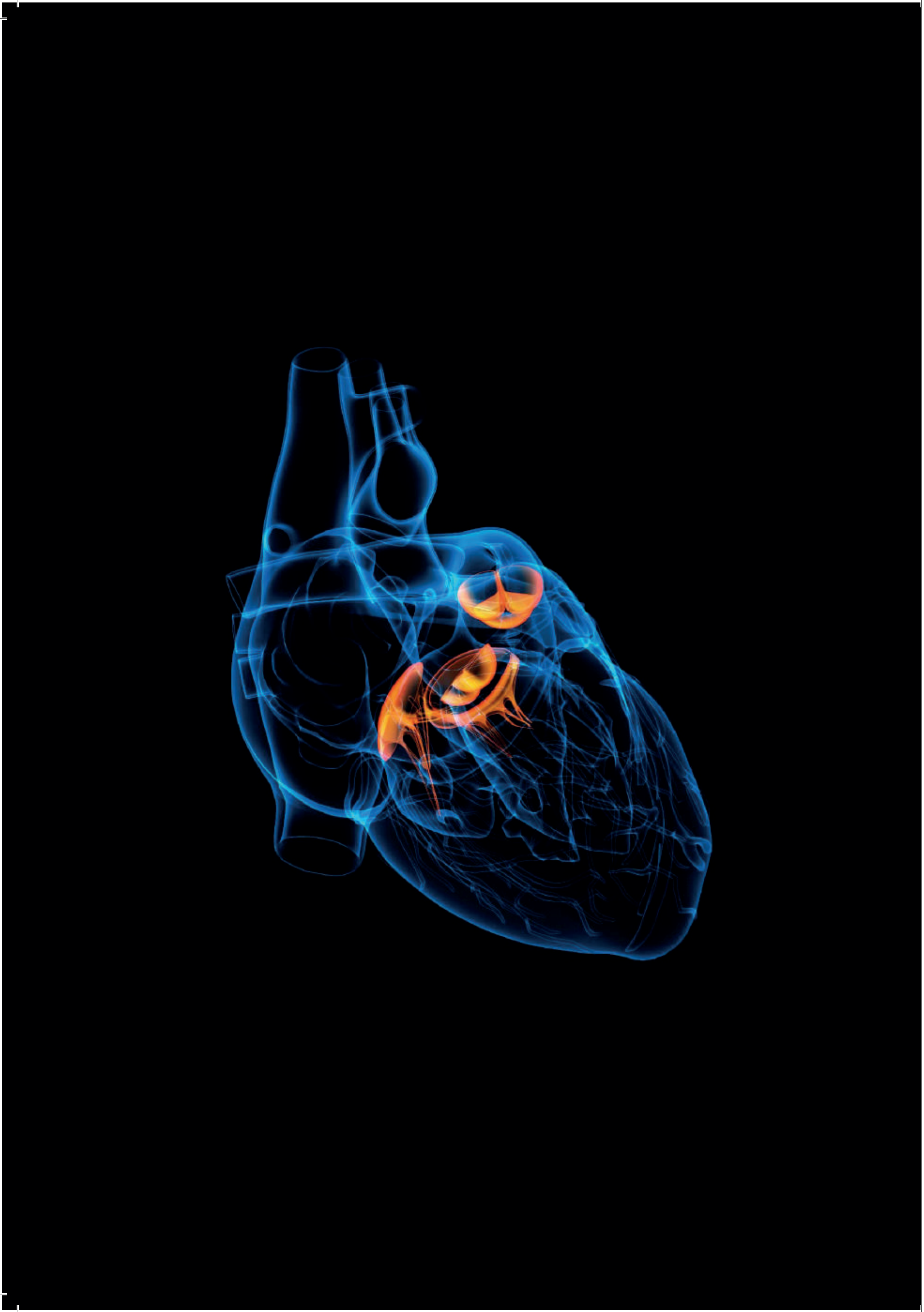


CHAPTER 11 Kissing balloon technique to secure the neo-left ventricular outflow tract in transcatheter mitral valve implantation

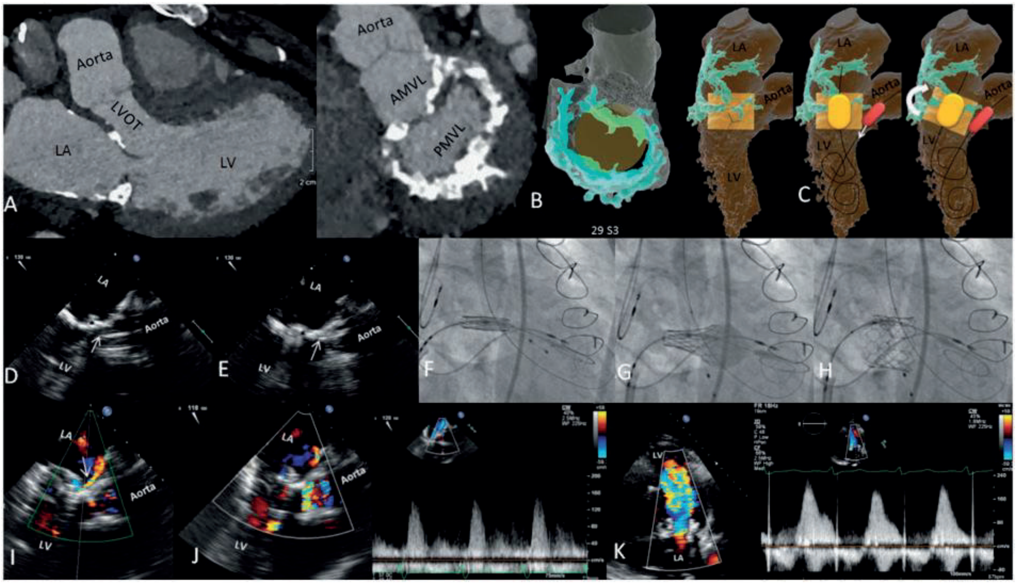
Zouhair Rahhab; Ben Ren; Peter P.T. de Jaegere; Nicolas M.D.A. Van Mieghem

Eur Heart J. 2018 Jun 14;39(23):2220.

A 51-year-old male with a past medical history of Hodgkin lymphoma treated with mantle-field radiation and two prior sternotomies for aortic valve disease was referred for transcatheter mitral valve implantation (TMVI) due to excessive mitral annular calcification and symptomatic severe mitral stenosis.

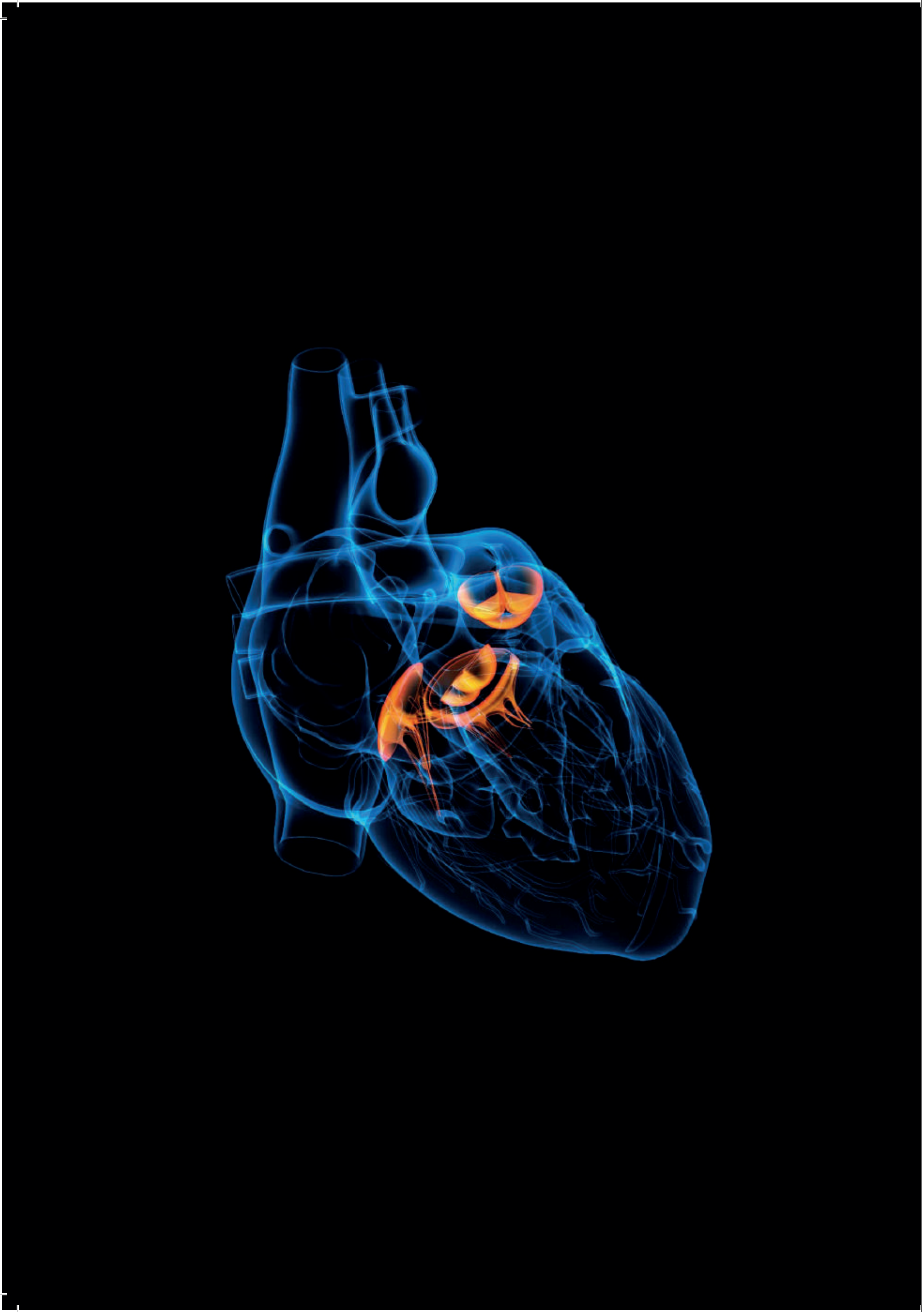
Based on 3D–4D multislice computed tomography reconstruction, 3D printing and multiple TMVI simulations predicted neo-left ventricular outflow tract (LVOT) obstruction. Under transoesophageal guidance a 20mm valvuloplasty balloon was positioned in the LVOT to locate the entrance of the LVOT by fluoroscopy. Kissing balloon technique was subsequently applied by simultaneous inflation of the 20mm valvuloplasty balloon and a 29mm SAPIEN3 valve (Edwards Lifesciences, Irvine, CA, USA). The rationale for the LVOT balloon inflation was to identify the landing zone and optimally orientate the transcatheter valve in order to secure a properly sized neo-LVOT.

This case illustrates that the kissing balloon technique may guide positioning of transcatheter heart valve and secure patent neo-LVOT in TMVI.



(Panel A) Excessive mitral annular calcification on computed tomography (Panel B) simulation of the implantation of a SAPIEN3 29mm valve predicting paravalvular leakage and LVOT obstruction. (Panel C) Concept of the kissing balloon technique; inflated balloon in the LVOT (red) while deploying the valve in mitral position (yellow) will prevent neo-LVOT obstruction by redirecting the valve. (Panels D–F) A 20mm valvuloplasty balloon identified the LVOT and guided positioning of SAPIEN3 29 valve; (Panel D) too deep positioning of the balloon
in the left ventricle (white arrow = the balloon; *anterior mitral valve leaflet) (Panel E) perfect positioning of the balloon in the LVOT (white arrow = tip of the balloon; *anterior mitral leaflet) (Panel F) guidance of the SAPIEN3 valve in mitral position (Panel G) implantation of the SAPIEN3 valve with inflated balloon in LVOT preventing neo-LVOT obstruction (kissing balloon technique). (Panel H–K) Successful valve implantation with (Panel I) trivial paravalvular leakage and (Panel J) without LVOT obstruction (LVOT outflow max velocity of 1.5m/s); (Panel K) pre-discharge transthoracic echocardiography colour Doppler showing mitral inflow and mild stenosis (peak V 1.8m/s; mean gradient of 5mmHg).

AMVL: anterior mitral valve leaflet; LA: left atrium; LV: left ventricle; PMVL: posterior mitral valve leaflet.



Samenvatting

Aortaklepstenose (vernauwing van de aortaklep) is een veel voorkomende hartklepaandoening. De prevalentie van deze aandoening neemt toe met de leeftijd. Voor lange tijd was chirurgische aortaklepvervanging (surgical aortic valve replacement - SAVR) ''de gouden standaard''. Echter, een belangrijke proportie van de patiënten (≥30%) werd afgewezen voor deze invasieve behandeling vanwege leeftijd, verminderde pompfunctie van het hart en comorbiditeit. Onbehandelde patiënten met een ernstige symptomatische aortaklepstenose hebben een overlijdensrisico van minstens 25% binnen het eerste jaar. Percutane aortaklep vervanging (Transcatheter Aortic Valve Implantation TAVI) is in eerste instantie ontwikkeld om de inoperabele en hoogrisico patiënten te behandelen. Bij een TAVI behandeling wordt een gekrompen hartklep via een sheath (een buis) door een slagader (meestal de liesslagader, soms de slagader in de hals, onder het sleutelbeen) of door de punt van het hart opgevoerd naar de verouderde en verkalkte aortaklep. De percutane hartklep wordt ontplooid, het frame zet uit en verankert zich in de originele verkalkte aortaklep. De originele aortaklep wordt weggedrukt en de percutane hartklep neemt de functie over. In de meerderheid van de gevallen wordt de procedure in het Erasmus Universitair Medisch Centrum tegenwoordig uitgevoerd onder lokale verdoving. Daarnaast is het niet nodig om het borstbeen te openen (thoracotomie) of om een hart-long machine te gebruiken. Hierdoor is TAVI minder invasief dan de conventionele chirurgische aortaklepvervanging (SAVR). Professor Alain Cribier voerde de eerste succesvolle TAVI uit bij een mens in 2002. Sindsdien zijn er meerdere studies in alle risicogroepen uitgevoerd, initieel bij patiënten met een inoperabel of hoog risico voor chirurgie en later ook bij patiënten met een zogenaamd intermediair of zelfs laag risico voor op overlijden rondom conventionele chirurgie. Deze gerandomiseerde studies rapporteerden goede klinische uitkomsten na TAVI die minstens in lijn liggen met wat kan verwacht worden bij traditionele aortaklep chirurgie. Als gevolg daarvan, hebben de Europese en Amerikaanse richtlijnen aanbevelingen geformuleerd voor TAVI bij alle oudere patiënten met een ernstige aortaklepstenose ongeacht het operatierisico.

Geavanceerde beeldvorming, toegenomen ervaring van de operateur en nieuwe catheter gebonden klepplatforms hebben geleid tot verbeterde procedure veiligheid en kleprestaties. Recentelijk zijn twee grote onderzoeken gepubliceerd waarbij patiënten met een ernstige aortaklepstenose en laag operatie risico gerandomiseerd werden naar TAVI of SAVR. TAVI was geassocieerd met minder complicaties, kortere opname duur, sneller herstel en minder heropnames. Tegelijk is de weg vrijgemaakt voor een nieuwe golf van indicaties:

Nieuwe generatie kleppen hebben de uitkomsten van TAVI in bicuspide aortaklep stenose (BAV; 2-slippige aortaklep) aanzienlijk verbeterd. Toch blijft een combinatie van een gecalcificeerde raphe en overmatige verkalking van de aortaklepblaadjes ongunstig voor TAVI en geassocieerd met meer complicaties en een slechtere uitkomst/2-jaars overleving.

TAVI wordt ook onderzocht bij asymptomatische patiënten met een ernstige aortaklep stenose. Deze patiënten hebben een jaarlijks risico op plotse hartdood van ≈ 1.5%. Ernstige aortaklepstenose verhoogt de nabelasting van de linker kamer (de druk waartegen het hart moet oppompen om het bloed in de slagader te krijgen) waardoor er compensatoir verdikking en verlittekening van de hartspier ontstaat. De hoeveelheid verlittekening van de hartspier is omgekeerd evenredig aan de mate van herstel van linker kamer functie na aortaklep vervanging en is geassocieerd met mortaliteit op de lange termijn. Bij patiënten met hartfalen is afterload reductie d.m.v. medicatie de hoeksteen van behandeling. De afterload van de linker hartkamer bestaat uit een arteriële en valvulaire component (aortaklepstenose). Het verrichten van een TAVI bij hartfalen patiënten met een matige aortaklepstenose naast de medicamenteuze behandeling, ontlast de linker hartkamer doordat zowel de arteriële als de valvulaire component van de afterload worden aangepakt waardoor dit in potentie gunstiger kan zijn voor de patiënt dan wanneer alleen de arteriële component wordt aangepakt.

Tenslotte wordt TAVI bij patiënten met ernstige aortaklep insufficiëntie onderzocht. Nieuwe generatie kleppen hebben de kans op complicaties verminderd. Het voornaamste probleem is dat patiënten met ernstige aortaklepinsufficiëntie weinig tot geen verkalking van de aortawortel hebben waardoor de klep zich niet adequaat kan verankeren. Hierdoor neemt het risico op kleploslating en paravalvulaire lekkage toe. Nieuwe klepsystemen zijn ontwikkeld op basis van clip fixatie mechanisme waarbij de percutane klep zich fixeert aan de natieve klepbladen in plaats van de annulus.

Ondanks deze veelbelovende resultaten is TAVI nog steeds geassocieerd met complicaties die invloed kunnen hebben op uitkomsten. Daarop zijn we verder ingegaan.

Complicaties

Paravalvulaire lekkage (PVL)

PVL (terugstroom van bloed rondom de percutane klep) wordt gezien als de Achilles hiel van TAVI. De terugstroom van bloed kan leiden tot volume overbelasting en resulteren in linker kamer dilatatie (verwijding) en uiteindelijk in hartfalen. Daarnaast kan het zorgen voor verminderde doorbloeding van de kransslagaderen van het hart en leiden tot zuurstoftekort (ischemie) van de hartspier. Verschillende studies hebben aangetoond dat ≥ matig PVL vaker voorkomt bij TAVI dan bij SAVR en dat ≥ matig PVL geassocieerd is met mortaliteit. Om het probleem van PVL aan te kunnen pakken is het belangrijk om de factoren die hier invloed op hebben te kennen. In hoofdstuk 1 en 2 worden deze factoren uitgebreid besproken en worden ze onderverdeeld in patiënt-, procedure en post-procedure gerelateerde factoren. In hoofdstuk 2 hebben we aangetoond dat de Medtronic CoreValve geassocieerd is met PVL. We weten van CT studies dat het frame van de Medtronic CoreValve klep - met name het inflow gedeelte- vaker elliptisch is terwijl het frame van de Edwards klep vaker circulair is. De Edwards klep beïnvloedt de vorm van de annulus terwijl de Medtronoic CoreValve zich probeert aan te passen aan de vorm van de annulus.

Door de komst van nieuwe generatie hartkleppen (met een sealing mechanisme en repositioneerbare eigenschappen) is het percentage van ≥matige PVL drastisch verminderd. In de PARTNER 3 studie werden lage risico patiënten met een symptomatische ernstige aortaklepstenose gerandomiseerd naar TAVI met de laatste generatie Sapien 3 klep of SAVR. Deze studie liet zien dat er geen verschil was in de prevalentie van ≥matige PVL tussen de twee groepen (TAVI of SAVR). Echter, meer patiënten in de TAVI groep hadden milde PVL. De impact van milde PVL op uitkomsten is momenteel een ‘’hot topic’’ en wordt volop bediscussieerd. Het is onduidelijk of ook milde PVL invloed heeft op mortaliteit.

Vasculaire complicaties (VCs)

TAVI is in vergelijking met SAVR geassocieerd met meer VCs. Dit komt omdat het klepsysteem bij TAVI in de meerderheid van de gevallen door een bloedvat wordt opgevoerd waardoor het vat beschadigd kan raken. TAVI geïnduceerde VCs zijn geassocieerd met mortaliteit, verlengde opnameduur, verminderde kwaliteit van leven en de noodzaak tot bloedtransfusies. Belangrijke risicofactoren zijn het vrouwelijke geslacht, ondergewicht, verkalking van de liesslagader en de ratio van sheath ten opzichte van de liesslagader. Het Valve Academic Research Consortium (VARC) document heeft uniforme definities geformuleerd om wereldwijd dezelfde definities aan te houden voor eenduidige rapportage. De incidentie van VCs wordt in de literatuur onderschat aangezien er in de meerderheid van de studies geen onafhankelijke rapportage is en er dus sprake kan zijn van “reporting bias” en onderrapportage. In hoofdstuk 3 hebben we een meta-analyse uitgevoerd waarbij we gekeken hebben naar (1) de incidentie van majeure VCs na transfemorale-TAVI (beoordeeld door een onafhankelijke commissie), en (2) naar het effect van nieuwe generatie kleppen met een kleiner klepsysteem en ervaring van de operateur op de incidentie van majeure VCs. We hebben aangetoond dat de incidentie van majeure VCs na transfemorale-TAVI 7.7% is en dat nieuwe generatie kleppen (met een kleiner klepsysteem) en operateur ervaring geassocieerd zijn met minder majeure VCs. De MASH (MANTA vs. Suture-based vascular closure after transcatHeter aortic valve replacement) studie heeft aangetoond dat er geen verschil is wat betreft access site gerelateerd VCs tussen verschillende soorten sluiting systemen (plug gebaseerd vs. hechting gebaseerd).

Myocard schade (hartspier schade)

Het exacte mechanisme van myocard schade (stijging van cardiale biomarkers in het bloed) na TAVI is nog onbekend en het effect op uitkomsten is controversieel. Enkele studies hebben aangetoond dat myocard schade geassocieerd is met mortaliteit en minder verbetering van de pompfunctie van het hart na TAVI. Een mogelijk mechanisme van myocard schade is zuurstof tekort van de hartspier als gevolg van aorta-insufficiëntie (lekkage van de aortaklep), ballon dilatatie, pacing geïnduceerd hypotensie (lage bloeddruk als gevolg van snel pacen), compressie van hartspierweefsel tijdens het ontplooien van de hartklep en embolisatie (verplaatsing) van kalk naar de kranslagaderen. In hoofdstuk 4 hebben we aangetoond dat 77%

van de transfemorale-TAVI patiënten myocard schade ontwikkelt en dat myocard schade niet geassocieerd is met 30-dagen mortaliteit. In een andere studie werd myocard necrose (afgestorven hartspierweefsel) alleen geobserveerd bij transapicale TAVI patiënten (behandeld via de punt van het hart) ondanks dat 96% van de transfemorale patiënten verhoogde biomarkers had. Een SAVR studie liet zien dat myocard fibrose (verlittekening van het hartspierweefsel) van ≥5% van de linker kamer massa geassocieerd is met mortaliteit. Daarnaast hebben we aangetoond dat klepmechanisme (de manier waarop de klep ontplooid wordt) geassocieerd is met myocard schade. Er werd minder myocard schade geobserveerd bij de mechanische ontplooide klep dan bij de ballon of zelf-expandeerbare klep. Een mogelijke verklaring is dat er meer hemodynamische stabiliteit is bij het ontplooien van de mechanische expandeerbare klep omdat de klep vroeg functioneert (na 1/3 ontplooiing) en er geen noodzaak is voor rapid pacing. Echter, de mechanische ontplooide klep was geassocieerd met onder andere problemen met de hartgeleiding en is ondertussen van de markt verdwenen.

Mitralisklep insufficientie en transcatheter edge to edge repair

Mitralisklep regurgitatie of insufficientie (MR) (lekkende mitralisklep) heeft een prevalentie van 2% in de algemene bevolking en komt vaker voor bij de ouderen. De etiologie van MR kan worden ingedeeld in primaire/degeneratieve MR en secundaire/functionele MR. Bij primaire MR is de klep zelf beschadigd terwijl secundaire MR het gevolg is van geometrische verstoring/verandering van de omliggende structuren (bijv. verwijding van de linker boezem of kamer).

Mitralisklepchirurgie is de ‘’gouden standaard’’ voor de behandeling van symptomatische patiënten met ernstige MR. Echter, een aanzienlijke deel van de patiënten wordt afgewezen voor chirurgie vanwege leeftijd, verminderde pompfunctie van het hart en comorbiditeit. Voor deze patiënten is percutane behandeling met MitraClip ontwikkeld. In de Europese richtlijnen van 2021 en de Amerikaanse richtlijnen van 2020 is er respectievelijk een IIb en een IIa indicatie voor de behandeling van primaire MR en een IIa indicatie (zowel de Europese als de Amerikaanse richtlijn) voor de behandeling van secundaire MR middels MitraClip.
De COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) studie heeft

aangetoond dat patiënten met secundaire MR die behandeld worden met MitraClip naast optimale medicamenteuze therapie het beter doen (wat betreft 2-jaars overleving en hartfalen hospitalisatie) dan patiënten die alleen optimaal medicamenteus behandeld worden. Patiënten selectie, optimale medicamenteuze hartfalen therapie en bekwame operateurs zijn belangrijke factoren voor een succesvolle MitraClip behandeling.

In hoofdstuk 6 rapporteren we de Nederlandse MitraClip ervaring met betrekking tot de veiligheid, uitvoerbaarheid en effectiviteit. De MitraClip ervaring in Nederland neemt toe, de device en technische succes percentages zijn uitstekend (respectievelijk 91% en 95%) en de intra-procedurele mortaliteit is laag (0.3%). In de loop der jaren zijn we meer patiënten gaan behandelen met ≥2 Clips en is de procedure tijd afgenomen. Betere registratie van dergelijke klepinterventies op nationaal vlak (zoals georganiseerd binnen de Nederlandse Hart Registratie – NHR) kan nog meer inzicht geven in de resultaten op korte en langere termijn.

MitraClip kan ook gebruikt worden voor de behandeling van patiënten met terugkerend MR na chirurgische mitralisklepherstel. In hoofdstuk 7 hebben we aangetoond dat MitraClip in dit scenario een veilige behandeloptie is met een hoge kans op succes en een lage mortaliteit van 2%. Als gevolg van de chirurgische ring kan er sprake zijn van schaduwvorming waardoor het in beeld brengen van het achterste mitralisklepblad een uitdaging is. Door gebruik te maken van additionele of aangepaste beeldvorming kan deze uitdaging overwonnen worden.

Creatieve oplossingen voor complexe interventies

Interventies voor structurele hartziekten kunnen soms improvisatie en ‘’out-of the box’’ thinking vereisen. In hoofdstuk 8 presenteren we een uitdagende casus van een 88-jarige man met een ernstige aortaklepstenose en als toevalsbevinding een abdominale aorta aneurysma. Beide aandoeningen werden volledig percutaan in één en dezelfde sessie behandeld. De casus illustreert hoe atherosclerose en perifeer vaatlijden dikwijls samen voorkomen en ook behandeling vereisen.
In hoofdstuk 9 hebben we aangetoond dat meerdere clip pogingen met de MitraClip kan leiden tot beschadiging van het mitraalklep apparaat waarbij chirurgie nodig kan zijn.

In hoofdstuk 10 en 11 hebben we een percutane mitralisklep vervanging (TMVR) verricht bij patiënten met ernstige verkalking van de mitraal annulus. Een belangrijke en potentieel levensbedreigende complicatie van TMVR is obstructie van de linker ventrikel uitstroombaan (LVOT). Nauwkeurige pre-procedurele planning door middel van 3D-CT en 3D printing kan helpen bij de voorspelling van LVOT obstructie. In hoofdstuk 10 hebben we een volledig repositioneerbare klep (Lotus) gebruikt waardoor de operateur in staat was om de diepte van implantatie aan te passen/corrigeren om zo min mogelijk interactie te hebben met de LVOT. In hoofdstuk 11 hebben we ‘’de kissing balloon’’ techniek toegepast waarbij een ballon in de uitstroombaan van de linker kamer simultaan wordt opgeblazen met de ballon die de bioprothese ontplooit. Hierdoor kantelt de klep weg van de LVOT en wordt de neo-LVOT veiliggesteld.

Conclusie

Catheter gebonden klepbehandelingen zijn in volle ontwikkeling en worden bij steeds meer indicaties toegepast. Europese richtlijnen positioneren catheter gebonden aortaklep implantatie als een valabel alternatief voor chirurgische aortaklepvervanging bij oudere patiënten met aortaklepstenose. Nieuwe indicaties worden bestudeerd. Traditionele verwikkelingen rondom catheter gebonden aortaklepvervanging zijn goed bestudeerd en lijken in meer of mindere mate opgelost. De mitraalklep is een meer complexe anatomische structuur en vraagt meer planning en creativiteit. Catheter gebonden clipping van de mitraalklepblaadjes is nu een erkende behandeling voor functionele en degeneratieve mitraalklepinsufficientie. Verdere technologische ontwikkelingen zijn nodig om behandelopties voor mitraalkleplijden verder uit te breiden.

Discussion

Expanding TAVI indications

TAVI is an established treatment option for symptomatic patients with severe aortic stenosis at increased operative risk [1, 2]. Comprehensive three-dimensional computed tomography planning, multi-disciplinary patient selection, growing operator experience and the introduction of refined transcatheter valve platforms improved procedural safety and bioprosthetic valve performance. TAVI has matured into a lean procedure and is currently being explored in a wide range of indications.

The shift to lower risk patients may apply to younger patients with a longer life expectancy. Valve durability becomes a matter of concern since long-term data is lacking. Preserved valve function up to 5-years after TAVI has been shown in the early RCTs [3, 4]. However, it is known from surgical bioprosthetic valves that structural valve deterioration only starts to occur beyond 5-10 years post-procedure [5, 6]. The low-risk studies (i.e. PARTNER 3 and Medtronic low-risk) will have a 10-year follow-up and will give us more insights in valve durability [7, 8].

The outcome of TAVI in patients with a bicuspid aortic valve (BAV) has significantly been improved by the introduction of new generation transcatheter heart valves (THVs) [9, 10]. Still, particular BAV phenotypes including the presence of a calcified raphe in combination with excess leaflet calcification is associated with an increased risk of procedural complications and mortality [11].

TAVI is now also under investigation in asymptomatic patients with severe aortic stenosis who have a 1.5% annual risk of sudden death and in patients with depressed LV function and moderate AS. Indeed, earlier valve replacement may prevent myocardial fibrosis and may also unload the LV by reducing the global LV afterload. As such TAVI for moderate AS may complement established pharmacological treatment with neurohormonal antagonists to reduce afterload in heart failure. Finally, TAVI is being explored in symptomatic patients with severe native aortic regurgitation. The improved features of new generation THVs significantly reduced the complication rate [12]. The main problem of treating native aortic regurgitation with TAVI is the absence/insufficient annular calcification which may hamper adequate anchoring of THV. New THV designs have been proposed that rely on a clip fixation mechanism which anchors the THV on the native aortic valve leaflets rather than in the annulus.

Despite the maturation of TAVI and the improved procedural safety, TAVI is still associated with several complications:

Paravalvular leakage (PVL)

Moderate or severe PVL is more frequently seen after TAVI than SAVR and is associated with mortality [4, 13]. In chapter 1 we have extensively discussed the patient-specific, procedural and post-procedural determinants of PVL. In chapter 2 we have shown by a propensity score adjusted multivariable analyses that the self-expanding Medtronic CoreValve (MCS) is associated with more PVL than the balloon expandable Edwards Sapien valve (ESV), (odd: 6.047 [95%CI; 1.307 – 27.976]. The higher incidence of PVL after MCS implantation can be explained by the findings of CT revealing that the MCS valve – especially at the inflow or ventricular end – is more often elliptical while the ESV is more often circular [14-16]. The MCS conforms to the geometry of the patient's annulus while ESV dictates the geometry of the annulus. Asymmetrical expansion of the MCS may contribute to PVL [15, 17].

The rate of ≥ moderate PVL has been dramatically reduced by new generation THV (with repositionable/retrievable features and sealing fabric) and growing operator experience [7, 8]. In the PARTNER 3 study symptomatic patients with severe aortic stenosis at low-operative risk were randomly assigned to transfemoral-TAVI with the latest generation balloon-expandable valve (Sapien 3) or SAVR [7]. There was no significant difference in the rate of ≥moderate PVL between TAVI vs. SAVR (respectively 0.8% vs. 0% at 30-days; 0.6% vs. 0.5% at 1 year) [7]. However, the rate of mild PVL was significantly higher with TAVI at 30-days and 1-year (respectively 8.7% vs. 2.9%; 29.4% vs. 2.1%) [7]. The impact of mild PVL on outcome is currently a hot topic and is still under debate.

Vascular complications

TAVI requires a large bore arteriotomy to accommodate the delivery system, which make it prone to vascular access site complications (VCs) [18, 19]. TAVI-induced VCs are correlated with mortality, increased length of stay, reduced quality of life and need for blood transfusion [18, 20, 21]. The ‘’true’’ incidence of major VCs in the literature may be underreported due to self-reporting bias and the absence of an independent clinical event committee (CEC) in the majority of studies. In chapter 3 we performed a meta-analysis to assess the incidence of major VCs after transfemoral-TAVI, adjudicated by an independent CEC, and we have shown that the major VC rate is ≈ 7.7%. This study may serve as a benchmark for other centres and trials. Furthermore, we have shown that THV devices with smaller profiles came with a lower incidence of major VCs and that operator experience is associated with fewer major VCs. The latter is in line with previous reported studies [22, 23]. The Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC Plus) study showed a significant reduction of major VC over time (15% vs. 7.9%, p = 0.023) and showed that almost 2/3 (64%) of the VCs were related to closure device failure (suture-based) [24]. New closure devices (e.g. collagen based) might reduce the rate of major VCs. Interestingly, the recently published MASH-TAVI (Manta™ Versus Suture-based Closure After Transcatheter Aortic Valve implantion) trial randomized 210 TAVI patients to either MANTA (collagen-based) closure device or 2 ProGlides (suture-based) and showed that collagen-based closure was not superior to suture-based closure in terms of access site-related VC (10% vs 4%; p=0.57) [25].

Myocardial injury

The exact pathomechanism of myocardial injury (i.e. cardiac biomarker riske) after TAVI is unclear and the effect on outcome is controversial. Several studies showed that myocardial injury is associated with mortality and less LVEF improvement after TAVI [26-28]. In our study (Chapter 4), the occurrence of myocardial injury after transfemoral-TAVI was 77% and was not associated with 30-day mortality. In a cardiac magnetic resonance study, new myocardial necrosis was only observed in transapical TAVI procedures despite increased cardiac Tropinine T in 96% of the transfemoral TAVI cohort [29]. In a SAVR study, myocardial fibrosis extending to ≥5%

of the LV mass was associated with increased mortality [30]. It seems that myocardial necrosis/fibrosis rather than increased cardiac troponin levels is associated with mortality. Furthermore, we have shown that prosthesis expansion mechanism is an independent predictor for myocardial injury. There was less myocardial injury after the use of the mechanically expanded (MEV) Lotus valve than with the other valve mechanisms which hypothetically might be explained due to more hemodynamic stability during the implantation of a MEV since there is early valve function and no need for rapid pacing. However, MEV was associated with new left bundle branch block and permanent pacemaker implantation. One can only speculate on how the finding of less myocardial injury would compare to the higher incidence of new conduction disorders in terms of long-term survival. Of note the mechanically expanding transcatheter valve system is withdrawn from the market. Further studies should shed further light on the significance of myocardial injury after TAVI and its relationship with long term clinical outcome.

Percutaneous mitral valve edge-to-edge repair with MitraClip in native MR

Based on the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) study, the most recent American guidelines for valvular heart disease have formulated a IIa recommendation for selected patients with severe functional MR (i.e. symptomatic despite optimal medical therapy, LVEF 20-50%, LVESD ≤ 70mm and an SPAP ≤70 mmHg) (31, 32). For symptomatic patients with severe primary MR with a high or prohibitive surgical risk there is a IIa (American guidelines 2020) and a IIb (European guidelines 2021) recommendation [1, 31, 33].

In chapter 6 we report the Dutch MitraClip experience from its inception in 2009 until 2016. A total of 1151 consecutive MitraClip patients were included. The majority (72%) of patients had functional MR. Device and technical success were respectively 91% and 95%. Significant MR reduction (reduction of MR ≥1 grade from baseline) was achieved in 94%. Intra-procedural death and conversion to emergent surgery occurred in respectively 0.3% and 0.5%. Over the years device time decreased and more patients were treated with ≥2 Clips. We have shown that MitraClip is a safe and effective procedure. However, our data is limited to procedural outcome. In order to evaluate the durability of device success, clinical outcome and echocardiographic follow-up data is needed. Furthermore, it is important to have more national data (e.g. NHR Nederlandse Hart Registratie) in order to evaluate/assess the importance of this therapy.

MitraClip after surgical mitral valve repair

Reoperation after failed surgical mitral valve repair (SMVR) can be technically challenging and is associated with increased risk of mortality and morbidity (such as prolonged ventilation, renal failure stroke and increased length of stay) compared to a first mitral valve surgery [34]. In analogy with TAVI after failed surgical aortic bioprothesis, there is a need for catheter based interventions after failed SMVR. In chapter 7 we report the largest series of patients treated with MitraClip after failed SMVR. We have shown that (1) MitraClip is feasible and safe after failed SMVR in selected patients with technical and device success rates of respectively 90% and 89% (2) the median time between SMVR and MitraClip was 5.3 years and (3) additional/modified imaging techniques (i.e. transgastric view, TEE with modified angles and intra-cardiac echocardiography) may facilitate leaflet grasping and shorten device time by dealing with technical challenges caused by shadowing from the annuloplasty ring.

Creative solutions to complex interventions

Catheter based strategies often require improvisation and ‘’out-of-the box’’ thinking. In chapter 8 we describe an interesting case of a patient with a severe low-flow low-gradient aortic stenosis and an unexpected finding of an abdominal aortic aneurysm. In order to minimise the number of hospitalisations the patient was offered a ‘’ one-stop shop’’ treatment. Both conditions were treated in the same setting using a complete percutaneous approach.

In chapter 9 we have shown that leaflet grasping and clipping attempts during a MitraClip procedure may not be trivial and may significantly damage the mitral apparatus requiring surgical bailout.

In chapter 10 and 11 we performed transcatheter mitral valve replacement (TMVR) in patients with severe mitral annular calcification (MAC). TMVR is an emerging treatment option for inoperable or high-risk patients with severe mitral valve disease.

A potential and fatal complication is left ventricular outflow tact (LVOT)-obstruction [35]. In severe MAC, the calcification can be extended in the LVOT and LV muscles which may result in a smaller LVOT and increase the risk of LVOT-obstruction. The length of the anterior leaflet has also been identified as a risk factor [36, 37]. Other risk factors are aorto-mitral angle <120˚ and low implantation depth [36]. Meticulous pre-procedural planning including 3D-CT and 3D printing can help predict LVOT-obstruction [38, 39]. Yoon et al. and Wang et al. showed that an estimated neo-LVOT area of respectively ≤ 1.7cm^2 and ≤ 1.9cm^2 is associated with LVOT-obstruction [38, 40].

In chapter 10, we used a fully repositionable and retrievable THV in order to adjust the depth of implantation and avoid interference with the LVOT. In chapter 11, we applied the kissing balloon technique (simultaneous inflation of the valvuloplasty balloon and a Sapien 3 valve) to guide positioning of the THV and secure the neo-LVOT. Other percutaneous techniques to reduce the risk of LVOT-obstruction are alcohol septal ablation (ASA) and a technically complex leaflet laceration method [41, 42].

Conclusion

Catheter based left-sided heart valve interventions are in progress and are currently being explored in a wide range of indications. Contemporary European guidelines position TAVI as a valuable alternative to surgery for elderly patients with symptomatic severe aortic stenosis. New indications are focus of ongoing research. Traditional complications related to TAVI have been well studied and seem to be at least partially resolved. The mitral valve is a more complex structure that demands more planning and creativity. Transcatheter edge-to-edge repair has become an established treatment for functional and degenerative mitral regurgitation. Continued device iterations and technological innovations are required to expand catheter based solutions for mitral valve disease.

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PhD Portfolio

Research activities	Year	Workload (ECTS)
Courses		
Good Clinical Practice	2016	0.30
Online course data management	2016	0.30
Erasmus MC - ESP09 Regression Analysis	2016	1.40
Cath conference “Introductie regional cathlabsysteem	2016	0.30
Cath conference “De rol van FFR post stenting	2016	0.30
Cath conference “Outcome improvement in modern generation DES: lessons learned from P-SEARCH event adjudication	2016	0.30
Cath conference “Hemodynamics part I: understanding the pressure-volume loop”	2016	0.30
Cath conference “Thoraxchirurgie anno 2017, nieuwe inzichten	2017	0.30
COEUR COURSE Imaging and symposium	2017	0.50
COEUR Course Congenital Heart Disease	2017	0.50
Erasmus MC - EWP24 Survival Analysis for Clinicians	2017	1.40
COEUR Course Intensive Care Research Part I	2017	0.50
Cath conference “FFR and CFR: similarities, differences, and when to prefer each”	2017	0.30
Erasmus MC - BROK® (Basic course Rules and Organisation for Clinical researchers)	2017	1.50
Erasmus MC - CC02A Biostatistical Methods I: Basic Principles Part A	2017	2.00
COEUR Course Cardiovascular Imaging and Diagnostics Part II: Clinical non-invasive Cardiac Imaging	2017	0.50
Cath conference “PCSK9 inhibitors”	2017	0.30
EuroPCR conference and two poster presentations (2017)		1.80
Cath conference “De Thoraxcentrum CTO experience”	2017	0.30

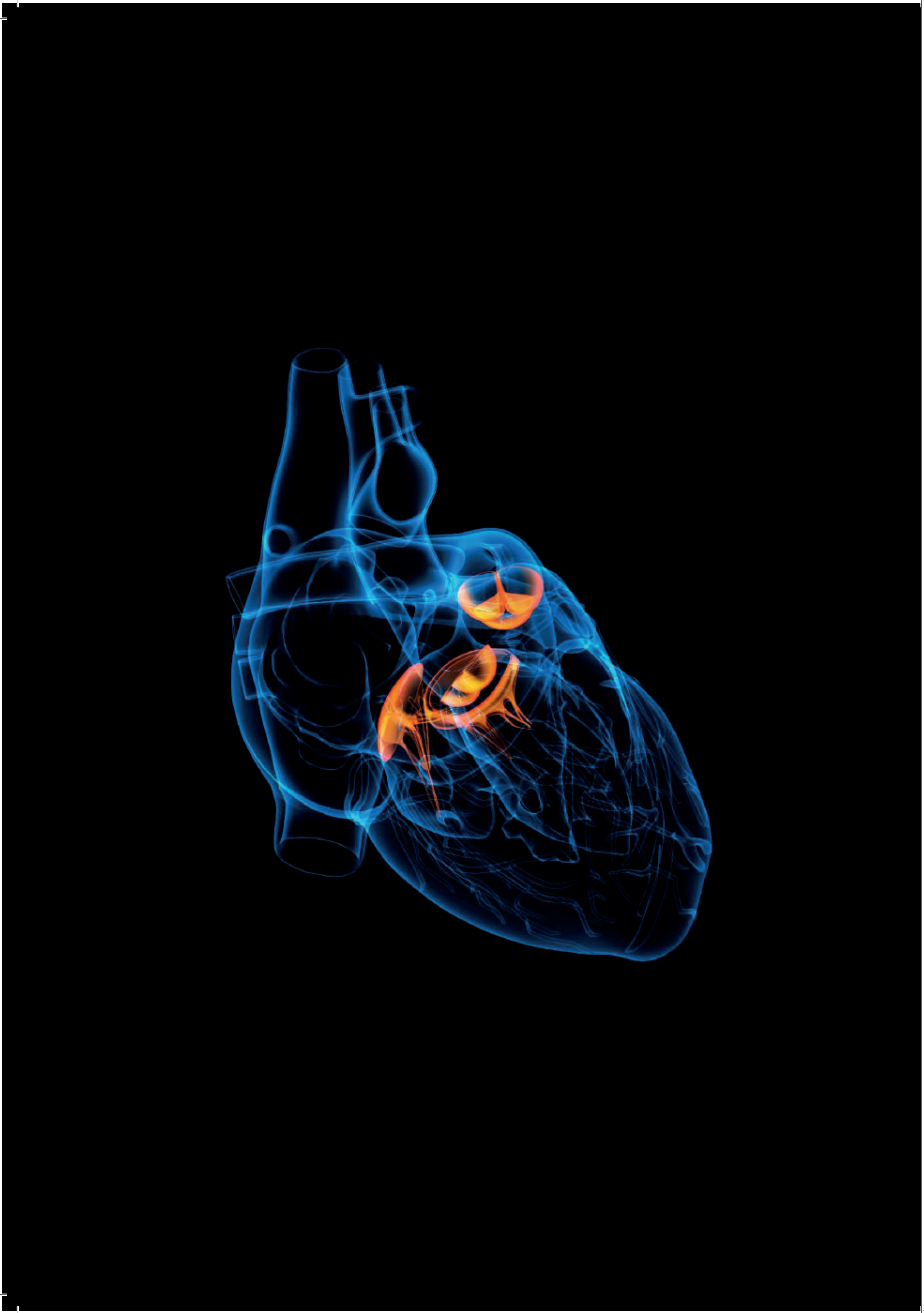
COEUR Course Cardiovascular Imaging and Diagnostics Part III	2017	0.50
Cath conference “Update congenitale interventies”	2017	0.30
Cath conference “Role of early angiography in survivors of OHCA”	2017	0.30
TCT conference and poster presentation (2017)		1.80
Online course “10 tips for writing a truly terrible journal article”	2017	0.30
COEUR Course Pathophysiology of IHD	2018	0.50
TEACH Course	2018	0.30
Erasmus MC (Graduate school) - Scientific Integrity	2022	0.30

Conferences and symposia

London Valves course and oral presentation	2016	1.50
TCT course and poster presentation	2016	1.80
NVVC najaarscongres and oral presentation	2016	0.90
Symposium New innovations in Cardiology	2016	0.30
Symposium ” Discoveries in Atrial Fibrillation Pathophysiology: Implications for AF Therapy ”	2017	0.40
JIM conference and poster presentation	2017	1.20
ESC conference and poster presentation	2017	1.80
London valves conference and oral presentation	2017	1.20
JIM conference (live) case presentation	2018	0.30
28th International Conference on Cardiology and Healthcare	2018	0.90

Teaching activities

Mentor of Junior Medschool	2016	0.70
Teaching cathlab nurses	2017	0.60
Teaching cathlab nurses	2017	0.60
Journal Club	2018	0.30
Journal Club	2019	0.30
Journal Club	2019	0.30
		------ +
Total EC		**30.50**



List of publications

First author

1. Rahhab Z, Ren B, Oei F, de Jaegere PP, Van Mieghem NM. Mitral Valve Injury After MitraClip Implantation. JACC Cardiovasc Interv. 2016 Sep 26;9(18):e185-6.

2. Ren B*, Rahhab Z*, von der Thüsen J, Daemen J, Geleijnse ML, de Jaegere PP, Kappetein AP, Van Mieghem NM. Transcatheter Lotus Valve Implantation in a Stenotic Mitral Valve. JACC Cardiovasc Interv. 2016 Nov 14;9(21):e215-e217. * Equally contributed

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7. Rahhab Z, Van Mieghem N. Textbook of catheter-based cardiovascular interventions; Cerebral Embolic Protection devices during TAVI. Book chapter 100 pages 1739 -1750. 2018 Jan.

8. Rahhab Z, Ren B, de Jaegere PPT, Van Mieghem NMDA. Kissing balloon technique to secure the neo-left ventricular outflow tract in transcatheter mitral valve implantation. Eur Heart J. 2018 Jun 14;39(23):2220

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Second author

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14. Rodríguez-Olivares R, Rahhab Z, Faquir NE, Ren B, Geleijnse M, Bruining N, van Mieghem NM, Schultz C, Lauritsch G, de Jaegere PP. Differences in Frame Geometry Between Balloon-expandable and Self-expanding Transcatheter Heart Valves and Association With Aortic Regurgitation. Rev Esp Cardiol (Engl Ed). 2016 Apr; 69(4):392-400.

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Third author

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for thepredicton of valve morphology and calcium displacement after TAVI with the Medtronic CoreValve and the Edwards SAPIEN valve. EuroIntervention. 2016 Jan 22;11(9):1044-52.

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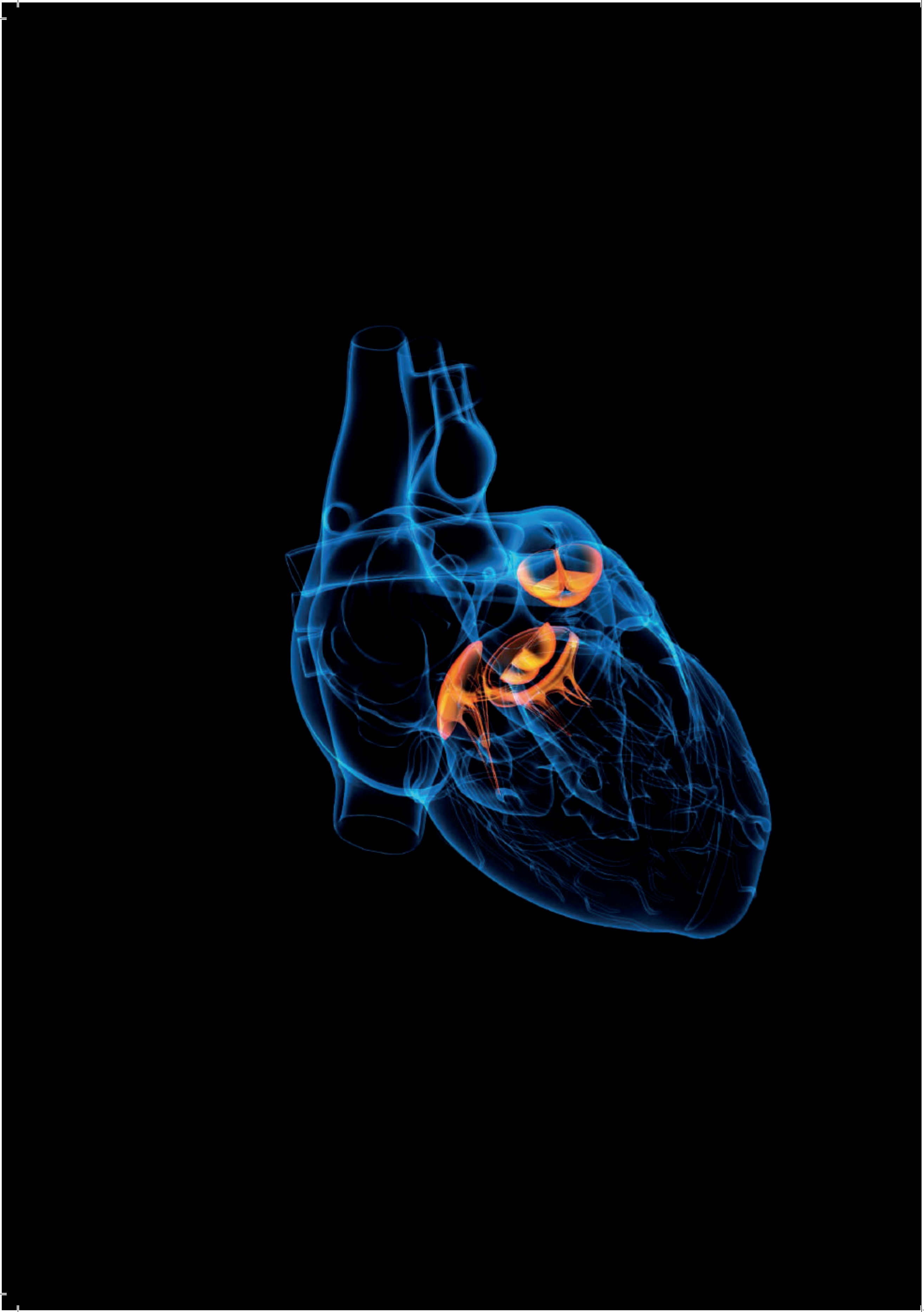
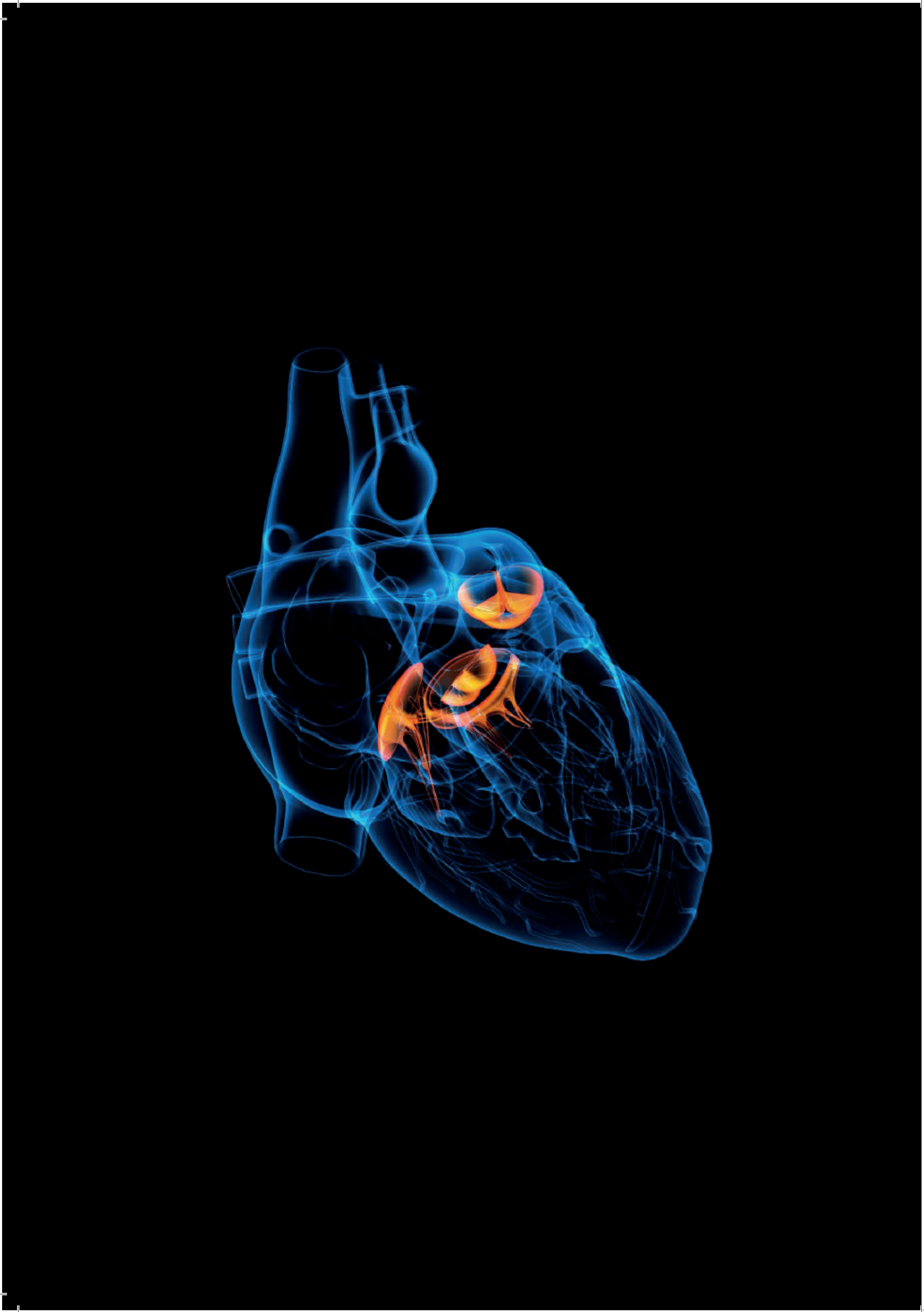


About the author

Zouhair Rahhab was born on the 15th of December 1990 in Rotterdam, The Netherlands. He graduated from secondary school (Erasmiaans Gymnasium, Rotterdam) in 2009. In the same year he entered medical school at the Erasmus University in Rotterdam. In 2012 he participated as a medical student in scientific research at the department of interventional cardiology of the Erasmus University initially under supervision of prof.dr. Schultz and later prof.dr. de Jaegere and prof.dr. van Mieghem. In 2016 he obtained his medical degree which was followed by a PhD trajectory focused on transcatheter left-sided heart valve interventions. During this period, he had the opportunity to present his work at national and international conferences and to publish manuscripts in peer-reviewed journals. He was a member of the TAVI team by performing CT analysis, attending the heart team and assessing patients in the outpatient clinic. In 2018 he started working as a clinical resident at the cardiology department of the Maasstad ziekenhuis Rotterdam. As of 2020, he started working at the department of cardiology in the Amphia ziekenhuis Breda and subsequently started his specialty training at the Amphia ziekenhuis.



Acknowledgements/ Dankwoord

Dear prof.Schultz, as a medical student I walked into your office to discuss research opportunities. You welcomed me with open arms and gave me some of your precious time for which I want to thank you. Although our collaboration was short-lived because of your departure to Australia it was very pleasant. Thank you and I wish you all the best in Perth. After your departure I came under the wings of prof. Van Mieghem and prof. De Jaegere.

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Naast mijn promotor zie ik je ook als mijn vriend/ grote broer. Je deur stond altijd open en ik kon altijd bij je terecht voor adviezen. Het was gezellig bij je in de kamer en er werden grappen gemaakt. We hebben vele leuke momenten gehad o.a. het etentje in de Euromast waarbij we leuke gesprekken hebben kunnen voeren. Deze mooi momenten zal ik voor altijd koesteren. Ik ben je eeuwig dankbaar, grote broer !

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