Transcatheter interventions for structural heart diseases

Present and future

Abdelghani Abdelzaher Ahmad, M.

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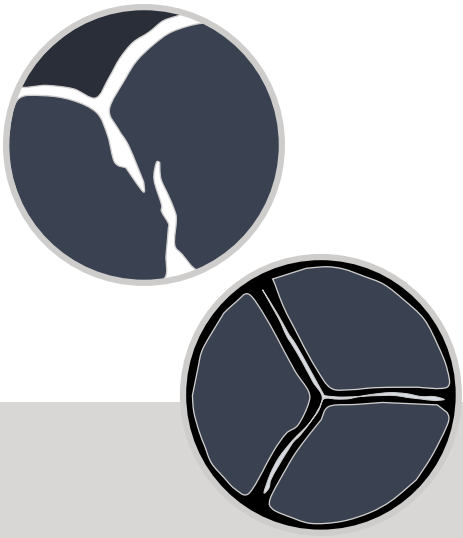

Transcatheter Interventions for Structural Heart Diseases

Present and Future

Mohammad Abdelghani

Transcatheter Interventions for Structural Heart Diseases:
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Mohammad Abdelghani Abdelzaher Ahmad

Transcatheter Interventions for Structural Heart Diseases: Present and Future

Dissertation, University of Amsterdam, The Netherlands

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Transcatheter Interventions for Structural Heart Diseases: Present and Future

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door

Mohammad Abdelghani Abdelzaher Ahmad

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Faculteit der Geneeskunde

To my parents

To my wife *Rana* and my children *Farida*, *Omar*, and *Anas*

To my patients

TABLE OF CONTENTS

Chapter 1 General introduction and outlines of the thesis 11

Part A: Transcatheter aortic valve implantation; beyond feasibility towards optimization

Section A.1. Decision-making and expanding the indications of TAVI

Chapter 2 Decision making and heart teams in valvular heart disease: the transcatheter aortic valve implantation team model. The ESC Textbook of Cardiovascular Medicine; 3rd edition, Chapter 58.3. 23

Chapter 3 Transcatheter aortic valve implantation for mixed versus pure stenotic aortic valve disease. EuroIntervention 2017;13(10):1157-1165. 39

Section A.2. Assessment of paravalvular leakage after TAVI

Chapter 4 Adjudicating paravalvular leaks of transcatheter aortic valves: a critical appraisal. European Heart Journal 2016;37(34):2627-44. 55

Chapter 5 Echocardiographic and angiographic assessment of paravalvular regurgitation after TAVI: optimizing inter-technique reproducibility. EHJ Cardiovascular Imaging 2016;17(8):852-60. 95

Chapter 6 Videodensitometric quantification of paravalvular regurgitation of a transcatheter aortic valve: in-vitro validation. EuroIntervention 2018;13(13):1527-1535. 115

Chapter 7 A Novel Angiographic Quantification of Aortic Regurgitation after TAVR Provides an Accurate Estimation of Regurgitation Fraction Derived from Cardiac Magnetic Resonance Imaging. JACC Cardiovascular Interventions 2018;11(3):287-297. 133

Section A.3. Long-term clinical and hemodynamic outcomes after TAVI

Chapter 8 Prevalence, predictors, and prognostic implications of residual impairment of functional capacity after transcatheter aortic valve implantation. Clinical Research in Cardiology 2017;106(9):752-759. 155

Chapter 9 Long-term durability and hemodynamic performance of a self-expanding transcatheter heart valve beyond 5 years after implantation: A prospective observational study applying the standardized definitions of structural deterioration and valve failure. EuroIntervention 2018;14(4):e390-e396. 173

Part B: Transcatheter interventions for other cardiac valves

Chapter 10 A simplified and reproducible method to size the mitral annulus: implications for transcatheter mitral valve replacement. EHJ Cardiovascular Imaging 2017;18(6):697-706. 191

Chapter 11 Infective endocarditis after Melody valve implantation in the pulmonary position: A systematic review. J Am Heart Assoc 2018;7(13):e008163. 211

Part C: Transcatheter closure of inter-atrial communications; foreseeing device-host interactions

Chapter 12 Residual tricuspid regurgitation after percutaneous atrial septal defect closure. Eur Heart J Cardiovasc Imaging. 2019;20(2):225-232. 239

Chapter 13 Aortic root geometric and dynamic changes after device closure of interatrial shunts. J Am Soc Echocardiogr. 2019;32(8):1016-1026. 261

Part D: Summary and conclusions

Samenvatting en conclusies (Dutch) 289

Summary of the thesis 293

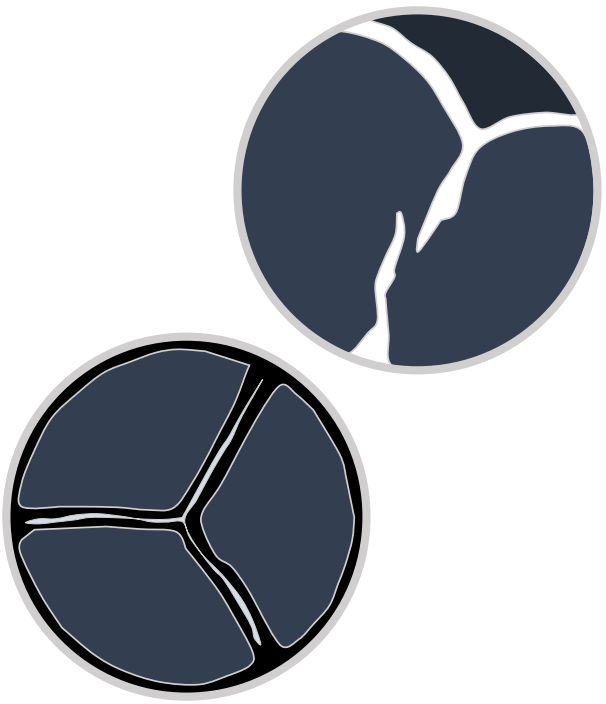
Conclusions 296

Part E: Future perspective

Chapter 14 Acute performance of a novel restorative transcatheter aortic valve: preclinical results. EuroIntervention. 2017;13(12):e1410-e1417. 301

Part F: Appendices

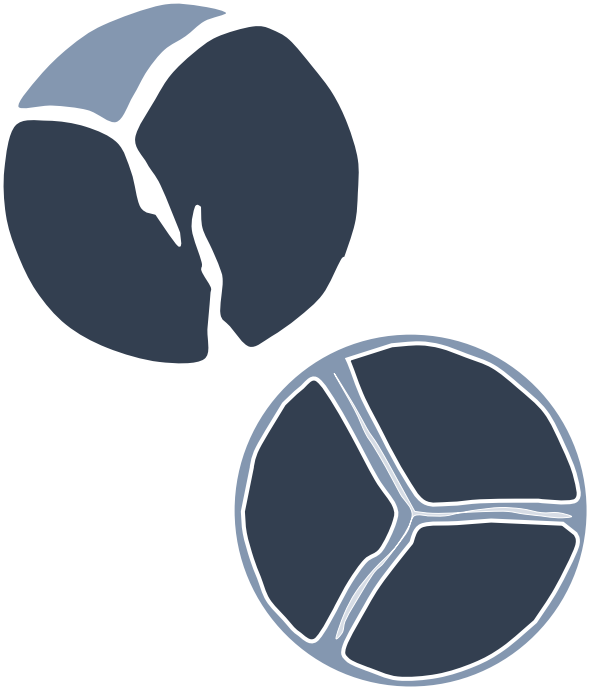
Authors and affiliations	317
Curriculum vitae	321
PhD portfolio	323
List of publications	325
Acknowledgement	331
Arabic acknowledgement	338



Chapter 1

General introduction and outlines of the thesis

Mohammad Abdelghani



Although the term "structural heart disease" is commonly used in medical literature, no established definition exists to specify what it refers to. Generally, structural heart diseases (SHD) constitute a group of congenital and acquired cardiac disorders characterized by macroscopic derangement of cardiac structure, typically leading to volume overload, pressure overload, and /or thromboembolism. In addition to this proposed definition, some authors restrict SHDs to "non-coronary disorders susceptible to percutaneous interventional treatment"[1,2]. Other authors have also called for exclusion of complex congenital heart diseases (CHD) from the spectrum of SHDs, owing to their early presentation and complex anatomy, pathophysiology, and (non)natural history; all requiring specialized knowledge and expertise, typically with a pediatric cardiology background[3]. Putting all these considerations together into account, the spectrum of SHDs (from the interventional cardiology perspective) includes: valvular heart diseases, simple CHDs presenting in adulthood, repaired complex CHD presenting in adulthood with residual/recurrent isolated defect(s), cardiac cavity requiring isolation/obliteration (e.g. atrial appendage and ventricular aneurysms), and hypertrophic obstructive cardiomyopathy. Rather than just a formality or an idiomatic dispute, the definition of SHD is important in order to standardize the quality requirements of centers and operators to be allowed to care for SHD patients as well as to define the conditions requiring Heart Team decision-making.

The incidence of different pathologies within the spectrum of SHDs is generally low, with two exceptions that represent a growing health care demand in an increasingly ageing population[4], namely; valvular[5] and adult congenital heart diseases. One out of eight elderly individuals (over 75 years) has significant valvular heart disease (VHD)[5]. Accordingly, the prevalence of clinically significant VHD is expected to double before 2050[6]. The burden of adult congenital heart disease (ACHD) is also growing[7] largely driven by survival to adulthood and advances in the management options of patients with complex CHDs. In spite of the advances in the diagnosis and treatment of ACHD, mortality is still high not only in severe, but also in non-complex ACHD (especially in women)[7].

Correction/repair –rather than conservative treatment– is usually the treatment of choice of severe forms of SHDs. While surgical treatment has been the only effective treatment for over a century, less invasive transcatheter solutions have been proposed as of the Fifties of the last century. In 1953, Rubio-Alvarez, Limon, and Soni published their pioneering work on percutaneous relief of critical pulmonic valve stenosis[8]. In 1965, Davies published in the Lancet his preclinical work on transcatheter aortic valve implantation to relieve acute aortic valve regurgitation through an aortotomy and concluded his article with the following statement: "It is hoped that in man the passage of such a valve retrogradely from the femoral artery to the level of the descending thoracic aorta (or perhaps even proximal to that) will provide sufficient relief to the heart

and circulation to render the patient fit for definitive surgery on the aortic valve some days or weeks later", clearly envisioning what was possible decades later and known today as transcatheter aortic valve implantation (TAVI)[9]. In 1992, Andersen, Knudsen, and Hasenkam described a stented valve they have developed and implanted in pigs[10]. Their modern design involved mounting a porcine aortic valve into an expandable stent, mounting this stent-valve on a balloon catheter, and implantation was achieved through balloon inflation to expand the stent-valve. A few years later, Bonhoeffer and colleagues and Cribier and colleagues performed the first in man transcatheter pulmonary and aortic valve replacements in 2000 and 2002, respectively[11,12]. Parallel to this success story in VHDs, interventions for CHDs matured gradually as of the sixties and seventies of the twentieth century. Portsmann was able to successfully close a patent ductus arteriosus without sternotomy for the first time in 1967[13]. A few years later, King and Mills pioneered the percutaneous closure of atrial septal defects; first in dogs in 1973 then in man in 1975[14].

As opposed to surgical treatment, transcatheter solutions for SHDs are characterized by: 1) less invasiveness, and thus more suitability for high risk patients (e.g. due to aging and/or comorbidities) and high risk clinical contexts (e.g. redo and emergency settings); and 2) less predictable and –frequently– less complete correction of the lesion. The former feature made the patient population targeted by these techniques tend to be an older, more complex, and higher risk population and this has stimulated the adoption of multidisciplinary team approach to optimize patient selection and planning for these interventions. The latter feature has stimulated the adoption of multimodality imaging to compensate for the lack of "direct surgical inspection". Backed with these two fundamental backbones (multidisciplinary heart team and multimodality imaging approaches), the number of transcatheter interventions for SHDs has increased exponentially in the last decade and is expected to further increase in the coming years to meet the aforementioned increasing demand.

The primary goals of the present thesis are:

- To highlight the rule of the **multidisciplinary approach** in the decision making and planning of SHD interventions and to highlight the importance of a comprehensive approach in assessing patients' eligibility as well as adequacy of outcomes (utility).
- To develop **novel imaging techniques** for planning the procedure and for the assessment of the acute and long-term performance of SHD repair techniques.
- To shed light on some **device-specific complications** after SHD interventions (e.g. device erosion of inter-atrial septal devices, endocarditis of the bovine jugular vein transcatheter pulmonary valve, and paravalvular leakage of transcatheter aortic valves).

PART A: TRANSCATHETER AORTIC VALVE IMPLANTATION; BEYOND FEASIBILITY TOWARDS OPTIMIZATION

This part of the thesis focuses on transcatheter aortic valve implantation (TAVI) which paved the way for the revolution of VHD interventions. At the time this thesis was conducted, TAVI has grown beyond the proof of concept, feasibility, safety, and efficacy in patients who cannot undergo surgery into technical maturation and optimization and to gradual expansion of its indications.

SECTION A.1. Decision-making and expanding the indications of TAVI

Section 1 addresses the planning aspects of TAVI with a focus on established and expanding indications. Although Heart Team-based decision making is recommended by practice guidelines[15] in TAVI planning, the exact role of the Heart Team is not established. **Chapter 2** focuses on the role of the Heart Team in determining the eligibility for TAVI. The choice between surgical and transcatheter aortic valve replacement in patients at different levels of operative risk is being discussed. **Chapter 3** explores whether TAVI is a good option in patients with high grade aortic regurgitation combined with stenosis (mixed aortic valve disease) which is currently an off-label indication for TAVI[16].

SECTION A.2. Assessment of paravalvular leakage after TAVI

Paravalvular leakage (PVL) remains common after TAVI (as compared to surgical aortic valve replacement) and has once been considered the Achilles' heel of this technology[17]. While the maturation of the technology and the techniques of TAVI has led to a significant reduction of the rate of PVL, its quantification remains challenging as optimal cut-points defining severity are either lacking or not adequately validated[18,19]. **Section 2** aims at improving currently available methods and developing novel dedicated methods for the assessment of PVL after TAVI. **Chapter 4** critically discusses established, relatively new, and upcoming methods used for the assessment of PVL after TAVI. **Chapter 5** tries to improve the accuracy of the well-established first line imaging modality of PVL; echocardiography and to increase its agreement with angiography. **Chapters 6** and **7** are dedicated for the validation of a novel angiographic method (videodensitometry) developed specifically to quantitate PVL within the cath-lab when the assessment is most crucial as to guide timely corrective measures. The technology is based on contrast aortography, where the contrast density in the left ventricle (if any) is automatically quantified and compared to that in the aortic root. **Chapter 6** describes and in-vitro experiment exploring how far videodensitometric assessment of PVL severity represents the regurgitation volume and fraction (measured with a transonic flow probe). **Chapter 7** describes a similar experiment that was conducted in-vivo, comparing videodensito-

metric assessment of PVL severity to the regurgitation fraction, this time derived from cardiac magnetic resonance imaging.

SECTION A.3. Long-term clinical and hemodynamic outcomes after TAVI

Section 3 looks at the intermediate-to-long term results after TAVI on three levels; symptoms, survival, and valve durability. TAVI futility implies lack of adequate survival and quality of life gains in the intermediate term, or more simply, failure to satisfy patient's expectations. **Chapter 8** focuses on the symptomatic (functional) outcomes in the intermediate term after TAVI, exploring the predictors of residual impairment of functional capacity. **Chapter 9** presents one of the longest follow up data beyond 5 years after TAVI, with a special focus on durability and hemodynamic performance of the transcatheter aortic valve. The study utilized core lab adjudication of echocardiographic data and applied standardized definitions of structural deterioration and bioprosthetic valve failure.

PART B: TRANSCATHETER INTERVENTIONS FOR OTHER CARDIAC VALVES

In **Part B**, some transcatheter interventions for VHD other than the aortic valve are exemplified. One of the main challenges complicating transcatheter valve replacement for atrio-ventricular valves is the complexity of annulus geometry. The mitral valve annulus is a non-planar non-circular structure and is difficult to delineate from the aorto-mitral continuity anteriorly. **Chapter 10** describes a simplified and reproducible method to assess the mitral valve annulus on multislice computed tomography in the setting of transcatheter mitral valve replacement. **Chapter 11** addresses another type of transcatheter valve replacement, in the pulmonary position. The chapter highlights the magnitude of the growing problem of infective endocarditis after transcatheter pulmonary valve implantation with the Melody valve and tries to explore its natural history through a systematic literature review.

PART C: TRANSCATHETER CLOSURE OF INTER-ATRIAL COMMUNICATIONS; FORESEEING DEVICE-HOST INTERACTIONS

Part C discusses percutaneous closure of atrial septal defect (ASD) and patent foramen ovale (PFO) with a special focus on the impact of the procedure on tricuspid valve function and of the device on the adjacent aortic root. **Chapter 12** investigates the modified natural history of tricuspid regurgitation after percutaneous ASD closure and the determinants of its regression, as well as its prognostic importance. **Chapter 13** describes

a mechanistic analysis of the mechanical impact of ASD/PFO closure devices on aortic root geometry and dynamics, in light of the increasing awareness of the problem of device erosion into the aortic root.

PART D: SUMMARY AND CONCLUSIONS

PART E: FUTURE PERSPECTIVE OF PROSTHETIC HEART VALVES

Thrombogenicity, propensity to infective endocarditis, and relatively short durability are intrinsic shortcomings of all bioprosthetic valves. The concept of Endogenous Tissue Restoration (ETR) implies that prosthetic valve leaflets are made of a bioabsorbable material to be progressively replaced by endogenous tissue, potentially avoiding the aforementioned shortcomings of animal-based bioprosthetic valves[20]. In **Chapter 14**, the early pre-clinical results of a transcatheter aortic valve with bioabsorbable leaflets are reported.

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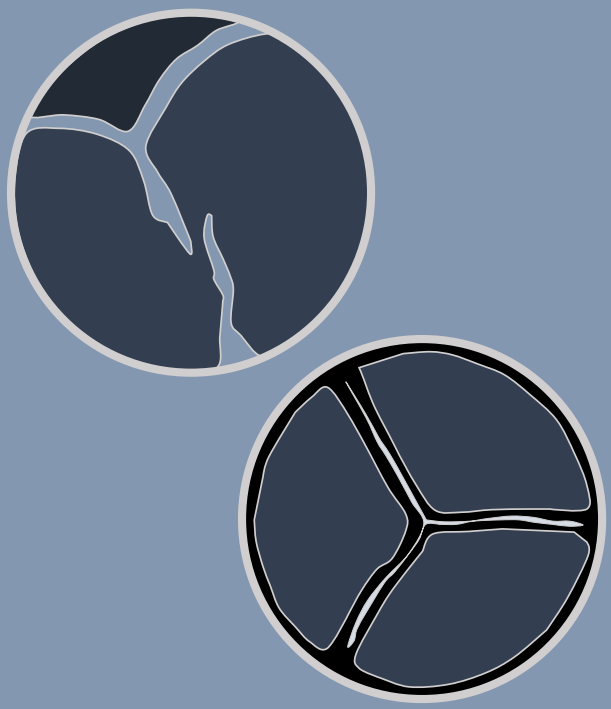
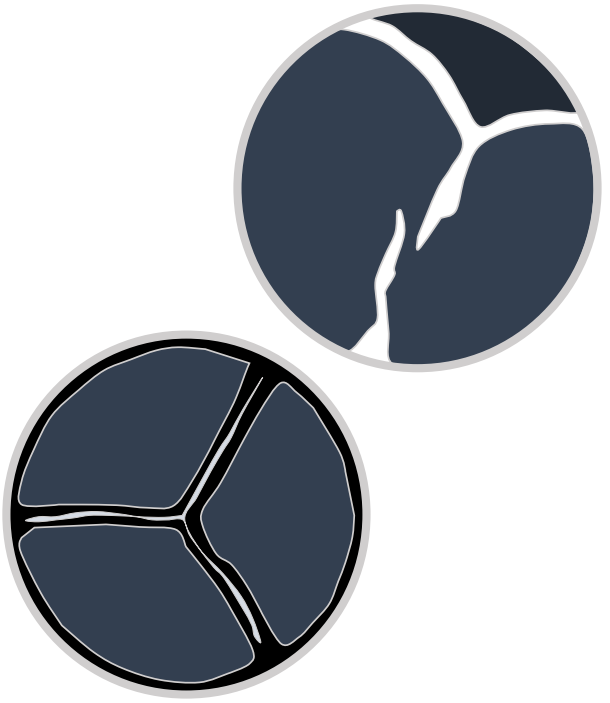
PART A

Transcatheter aortic valve implantation; beyond feasibility towards optimization



Section A.1

Decision-making and expanding the indications of TAVI

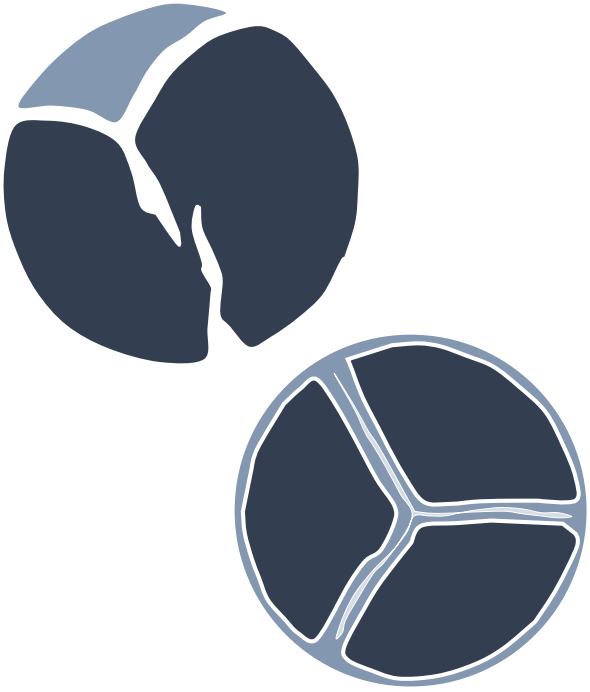


Chapter 2

Decision making and heart teams in valvular heart disease: the transcatheter aortic valve implantation team model

Abdelghani M, Makhdom F, Piazza N

Chapter 58.3. The ESC Textbook of Cardiovascular Medicine. 3rd edition. Camm AJ, Lüscher TF, Maurer G, and Serruys PW. Oxford University Press, 2018.



ABSTRACT

Benefits from transcatheter aortic valve implantation (TAVI) in the pivotal trials can be largely ascribed to the multidisciplinary decision- making and care, a process that can be executed only by an integrative team. The Heart Valve Team can include, in addition to interventional cardiologists with expertise in transcatheter valve interventions and cardiac surgeons with expertise in valve surgery, general clinical cardiologists, echocardiologists/cardiac imaging specialists, cardiac anaesthesiologists, intensivists, nurses, and/or social workers, among others. The main functions of this Team are assessment of a patient's eligibility for TAVI, procedural planning, and setting a post- procedural extended care plan.

RATIONALE, DEFINITION, AND FRAMEWORK OF A TAVI HEART VALVE TEAM

Both regulatory authorities and cardiology/cardiothoracic surgery societies recommend the collaboration of a heart team in different stages of TAVI-patient care,[1-3] to (1) optimize patients' care and satisfaction, (2) effectively manage resources, (3) promote evidence-based practice, and (4) offer the treating physicians a cross-training environment and a reduced probability of malpractice and medico-legal liability.

Although a multidisciplinary approach emerges as a necessity in the face of the increasing diagnostic and therapeutic options and the more focalized specialization of healthcare providers, implementation of—and adherence to—a Heart Team workflow remain challenging. Scheduling and time consumption (of already overwhelmed medical personnel), reimbursement constraints, human interactions (especially between the interventionist and the surgeon), unclear decision-making workflow (consensus vs hierarchical vs guidelines based), and the challenging communication with the patient and family (more familiar with the family/ referring physician) are barriers in implementing an integrative multi-party workflow. Assessing the competence of a Heart Valve Team is also challenging, yet necessary, and may include the rates of the Valve Academic Research Consortium endpoints,[4] patients' satisfaction indices, and cost-effectiveness measures.

In addition to the fundamental partnership between an interventional cardiologist with expertise in transcatheter valve interventions and a cardiac surgeon with expertise in heart valve surgery, the Heart Team usually includes echocardiologists/cardiac imaging specialists, and clinical (valvular heart disease) cardiologists. Cardiac anesthesiologists, intensivists, nurses, and social workers are, among others, further potential members of a comprehensive Heart Valve Team. Depending on the burden of co- morbidities, internists, pulmonologists, nephrologists, neurologists, vascular surgeons, and other medical/surgical specialists might be involved. A Heart Team meeting can take place on, for example, a weekly basis, where all members are present to discuss the candidate cases. It is suggested that the cardiac surgeon takes the team lead in cases where there is a need for surgical access, while the interventional cardiologist takes the lead in percutaneous TAVI.[5] The Heart Valve Team coordinator (usually a senior nurse with cardiac and geriatric care expertise) is a key element in a Heart Team workflow. The responsibilities of the Heart Valve Team coordinator are diverse and dynamic, but typically involve[6] (1) streamlining patients' care, including patient referrals and transfers and scheduling diagnostic, procedural, and follow- up services; (2) registry data collection; (3) patient and family education and integration into the decision- making process; and (4) programme coordination, including developing standardized protocols of care and communication, preparing the Heart Team meetings, and designing a programme evaluation plan.

FUNCTIONS OF A TAVI HEART TEAM

Table 1 summarizes the functions of the Heart Valve Team in the setting of TAVI, which involves pre-, peri-, and post-procedural roles.

A. Assessment of patient's eligibility for aortic valve replacement:

Based on currently available evidence (**Figure 1**), the choice between TAVI and surgical aortic valve replacement (SAVR) can be straightforward in some patient subgroups (**Figure 2**), but frequently entails a complex risk/benefit assessment that is individualized to each patient (**Figure 3**). The Heart Valve Team's choice between therapeutic options should involve (1) confirming the severity of aortic stenosis, and that it is responsible for a considerable proportion of patient's complaints; (2) comparison of treatment options

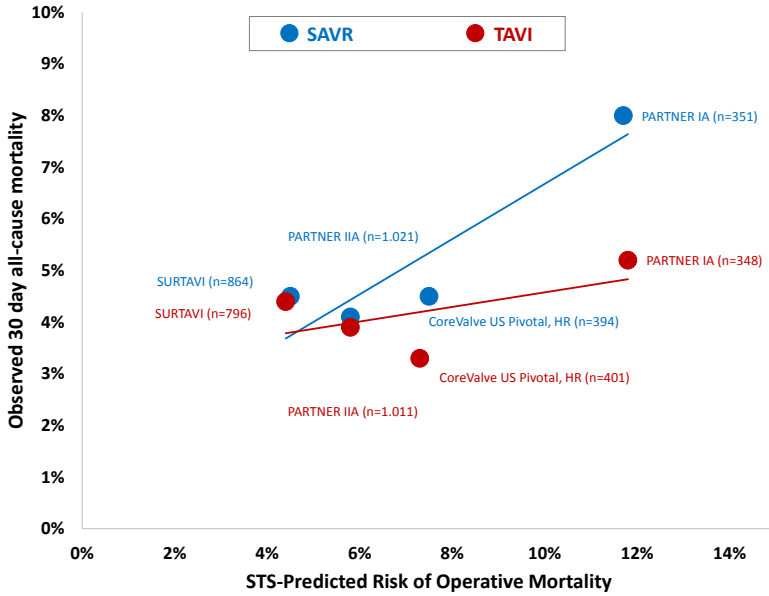


Figure 1. Early mortality after TAVI vs. SAVR in randomized controlled trials.
Thirty-day mortality rates after transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR) compared in four randomized trials. Mortality rates (on the Y-axis) are plotted against the respective predicted risk of operative mortality based on the Society of Thoracic Surgeon (STS) score, and trend lines are superimposed. In patients with a higher predicted risk, TAVI offers a more pronounced survival benefit over SAVR (with a mortality rate that is considerably lower than predicted by the STS score). In patients with an intermediate-low predicted risk, no such advantage of TAVI over SAVR is seen, and the mortality rate tends to be close to what is predicted by the STS score.
References: PARTNER IA: Smith et al - N Engl J Med. 2011;364:2187-98; US pivotal (HR): Adams et al - N Engl J Med. 2014;370:1790-8; PARTNER II: Leon et al - N Engl J Med.2016;374:1609-20; SURTAVI: Reardon et al - N Engl J Med 2017;376:1321-31.

Table 1. Functions of the heart valve team in patients with severe symptomatic aortic stenosis considered for transcatheter aortic valve implantation:

I. Assessment of patient's eligibility
1. Confirmation of the severity of AS
2. Confirmation of the relationship between patient's complaints and AS (symptoms likely to improve after valve replacement)
3. Excluding markers of futility: a) Estimation of life expectancy b) Assessment of frailty (e.g. by the Clinical Frailty Scale), nutritional status (e.g. body mass index and serum albumin), and physical and cognitive function and independence c) Assessment of cardiovascular conditions (e.g. pulmonary hypertension) and non-cardiovascular comorbidities (e.g. chronic lung disease) and whether their severity precludes a meaningful clinical benefit after valve replacement
4. Assessment of operative risk: a) Surgical risk scores (e.g. STS-PROM and EuroSCORE II) b) Major comorbidities not captured by the surgical risk scores (e.g. liver disease) c) Anatomical impediments to the procedure (e.g. previous CABG with vulnerable conduit increasing the risk of SAVR, or extensive calcification of the LVOT or of a bicuspid aortic valve increasing the risk of TAVI)
5. Management plan for comorbid cardiac conditions requiring intervention (e.g. significant valvular, aortic, or coronary artery disease)
6. Discussion of treatment options with the patient and his/her family and referring physician. The patient should actively participate in this discussion through emphasizing his/her: a) Preference b) Most distressing complaints, priorities, and expectations from the procedure c) Willingness to accept operative/later risks
II. Pre-procedural preparations:
1) Imaging of the heart, the aortic valve, and the vascular tree (including the aorta, the coronary arteries, and the potential vascular access sites)
2) Dental assessment and management
3) Assessment of the thrombotic/bleeding risks
III. Procedural planning:
1) Estimating the risk and the complexity of the procedure and whether a minimalist setting or a more conservative approach is warranted
2) Choosing the device, the access, and the mode of anesthesia
3) Anticipation and preemptive complication-combat planning
IV. Post-procedural care:
1) In-hospital surveillance duration (including rhythm monitoring)
2) Recovery, discharge, follow-up, and rehabilitation planning
3) Handing-off the care to the heart valve clinic or to the referring center

Abbreviations: AS, aortic stenosis; CABG, coronary artery bypass grafting; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVOT, left ventricular outflow tract; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons-Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

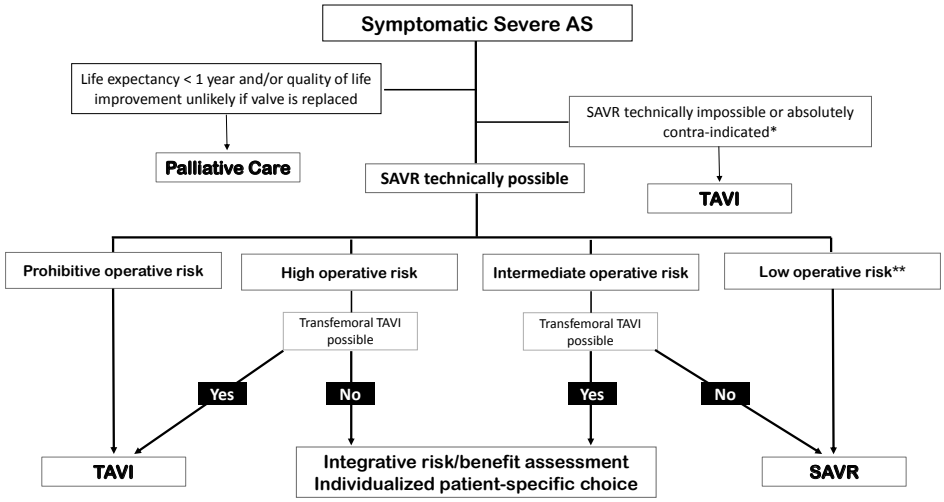


Figure 2. Decision tree for patients with symptomatic severe aortic stenosis considered for transcatheter aortic valve implantation.

* e.g. due to porcelain aorta or hostile chest.

**TAVI should not be considered in low risk young patients.

Abbreviations: AS, aortic stenosis; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

(based on their safety, feasibility, and reasonability); and (3) discussing these options with the patients and their families and referring physicians (**Figure 3**).

The classical, well-validated score-based operative risk estimation is the most widely used tool by Heart Valve Teams to guide the choice between therapeutic options in patients with severe symptomatic aortic stenosis.[7] The risk estimation based on these scores seems, however, to be partially artificial, as evidenced by a significant discordance with patients' definition of 'acceptable risk'. The latter was shown to be significantly variable among patients and to be largely determined by the severity of quality of life impairment before valve replacement. Overall, patients with severe symptomatic aortic stenosis seem to frequently accept a perioperative mortality risk that the current guidelines and risk assessment algorithms consider unacceptably high (prohibitive).[8,9] Some specific TAVI risk calculators have been proposed.[10-12] However, well-validated, generic (device-neutral) TAVI risk scores that include frailty- and disability-related covariates and accurately predict 30-day and/or 1-year mortality are so far unavailable. An integrative risk assessment is, therefore, recommended as a substitute for the exclusive score-based risk assessment.[13,14] This integrative approach combines: (1) STS-predicted risk of mortality score; (2) main organ dysfunction not captured by risk scores (e.g. liver cirrhosis); (3) indices of frailty, nutritional deficiency, and physical and cognitive disability; and (4) specific anatomical impediments to the procedure[13] (**Figure 3**).

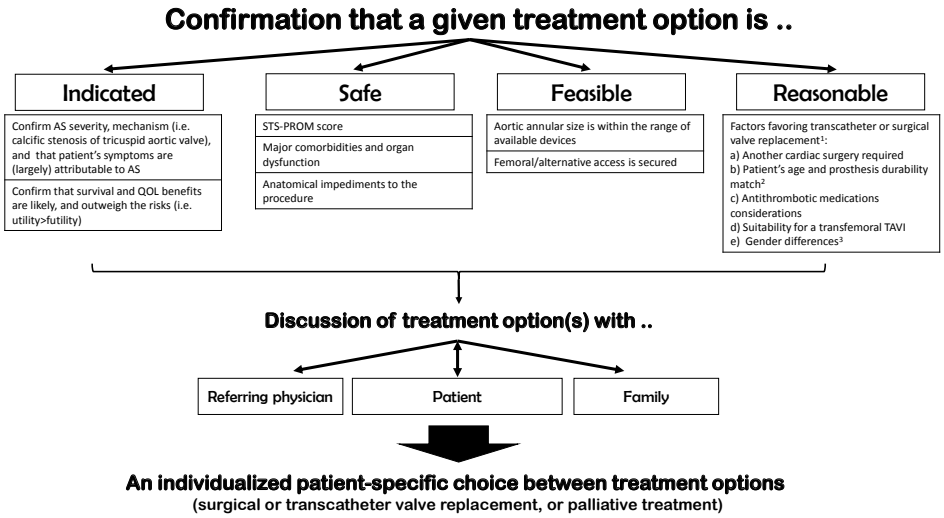


Figure 3. The integrative multi-dimensional risk/benefit assessment of therapeutic options for patients with symptomatic severe aortic stenosis considered for transcatheter aortic valve implantation (Please also see Table 1)**.**

[1]Factors favoring SAVR include: a) Need for concomitant vascular/valvular surgery, b) Younger age (favoring the choice of a mechanical prosthesis), c) Anticoagulation not contraindicated/or already on anticoagulation (favoring the choice of a mechanical prosthesis), 4) Transfemoral TAVI not an option. Factors favoring TAVI include: a) Older age, b) Transfemoral access possible, c) Female gender.

[2]No reliable data exist on long-term durability of transcatheter aortic valves.

[3]Current evidence suggests that, contrary to SAVR, TAVI yields better outcomes in females than in males.

Abbreviations: AS, aortic stenosis; STS-PROM, Society of Thoracic Surgeons-Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

Futility implies lack of adequate survival and quality of life gains in the intermediate term (e.g. survival with symptomatic and quality of life benefit <25% at 2 years[13]), or more simply, failure to satisfy patients' expectations. It is important for the multidisciplinary team to estimate the probability of futility considering the preference and the priorities of the patient, bearing in mind that physicians' and patients' appraisal of risks and benefits may differ.[15] As such, it is important to include a comprehensive geriatric assessment of the patient's eligibility and decision-making. This assessment should focus on excluding the degree of frailty that portends a poor survival (regardless of valve replacement)[16] or precludes a meaningful quality of life improvement after the procedure, thus making the procedure futile. Notwithstanding, frailty tests are part of the routine assessment of aortic stenosis patients undergoing valve replacement in only a minority of TAVI centers worldwide.[7]

When discussing the choice between TAVI and SAVR, the team should also consider the design differences between transcatheter and surgical prosthetic valves that make durability concerns more relevant to transcatheter aortic valves,[17] as well as the lack of

adequate data on the long-term durability of these valves. The patient's age and expected survival, the presence of indications/contraindications for anticoagulation (required for a surgical mechanical prosthetic valve), and the suitability for future valve-in-valve solutions are to be considered in the choice between mechanical versus transcatheter/surgical bioprosthetic valves.

All these aforementioned factors should be discussed with the patient and his/her family. Patient education is especially critical when the patient opts for the less- invasive treatment (TAVI) in a situation that is not supported by enough evidence (e.g. low-risk young patient) or when the probability of futility is high.

Finally, as the Heart Valve Team discusses the patient's eligibility for TAVI, some important co- morbid conditions need careful assessment, risk stratification, and a pre- emptive management plan:

Management of coronary artery disease in patients undergoing TAVI:

Up to 75% of patients undergoing TAVI have substantial obstructive coronary artery disease (CAD).[18] The theoretical downsides of delaying CAD management to after TAVI procedure are that (1) patients are exposed to haemodynamic stress during TAVI (e.g. hypotension during rapid pacing), and (2) the access to coronary ostia after TAVI can be challenging (especially when the device is partially supracoronary and in case of valve-in-valve implantation). In a global survey of 250 TAVI centres in 38 countries,[7] pre-TAVI coronary angiography was a routine in all centres, while physiological assessment of CAD severity was performed in a minority of centres (16.4%). Assessment of CAD severity was followed by treatment of severe CAD before TAVI in the majority of centres (79.6%). The major dilemmas in managing CAD in patients undergoing TAVI are how CAD is best assessed and whether ischaemia causes additional periprocedural risks and, accordingly, whether revascularization before/with TAVI is indicated. In patients undergoing TAVI, data on the influence of CAD on outcomes are conflicting, with most of the major trials and registries reporting no independent association between mortality and the presence of CAD.[19] In a recent meta-analysis, percutaneous coronary intervention prior to or concomitant with TAVI was shown to be associated with an increased risk of 30-day all-cause mortality, but not with 30-day cardiac or 1-year all-cause mortality. Percutaneous coronary intervention with TAVI increased the risk of vascular complications while conferring no special clinical advantage. The included studies were, however, all observational and were subject to selection bias, limiting the robustness of the conclusions.[20] In the absence of clear evidence or practice guidelines to standardize CAD management in patients undergoing TAVI, it is the Heart Team's responsibility to decide how to risk-stratify and manage CAD. When deemed necessary by the Heart Team, coronary revascularization in patients undergoing TAVI can be performed via percutaneous coronary intervention or minimally invasive bypass surgery (combined

with transaortic TAVI[21,22]). Feasibility of a percutaneous transvascular access, complexity of CAD, and haemodynamic stability are among the decisive factors for the choice between these options.

Management of mitral regurgitation in patients undergoing TAVI:
Significant mitral regurgitation is common in patients undergoing TAVI and persists in a significant proportion of them (especially those with annular dilation and/ or calcification), portending increased mortality and heart failure- related hospitalizations.[23,24] According to standard anatomical eligibility criteria, some of those patients can benefit from percutaneous mitral intervention. Concomitant transcatheter mitral and aortic valve implantation (via transvascular or transapical routes)[25-27] as well as combined MitraClip® and TAVI (performed in same- session or in staged settings)[28] were shown to be feasible.

In cases with combined significant valvular disease (e.g. aortic stenosis and mitral regurgitation), the multidisciplinary discussion among the Heart Team should identify the main reason for a patient's symptoms and the priority in correction. The presence of severe primary mitral regurgitation favours the choice of SAVR (combined with mitral valve surgery) over TAVI. In case TAVI is given a priority (e.g. mitral regurgitation is functional), it remains the responsibility of the Heart Team to anticipate and monitor mitral regurgitation regression, and to decide whether a transcatheter mitral valve intervention should be considered.

B. Periprocedural planning:

After the decision by the Heart Team is made that the patient is eligible for TAVI, a number of functions should still be performed/ supervised by the Heart Team (**Table 1**): (i) preprocedural preparations (e.g. imaging of the heart, the aortic valve, the coronary arteries, and the potential access site, as well as general clinical preparations such as dental review and preparation); (2) procedural planning (e.g. choosing the device, the access, the anaesthesia type, and the location of the procedure); (3) post-procedural care (e.g. deciding the duration of intensive care/hospital stay and of telemetry, discharge, and recovery/rehabilitation planning, and handing over the patient's care to the referring centre or to an affiliated heart valve clinic).

Device choice:
The priority should always be to let the experience of a given operator/institution grow in implanting and managing the challenges and complications of one/few valve system(s), rather than continuously starting new learning curves of new devices. As such, and although a single TAVI system can be used for the majority of cases in a given institution, some situations require specific technology. For example, annular sizes con-

sidered borderline for self-expanding TAVI devices are within a favourable range for balloon-expandable devices, and vice versa. In cases with aortopathy or excessive left ventricular outflow tract calcification, self- or mechanically expandable devices might be associated with a lower risk of annular rupture than a balloon-expandable device. A completely repositionable device is preferred in cases at high risk of coronary obstruction (e.g. low-lying coronary ostia, shallow aortic sinuses, bulky and heavily calcific leaflets, and/or valve-in-valve procedures).[29]

Planning the access, mode of anaesthesia, and location of the procedure:
The minimalist strategy of TAVI implies shifting to a default practice of transfemoral TAVI performed under local anaesthesia in a regular cath-lab. This strategy has been shown to shorten the length of intensive care/hospital stay and to lower resource use, without compromising the safety or efficacy of the procedure.[30-32]

In centres adopting this approach, it is the responsibility of the Heart Team to stratify patients in an efficient way that safely allocates patients to the default minimalist approach or to a more 'conservative' approach.[17] This implies a selective use of hybrid operating rooms, surgical cut- downs, invasive monitoring equipment, general anaesthesia, and transoesophageal echocardiography guidance.[17]

Anticipation and pre-emptive combat plan of complications:
Severe (life-threatening) periprocedural complications cannot be adequately predicted based on patients' baseline characteristics,[33] and perioperative mortality in patients emergently converted to surgery due to intraprocedural complications is very high.[34,35] Studies from large TAVI centres reported rescue cardiopulmonary bypass and conversion to surgery being needed in 1.2–6.0%[36] and 0.0–2.8%[35,37] of cases, respectively, and highlighted that successful rescue from procedural severe complications depends on the preparedness of the multidisciplinary team and on having a pre-emptive rescue plan.[37]

THE MULTIDISCIPLINARY HEART VALVE CLINIC

Representation of the Heart Team in a heart valve clinic helps optimize centralized care that includes clinical, advanced imaging, and interventional/ surgical consultation services.[5] Combining a high volume of patients with sophisticated technical support, the heart valve clinic represents a unique platform for patient care, physician training, and research.[38]

The aims of a heart valve clinic include[38] (1) facilitating coordination among all healthcare professionals involved in the management of patients with valvular heart

disease, including connecting the referring cardiologist to the cardiac interventionist/ surgeon and connecting non- surgical to surgical centres; (2) performance of relevant diagnostic tests to evaluate and follow up the severity of valvular heart disease and related symptoms and cardiac function, and ensuring the provision of these data to all healthcare professionals involved in the patient's management; and (3) careful follow- up of patients who underwent valve surgery/interventions and of patients with moderately severe valvular heart disease in whom a 'watchful waiting' strategy is opted for (e.g. identification of insidious onset of mild symptoms and performing provocative tests in apparently asymptomatic patients, and careful surveillance of myocardial function and pulmonary artery pressure). The backbone of the heart valve clinic is the dyad of a cardiologist with expertise in valvular heart disease and a specially trained nurse with streamlined referral pathways to imaging, surgical, and interventional services. Alternatively, cardiac imaging specialists, cardiac surgeons, interventional cardiologists, and cardiac anaesthesiologists can serve on a referral- only, part- time, or full- time basis in the heart valve clinic team.[38] Other 'devolved' models include a sonographer- led clinic in asymptomatic patients requiring only regular echocardiography, and a nurse- led clinic for patients with normally functioning prosthetic valves who do not require regular echocardiography. In these devolved clinics, a cardiologist consultation is required in cases with a change in symptoms, a clinical event, or the attainment of an echocardiographic threshold. These more simplistic 'devolved' models were shown to reduce the number of patients seen by a cardiologist and the number of echocardiographic studies and to increase the proportion of patients managed according to best practice guidelines compared to conventional clinics.[39,40]

CONCLUSION

Consolidation, maturation, and standardization of the Heart Valve Team structure and workflow should become a priority to optimize TAVI outcomes and extend its indications. Decision-making on the patient's eligibility should take into account not only the anatomical suitability and the perioperative risk of mortality but also utility versus futility from the perspectives of the patient's expectations and the societal cost- effectiveness. Periprocedural planning should be patient- rather than institution- specific and periprocedural management should remain multidisciplinary even when the procedure is planned to be minimalist.

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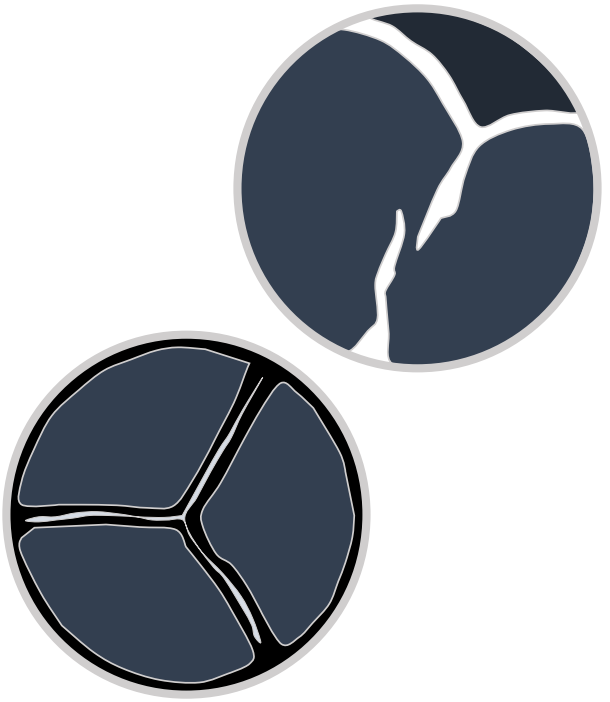

Chapter 3

Transcatheter aortic valve implantation for mixed versus pure stenotic aortic valve disease

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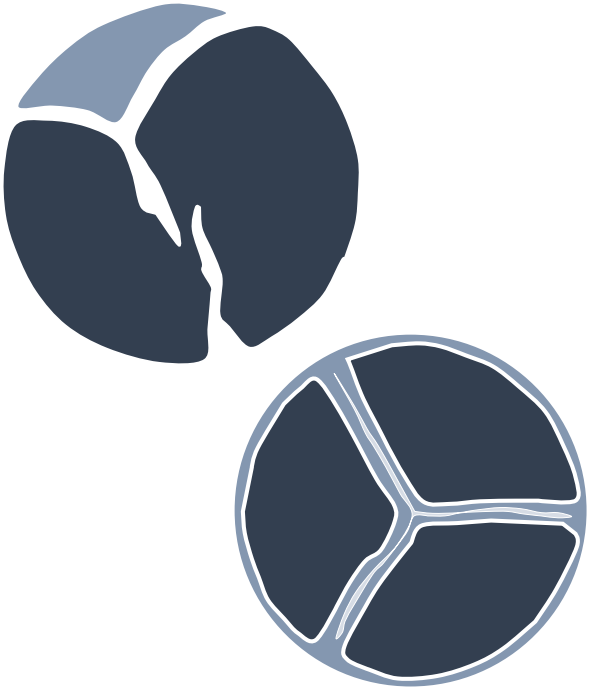

ABSTRACT

Aims:

In addition to patients with pure/predominant aortic stenosis (PAS), real-world transcatheter aortic valve implantation (TAVI) referrals include patients with mixed aortic valve disease (MAVD; severe stenosis + moderate-severe regurgitation). We sought to compare TAVI outcomes in patients with MAVD vs. PAS.

Methods and results:

Out of 793 consecutive patients undergoing TAVI, 106 (13.4%) had MAVD. Patients with MAVD were younger and had a higher operative risk, a severer adverse cardiac remodeling, and a worse functional status than patients with PAS. Moderate-severe prosthetic valve regurgitation (PVR) was significantly more frequent in patients with MAVD than in patients with PAS, (15.7% vs. 3.6%, p=0.003), even after propensity-score and multivariable adjustments. Moderate-severe PVR was associated with increased one-year mortality in patients with PAS (log-rank p=0.002), but not in patients with MAVD (log-rank p=0.27). Eventually, all-cause and cardiac mortality as well as the functional capacity were similar in the two study groups up to one-year.

Conclusions:

A significant proportion of patients referred for TAVI in a real-world registry has MAVD. Moderate-severe AR at baseline can influence the rate and modify the clinical sequelae of post-TAVI PVR. Eventually, clinical outcomes in patients with MAVD are comparable to patients with PAS in the acute and mid-term phases, in spite of a baseline higher risk. MAVD should not be considered a contra-indication for TAVI.

INTRODUCTION

In patients with severe symptomatic aortic stenosis (AS), transcatheter aortic valve implantation (TAVI) can improve quality of life and significantly reduce mortality[1-3]. However, the role of TAVI in the management of patients with native aortic valve regurgitation (AR) is less established[4]. Although mixed aortic valve disease (MAVD) is frequently encountered in clinical practice[5], data on its prevalence and natural history are scarce[6]. MAVD (moderately-severe AR co-existing with severe AS) was considered as an exclusion criterion in the landmark PARTNER trial[1-3] as well as in the SURTAVI trial[7]. Likewise, TAVI is not recommended in patients with AS who also have severe AR in some of the practice guidelines[8].

However, post-approval real-world TAVI practice has expanded to groups of patients who were excluded from the pivotal clinical trials, including patients with MAVD[9]. As TAVI is suggested to be increasingly performed in younger patients as well as in patients with bicuspid aortic valve disease, more MAVD will be encountered among TAVI referrals.

The aim of this study was to 1) define the frequency and characteristics of patients with MAVD referred for TAVI in a real-world multicenter registry, and to 2) compare the outcomes of TAVI in patients with MAVD vs. pure/predominant AS, using a propensity score adjusted analysis.

METHODS

The study included consecutive patients enrolled in a prospective multicenter TAVI registry from January 2008 to January 2015. List of participating centers, details of inclusion and exclusion criteria, and TAVI-procedure technical aspects have been previously described elsewhere[10]. The study protocol was approved by the ethics committee at each of the participating centers and all patients provided written informed consent. Patients were considered eligible for inclusion if they had severe symptomatic AS and were considered by the heart team as inoperable or at high surgical risk.

Aortic regurgitation (AR) severity was graded in accordance with the recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging[11,12]. According to the severity of AR at baseline, the study population was divided into two groups; pure/predominant aortic stenosis (PAS, if AR was mid-or-less), and mixed aortic valve disease (MAVD, if AR was moderate or severe). The cover index was calculated as; 100 x ([prosthesis diameter – computed tomographic annular diameter]/prosthesis diameter.

Outcomes

An independent committee (including a neurologist) adjudicated all events and all endpoints are reported according to the Valve Academic Research Consortium-2 (VARC-2) definitions[13].

The primary endpoint of the present study was device success, defined as absence of procedural mortality, correct positioning of a single device into the proper anatomical location, absence of prosthesis–patient mismatch with a trans-aortic mean pressure gradient (PG) <20 mmHg, and absence of moderate or severe prosthetic valve regurgitation (PVR)[13]. Secondary endpoints included individual valve performance indices (trans-valvular gradient and PVR), early safety endpoints (at 30 days) and clinical efficacy endpoints at 1 year.

Propensity analysis

To account for baseline and procedural differences between the two groups, a score for propensity[14] to MAVD has been developed using a multivariable logistic regression analysis to represent the probability of a given patient to have MAVD (range, 0.003-0.986). The model was inclusive and comprised 19 variables (**Table 1**). This model yielded a c statistic of 0.784 (95% confidence limits, 0.733-0.834; p<0.001), denoting a substantial ability to predict MAVD (vs. PAS).

Statistical methods

Quantitative variables are summarized as mean ± standard deviation-SD or median [interquartile range-IQR] and are compared by Student t test or Mann-Whitney test, as appropriate. Categorical variables are summarized as frequencies and proportions and are compared by the chi-square test.

The association between MAVD and the study endpoints was tested using uni- and multi-variable logistic regression analyses, and was expressed as odds ratio (OR) and 95% confidence interval (CI). In multivariable analysis, the propensity score for MAVD was entered to the model (the propensity score-adjusted multivariable regression analysis).

Cumulative survival curves for patients with MAVD vs. PAS were constructed using the Kaplan-Meier method and compared with the log-rank test. All analyses were performed with SPSS 23 (IBM, Armonk, NY, USA). All probability values were two-tailed, and a p value <0.05 was considered significant.

Table 1. Baseline and procedural characteristics according to the type of aortic valve disease:

		Aortic valve disease at baseline		
		Pure/predominant AS (n=687)	Mixed aortic valve disease (n=106)	*p*
Age		81.8±7.1	79.7±8.6	0.019
Male gender		333 (48.5%)	55 (51.9%)	0.532
BMI		26.4±4.7	25.2±4.4	0.005
EuroSCORE		20.0±14.3	23.7±16.3	0.025
STS-PROM		10.0±7.8	12.0±8.7	0.016
Surgical risk category (STS-PROM)	STS<=3.0	81 (11.8%)	14 (13.2%)	0.029
	STS=3.1-8.0	307 (44.7%)	33 (31.1%)	
	STS>8.0	299 (43.5%)	59 (55.7%)	
NYHA class	NYHA 1/2	135 (19.7%)	12 (11.3%)	0.044
	NYHA 3/4	552 (80.3%)	94 (88.7%)	
Aortic valve area (cm^2)		0.66±0.18	0.70±0.27	0.445
Trans-aortic peak PG (mmHg)		82.1±24.3	75.6±26.2	0.046
Trans-aortic mean PG (mmHg)		49.9±15.6	45.5±17.0	0.037
LVEF (%)		59.0±14.9	57.1±15.3	0.117
Impaired LVEF (<50%)		161 (23.7%)	31 (29.5%)	0.222
Low-flow low-gradient AS		74 (12.2%)	5 (7.0%)	0.244
LV diastolic diameter (mm)		50.5±9.1	52.8±11.4	0.004
Interventricular septal thickness (mm)		12.2±2.1	12.1±2.0	0.446
LV posterior wall thickness (mm)		11.6±2.0	11.5±1.7	0.675
Relative wall thickness		0.50±0.34	0.49±0.35	0.021
LV mass index (g/m^2)		139.7±42.5	155.1±46.7	<0.001
Moderate-severe mitral regurgitation		98 (16.3%)	18 (19.6%)	0.454
Pulmonary hypertension		147 (21.4%)	28 (26.4%)	0.258
Atrial fibrillation		92 (14.9%)	12 (12.1%)	0.540
Pervious PPM		63 (9.3%)	5 (4.8%)	0.188
Coronary artery disease		396 (57.6%)	66 (62.3%)	0.398
Previous myocardial infarction		100 (14.6%)	18 (17.0%)	0.557
Previous CABG		122 (17.8%)	29 (27.4%)	0.024
Previous PCI		226 (32.9%)	39 (36.8%)	0.440
Peripheral arterial disease		118 (17.2%)	17 (16.0%)	0.890
Previous carotid artery disease		104 (15.1%)	19 (17.9%)	0.471
Previous stroke		54 (7.9%)	10 (9.4%)	0.566
Porcelain aorta		53 (7.7%)	8 (7.5%)	1.000
Aortic aneurysm		37 (5.4%)	11 (10.4%)	0.076
Diabetes mellitus		221 (32.2%)	31 (29.2%)	0.577
Dyslipidemia		346 (50.4%)	47 (44.3%)	0.253
Systemic hypertension		523 (76.1%)	78 (73.6%)	0.545

Table 1. Baseline and procedural characteristics according to the type of aortic valve disease: (*continued*)

		Aortic valve disease at baseline		
		Pure/predominant AS (n=687)	Mixed aortic valve disease (n=106)	*p*
Chronic obstructive pulmonary disease		125 (18.2%)	21 (19.8%)	0.687
Creatinine clearance (ml/min)		48.8±21.7	44.5±22.3	0.022
Severe chronic kidney disease*		105 (15.7%)	26 (25.0%)	0.024
Hemoglobin (g %)		11.8±1.8	11.3±1.7	0.002
Previous valvuloplasty		39 (5.7%)	11 (10.4%)	0.082
Previous SAVR		9 (1.3%)	23 (21.7%)	<0.001
MSCT performed		449 (65.4%)	57 (53.8%)	0.023
Valve annulus diameter (mm)		24.7±4.3	24.4±4.3	0.431
Cover index (%)		12.2±13.5	10.1±14.9	0.152
Conscious sedation		63 (9.2%)	10 (9.4%)	0.858
TEE-guided procedure		561 (81.7%)	83 (78.3%)	0.423
Trans-femoral access		635 (92.4%)	102 (96.2%)	0.219
Device type	CoreValve	499 (72.6%)	76 (71.7%)	0.778
	Sapien-XT	168 (24.5%)	28 (26.4%)	
	Inovare	20 (2.9%)	2 (1.9%)	
Device size		27.3±2.3	26.9±2.6	0.119
Predilation		349 (50.8%)	41 (38.7%)	0.022
Postdilation		249 (36.2%)	44 (41.5%)	0.331

Variables in **bold** are included in the generation of the propensity score.

* Defined as a creatinine clearance <30 ml/min.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; EuroSCORE, logistic European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; MSCT, multi-slice computed tomography; NYHA, New-York Heart Association; PCI, percutaneous coronary intervention; PG, pressure gradient; PPM, permanent pacemaker; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TEE, trans-esophageal echocardiography.

RESULTS

Patient characteristics

Out of 793 consecutive patients undergoing TAVI, 106 (13.4%) had MAVD. Baseline and procedural characteristics of patients with MAVD vs. PAS are summarized in **Table 1**. Compared to patients with PAS, those with MAVD, although younger, were at higher surgical risk and had a higher New York Heart Association (NYHA) class. MAVD patients also had a lower trans-aortic pressure gradient (PG), and a larger left ventricular (LV) diastolic diameter and mass. They were also more likely to have history of coronary artery bypass grafting (CABG) or surgical aortic valve replacement (SAVR) and to have lower creatinine clearance and hemoglobin.

MAVD and procedural outcomes (Table 2)

Device failure (VARC-2 definition) was significantly more frequent in patients with MAVD than in patients with PAS in the overall patient population (26.4% vs. 10.0%, p<0.001) as well as after excluding patients with previous SAVR (22.9% vs. 9.7%, p=0.001). After propensity-score adjustment, the risk of device failure remained significantly higher in MAVD patients (OR: 2.14 [1.07-4.27], p=0.032).

In univariable analysis, the two components of prosthetic valve performance were worse in MAVD than in PAS; moderate-severe PVR (15.7% vs. 3.6%, p=0.003; OR: 2.89 [1.49-5.61], p=0.002) and residual trans-aortic mean PG ≥20 mmHg (15.4% vs. 3.6%, p<0.001; OR: 4.81 [2.22-10.43], p<0.001). After propensity-score adjustment, MAVD was no longer significantly associated with residual PG ≥20 mmHg (OR: 0.48 [0.06-3.97], p=0.49).

Table 2. Procedural and 30-day outcomes according to the type of aortic valve disease:

	Aortic valve disease at baseline		*p*
	Pure/predominant AS	***Mixed aortic valve disease***	
Device failure	69 (10.0%)	28 (26.4%)	<0.001
Moderate-severe PVR at discharge	35 (5.7%)	14 (14.9%)	0.003
Trans-aortic mean PG ≥20 mmHg	18 (3.6%)	12 (15.4%)	<0.001
Trans-aortic mean PG at discharge (mmHg)	9.5±5.5	12.9±9.0	<0.001
Periprocedural reduction (%) in mean PG	80.1±12.8%	67.4±40.6%	0.006
Impaired LVEF at discharge	109 (18.7%)	25 (27.8%)	0.048
LVEF at discharge (%)	61.3±13.6	55.8±13.1	<0.001
Moderate-severe MR at discharge	98 (16.3%)	18 (19.6%)	0.454
New-LBBB (within 30 day)	226 (35.6%)	36 (38.3%)	0.646
New-PPM (within 30 day)	128 (18.6%)	14 (13.2%)	0.22
Thirty-day all-cause death	62 (9.0%)	10 (9.4%)	0.857
Thirty-day all-stroke	25 (3.6%)	3 (2.8%)	1.000
Thirty-day major or life-threatening bleeding	101 (14.7%)	14 (13.2%)	0.768
Thirty-day acute kidney injury	122 (17.8%)	15 (14.2%)	0.409
Thirty-day severe acute kidney injury	26 (3.8%)	7 (6.6%)	0.189
Thirty-day major vascular complications	59 (8.6%)	9 (8.5%)	1.000

Abbreviations: LBBB, left bundle branch block; MR, mitral regurgitation; PVR, prosthetic aortic valve regurgitation. Other abbreviations are as in table 1.

On the other hand, MAVD remained significantly associated with moderate-severe PVR after excluding patients with previous SAVR (15.1% vs. 5.8%, p=0.011) as well as after propensity-score adjustment (OR: 2.824 [1.294-6.163], p=0.009) and multivariable adjustment (OR: 3.178 [1.060-9.530], p=0.039) (**Table 3**). In addition to MAVD, cover

Table 3. Regression analysis [odds ratio-OR (95% confidence limits)] of the association between mixed aortic valve disease at baseline and moderate-severe prosthetic aortic valve regurgitation:

Univariable analysis	2.890 (1.490-5.605), p=0.002
Multivariable analysis*	3.178 [1.060-9.530], p=0.039
Propensity-score adjusted analysis	2.824 (1.294-6.163), p=0.009

*****Included –in addition to mixed aortic valve disease - previous coronary artery bypass grafting or surgical aortic valve replacement, device type, cover index, access for implantation, transesophageal echocardiographic-guidance, and predilatation as covariates (details displayed in table 4).

Table 4. Multivariable regression analysis [odds ratio-OR (95% confidence limits)] of the predictors of moderate-severe prosthetic aortic valve regurgitation (significant covariates are written in bold.):

	Sig.	OR	95% C.I.	
			Lower	Upper
MAVD (vs. PAS)	**0.039**	**3.178**	1.060	9.530
Previous SAVR	0.709	0.644	0.064	6.479
Previous CABG	0.408	1.559	0.544	4.471
TEE guidance	0.846	0.898	0.305	2.650
Transfemoral access	0.456	2.342	0.249	22.001
Predilatation	0.292	1.632	0.656	4.063
Cover index	**<0.001**	**0.935***	0.902	0.970
Self-expanding THV	**0.002**	**8.435**	2.234	31.851

Abbreviations: CABG, coronary artery bypass grafting; MAVD, mixed aortic valve disease; PAS, pure/predominant aortic stenosis; SAVR, surgical aortic valve replacement; TEE, trans-esophageal echocardiography; THV, transcatheter heart valve.
*OR per 1% increment in oversizing

index (OR: 0.935 [0.902-0.970] per 1% increment in oversizing, p<0.001) and the implantation of a self-expanding device (OR: 8.435 [2.234-31.851], p=0.002) were associated with moderate-severe PVR in multivariable regression analysis (**Table 4**).

The incidence of all other procedural/30-day outcomes were similar between both groups, with the exception of LV ejection fraction (LVEF) which was significantly lower at discharge in MAVD patients than in PAS patients (55.8±13.1% vs. 61.3±13.6, p<0.001). Similarly, impaired LVEF (<50%) at discharge was more common in MAVD patients (28% vs. 19%, p=0.048) with the odds ratio being significant in univariable analysis (OR: 1.68 [1.01-2.78,], p=0.045) but not in propensity-score adjusted analysis (OR: 1.15 [0.58-2.28,], p=0.695).

One-year outcomes

At one-year, the overall mortality rate was 19.3% and was very much the same in the two study groups (MAVD: 19.8% and PAS: 19.2%, log-rank p=0.99) (**Figure 1**). Cardiac deaths constituted 70.5% of all mortalities, with their incidence being similar in both

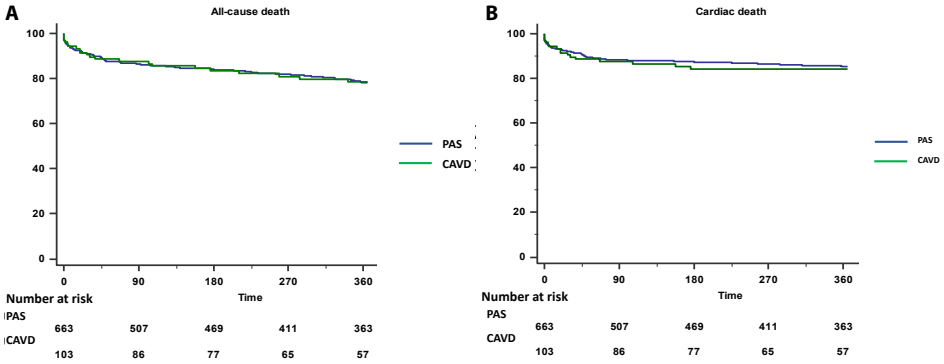

Figure 1. Kaplan-Meier survival curves for one-year all-cause (A) and cardiac (B) mortality after TAVI according to the type of aortic valve disease (pure/predominant aortic stenosis-PAS vs. mixed aortic valve disease-MAVD).

groups (MAVD: 15.1% and PAS: 13.4%, log-rank p=0.72). At the latest follow-up (median [IQR], 375 [79-742] days post-TAVI), dyspnea resolved completely (NYHA I) in 60% and 66%, was mild (NYHA II) in 30% and 26%, and was moderate-severe (NYHA III-IV) in 10% and 8% of MAVD and PAS patients, respectively (p=0.49). Accordingly, 76.4% of MAVD patients and 75.8% of PAS patients were alive beyond one-year in NYHA functional class I or II.

Impact of PVR on clinical outcomes

Overall, moderate-severe PVR developed in 49 (6.9%) of patients with available echocardiographic data at discharge (n=707) and was associated with a higher one-year all-cause mortality (28.6%) compared to patients with mid-or-less PVR (13.8%, log-rank p=0.005; HR: 2.20, 95% CI: 1.25-3.86). As a higher mortality was expected to arise from the more severe PVR in the MAVD group, the impact of PVR on outcomes was studied in each of the study groups (MAVD vs. PAS) separately. The increased risk of one-year mortality in patients with moderate-severe PVR vs. mid-or-less PVR was even more pronounced in the PAS group (31.4% vs. 13.8%; log-rank p=0.002; HR: 2.64, 95% CI: 1.40-4.96, p=0.004). On the other hand, in the MAVD group, moderate-severe PVR was not associated with a significant increase in one-year mortality (21.4% vs. 13.8%; log-rank p=0.629) (**Figure 2**).

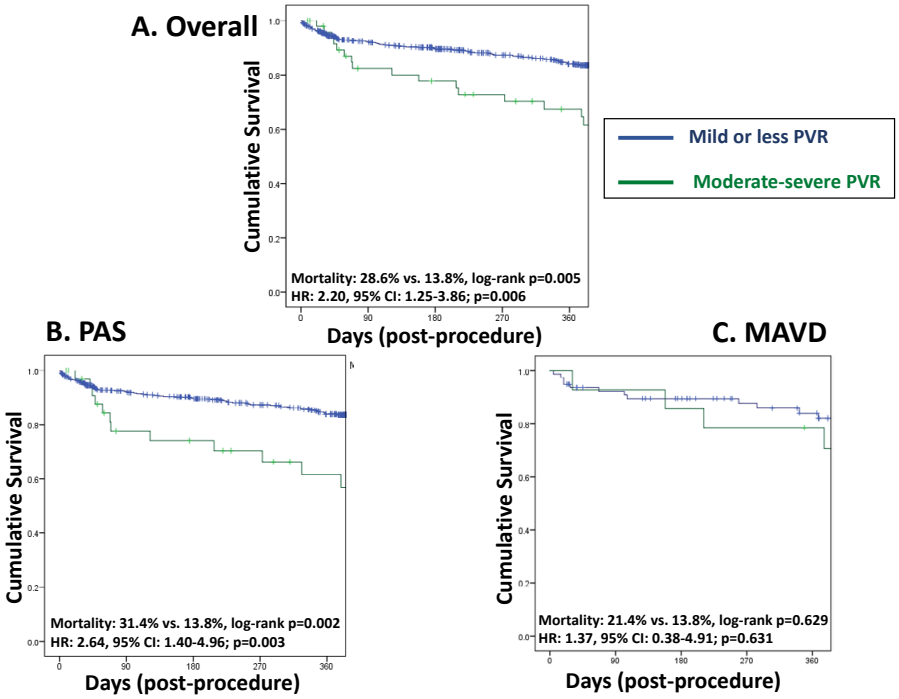

Figure 2. Kaplan-Meier survival curves for all-cause mortality after TAVI according to the severity of prosthetic valve regurgitation (PVR) in the entire patient population (A), in patients with pure/predominant aortic stenosis-PAS (B), and in patients with mixed aortic valve disease-MAVD (C).

DISCUSSION

The main findings of the present study are that: 1) MAVD is common among TAVI referrals in real world practice and is typically associated with more severe symptoms and adverse cardiac remodeling and a higher operative risk, and 2) The incidence of PVR is significantly higher in patients with MAVD but does not impair the long-term outcomes of those patients, possibly due to a protective preconditioning of the LV.

Mixed stenosis and regurgitation is common among patients undergoing isolated SAVR, representing 19.3% of patients in the STS database from 2002 to 2010 (n=141,905)[5]. Among patients undergoing TAVI, MAVD was reported in 11-17% of patients in all-comers multicenter registries[9,15-17]. In the present real world multicenter registry, 13% of TAVI patients had MAVD.

MAVD as a peculiar disease entity

Anatomically, a direct association between AR and aortic valve cusp calcification and bicuspidity has been reported by population-based studies[18]. Vianello et al[19] compared

the aortic valve histologic structure in patients with degenerative aortic valve disease presenting with pure AS and patients presenting with combined AS and AR. Overall, pure AS was characterized by real 'calcium replacement" of the valvular fibrous tissue, calcification of the lipid component, and bone-endochondral metaplasia, while MAVD was characterized by a higher percentage of tissue fibrosis. The authors suggested the consideration of MAVD as a separate nosological entity within the degenerative aortic valve disease spectrum, rather than considering AR as a comorbidity with AS. Those structural differences might account for a differential interaction between the device and the landing zone, and for the differential rate of PVR seen in the present study.

Hemodynamically, the combination of volume and pressure overload poses a twofold negative impact on LV mechanics and function[20,21]. Popescu et al[22] studied 181 patients with severe AS, 71 (39%) of whom also had significant AR (i.e. MAVD). Patients with MAVD were younger, more symptomatic, and had higher LV mass, pulmonary capillary wedge pressure, LV end-diastolic pressure, and pulmonary artery pressure and a lower LVEF than those with isolated AS. There is evidence that severe AS patients managed conservatively who have concomitant significant AR have a significantly lower event-free survival than patients with pure AS[23] and that even those with only moderate AS and AR are exposed to a higher rate of adverse events than those with severe pure AS24. Therefore, the combination of severe AS with moderate-severe AR represents a unique anatomical (on the valvular complex level) and functional entity.

In the present study, not only MAVD patients presented with more severe LV hypertrophy and functional impairment at baseline, but also they had higher overall estimates of operative risk (higher EuroSCORE and STS-PROM). Therefore, and also due to the aforementioned studies linking MAVD to worse outcome, an earlier intervention should be considered and, because of the high surgical risk, TAVI can be the preferred option. In our study, and earlier studies[22,24], patients with MAVD are younger than PAS patients at the time when valve implantation is indicated. Accordingly, MAVD represents a disease entity that will be increasingly encountered as TAVI indications are extended to younger patients.

TAVI outcomes in MAVD

We found that acute TAVI outcomes in MAVD patients were generally favorable, with the exception of an unequivocally higher risk of PVR which remained significant after accounting for patient-, procedure-, and device-related confounders. A similar association with the risk of PVR and the need for balloon post-dilation was reported in AS patients undergoing TAVI who also had >mild AR[9,17] or any degree of AR[15]. In the latter study, however, the group of patients with MAVD included a large number of patients with mild AR at baseline, a degree of regurgitation that typically does not bear significant hemodynamic consequences that make it hemodynamically distinct from PAS. Such a

relation between baseline AR and the risk of PVR is important to consider in order to understand, at least partially, the marked variability in the incidence of PVR among different TAVI studies, even among those involving the same device[25,26]. This inconsistency, which can be largely attributed to the limitations of the echocardiographic assessment of PVR[27], can also be partially explained by the inter-study variability in the severity of AR considered acceptable for inclusion.

In the present study, MAVD patients did very much the same in terms of mortality and symptomatic status up to one-year post-TAVI in spite of an increased risk at baseline and an increased rate of PVR after the procedure. It turns out, as has been confirmed in subgroup survival analysis, that the higher risk of PVR is compensated-for; possibly by the LV preconditioning[9,28]. Maneuvers that can be undertaken to reduce the severity of PVR have their own risks[29]. Therefore, identification of patient subgroups with poor or good tolerance to PVR is clinically-relevant[9].

It has been reported in patients with AR (as compared to AS patients) undergoing SAVR, that the post-operative decline of LV end-diastolic volume occurs faster than the normalization of LV mass, resulting in concentric remodeling, impaired LV relaxation, and to rise of diastolic filling pressure[30]. This gives another explanation of the well-toleration of PVR in those patients, who seem to "benefit" from some degree of regurgitation that probably prevents this concentric remodeling.

These findings collectively suggest that patients with MAVD gain an equivalent benefit from TAVI as do patients with PAS. Considering the worse symptomatic status and the poorer survival in patients with MAVD if left untreated, it turns out that this equivalent absolute outcome in fact reflects a higher relative benefit.

Limitations

The assessment of AR severity is challenging in the setting of severe AS. However, the classification of AR into mid-or-less vs. moderate-to-severe is less challenging than more granular classifications.

Propensity score adjustment accounts only for the "observed" covariates included in the propensity score construction. We adopted the following actions to limit such a limitation of the propensity score: 1) the model used for propensity score construction was inclusive of, not only covariates different between the two groups, but also other covariate relevant to the endpoints of interest, 2) the score was tested for its discriminative accuracy (revealed to be good as evidenced by a substantial c statistic, and 3) the score was used in conjunction with further model-based adjustment using multivariable regression analysis, after exclusion of significant multicollinearity between the propensity score and its derivative covariates.

Significant AR in conjunction with AS is frequent in bicuspid aortic valve pathology. As data are derived from a real-world registry, the challenges in identifying and confirm-

ing a bicuspid pathology on echocardiographic studies existed. Obviously it cannot be excluded that some of the extensively calcified valves have an underlying masked bicuspid etiology[31].

The present study did not include lower risk patients or those treated with the next generation transcatheter aortic valves and extending the findings to those patients should be cautious. However, correlates of MAVD were shown in our analysis to be independent of patient-, procedure-, and device-related characteristics.

CONCLUSION

A significant proportion of AS patients referred for TAVI in a real-world registry has moderate-severe AR and present with an overall higher cardiac adverse remodeling and operative risk. The incidence of PVR is significantly higher in patients with MAVD than in patients with PAS, but does not significantly impact on mortality. Overall, the outcome of patients with MAVD is comparable to that of patients with PAS in the acute and mid-term phases.

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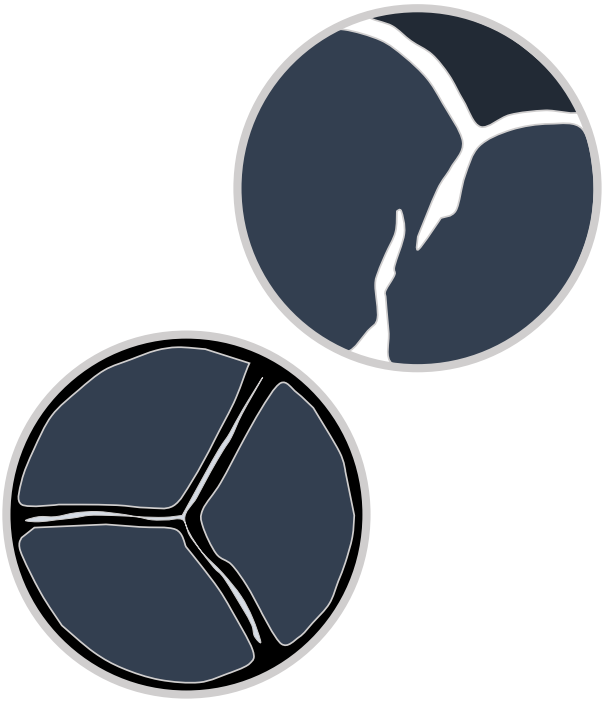
Section A.2

Assessment of paravalvular leakage after TAVI



Chapter 4

Adjudicating paravalvular leaks of transcatheter aortic valves: a critical appraisal

Abdelghani M, Soliman OII, Schultz C, Vahanian A, and Serruys PW

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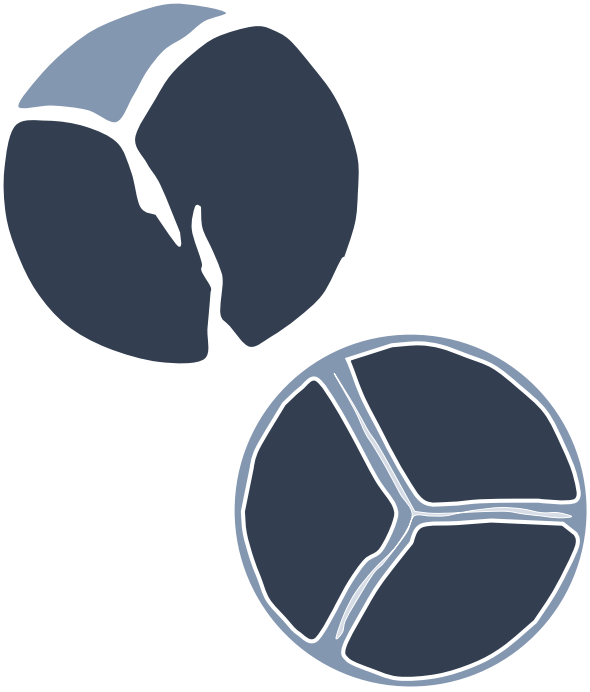

ABSTRACT

Paravalvular leakage (PVL) is an important complication of transcatheter aortic valve implantation (TAVI). It contributed to the erosion of the clinical benefits of TAVI and confidence of its adoption as a default therapy in low surgical-risk patients. Newer TAVI technologies are provided with effective paravalvular sealing as well as retrieval/reposition mechanisms that are believed to considerably lower the risk of PVL. Meanwhile, developments in timely detection and accurate quantitation of PVL remain lagging behind those technological advances. The Valve Academic Research Consortium-standardized criteria of PVL assessment are based on echocardiography and are, according to experts' opinion, not adequately validated. Peri-procedural diagnosis, based on angiographic, haemodynamic, and/or echocardiographic methods, is so far without standardization of acquisition or interpretation. The aim of this report is to review the strengths and limitations of the current technologies used for PVL adjudication. Understanding this strengths/limitations ratio is important to define an appropriate scheme for detection and quantitation of PVLs both in clinical trials and in routine clinical practice.

INTRODUCTION

The indications, approaches, and technologies of transcatheter aortic valve implantation (TAVI) are expanding. As the use of TAVI dramatically increases, mitigating the major weaknesses of the procedure becomes an urgent need. Among those weaknesses, paravalvular leakage (PVL) is one shortcoming that contributed considerably to the erosion of clinical benefits of TAVI as it adversely affects mortality, morbidity, and reverse cardiac remodelling.[1]

Paravalvular leakage is, however, a moving target. On one hand, huge advances have been made, principally in the area of improved valve design and size range, but most importantly in adequate annular sizing. On the other hand, the 'creep' of this technology to lower-risk younger patients, those with less valve calcium (believed to facilitate anchorage), and use in patients with bicuspid and/or predominantly regurgitant aortic valves is expected to increase the potential for PVL. In addition, there is a massive trend towards awake TAVI procedures,[2,3] limiting the option of using transesophageal echocardiography (TEE) to assess PVL in the peri-procedural stage.

Adequate adjudication of PVL has important implications on device design/iteration appraisal as well as therapeutic interventions to seal the leak:

- Limitations of the technologies available for PVL adjudication contributed to the inconsistency of data on PVL incidence, fate, and relation to outcomes. The reported rates of PVL in different trials and registries ranged from 40 to 67% for trivial–mild and from 7 to 20% for moderate–severe aortic regurgitation (AR).[4] The fate of AR has been described as 'improving',[5-7] 'deteriorating',[8,9] 'stable',[10,11] and 'variable'[6] in different reports. Furthermore, the reported association with clinical outcomes ranged from 'no relation'[5] to 'a strong relation' of even mild AR.[12]
- Many of the newer devices claim 'elimination' of PVL. Meanwhile, the uncertainty of how to define PVL severity remains unresolved. In fact, it is critical to agree on how to define and grade PVL before such a conclusion can be made.
- A critical downside of inadequate characterization of PVL severity is losing the chance to provide timely corrective measures in the cath lab. Relying on a single modality or parameter without appreciating its limitations will often mislead the clinician's decision-making. Moreover, the decision to re-intervene to seal the leak (percutaneously or surgically) should be based on solid quantitation of PVL.

The aim of this report is to review the relative strengths and weaknesses of the technologies available for PVL assessment. Good understanding of these limitations should help clinicians to tailor the diagnostic scheme for each clinical situation, help clinical trialists to better define imaging endpoints in TAVI trials, and urge researchers to improve the utility of available modalities and to propose novel alternatives.

ANGIOGRAPHY

Aortography has long been the 'reference standard' against which other methods of quantification of AR were compared[13] and is the initial screening tool in most laboratories. It might have some advantages over echocardiography for quantification of PVL, as it weighs the total amount of contrast leaking to the left ventricle (LV), which represents the sum of all regurgitant jets irrespective of their number, location, and direction.[14] Moreover, a general trend towards performing TAVI without general anaesthesia (GA) is rapidly spreading,[2,3] further emphasizing the reliance on angiography for intra-procedural diagnosis of PVL. However, angiographic grading is semi-quantitative and subjective and cannot differentiate transvalvular from paravalvular regurgitation. In addition, expense, use of contrast, exposure to irradiation, and invasive nature of the technique make it relatively unsafe and impractical for serial examinations.

Limited accuracy

In 1964, Sellers et al. reported their inveterate method of AR grading depending on the intensity and duration of LV opacification after contrast injection into aortic root.[15] The method was validated against operative findings of valve pathology as assessed by the surgeon.

Despite a reasonable agreement with the subjective pathological findings, further attempts to prove the accuracy of Sellers' grading were largely disappointing. The regurgitation volume (RV) and fraction (RF) measured by magnetic flowmeter[16] and by cardiac catheterization (using Fick's method and left ventriculography)[17-19] showed a marked overlap between different Sellers' grades. It was also recently shown that there is only a moderate correlation ($r = 0.42$) with a significant overlap between angiographic (Sellers') classes and cardiac magnetic resonance (CMR)-derived RF[20] (Figure 1). Moreover, 82% of patients with moderate–severe AR (grade 3–4/4) as determined by CMR-RF were classified by visual angiographic grading as mild (grade 1–2/4),[20] suggesting a tendency of angiography to underestimate AR severity compared with CMR.

Contrast-related risks

Acute kidney injury (AKI) is a common complication of TAVI occurring in up to 30% of cases and is independently associated with increased mortality. Although the mechanism of AKI following TAVI is multifactorial, the exposure to iodinated contrast and its amount are two important predictors of AKI.[21-26] A significant proportion (12–62%, according to the definition used[6,27-30]) of patients undergoing TAVI have some degree of preexisting renal dysfunction. Those patients are at an even increased risk for AKI if exposed to angiographic contrast.[26]

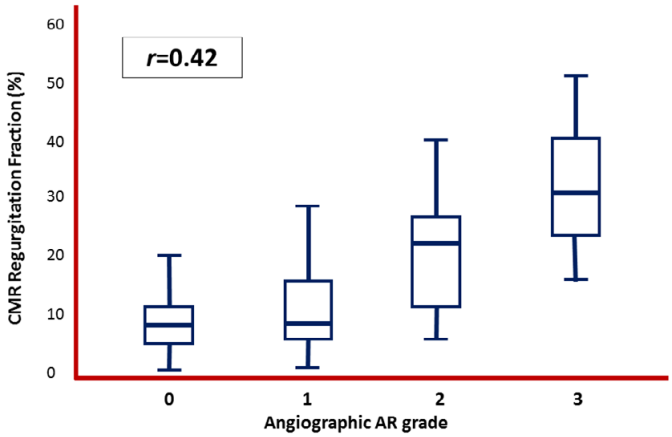

Figure 1. Box (interquartile range) and whiskers (95% confidence interval) plot showing a modest correlation and a significant overlap between angiographic (Sellers') classes and cardiac magnetic resonance-derived aortic regurgitation fraction. The overlap is maximum in the none–trace–mild range than in the more severe grades. Modified from Frick et al.,[20] with permission from Europa Digital & Publishing. CMR, cardiac magnetic resonance.

Limited reproducibility

Reproducibility of the visual aortographic AR grading is only moderate with inter- and intra-observer kappa values ranging from 0.45 to 0.68.[14,20] In the randomized CHOICE trial, the inter-observer kappa correlation coefficient for the diagnosis of more-than-mild AR by the angiographic core laboratory was 0.81,[31] denoting that reproducibility could be improved when acquisition and analysis are well-controlled.

Limitations in accuracy and reproducibility of visually graded aortography are partly to blame on the absence of standardization of image acquisition and agreed image quality criteria. This lack of standardization is a stark contrast to the majority of imaging modalities used in cardiology and is ironic considering that the use of aortography preceded other imaging modalities by decades.

Video-densitometric angiography

Several attempts have been made to make AR assessment by aortography more objective and quantitative.[32-36] Semi-automated weighing of pixel density in the LV [as a region of interest (ROI)] relative to that in the aorta (as a reference region) is feasible through video-densitometric (VD) angiography. Contrast time–density curves could be generated and the area under contrast time–density curves (AUC) could be computed.[14,36,37] Regurgitation fraction could be estimated using the AUC of the LV compared with aorta (relative AUC) and has been validated in an experimental study.[36] The regression line with RF measured by magnetic flowmeter approximated unity with a slope of 0.98.[36]

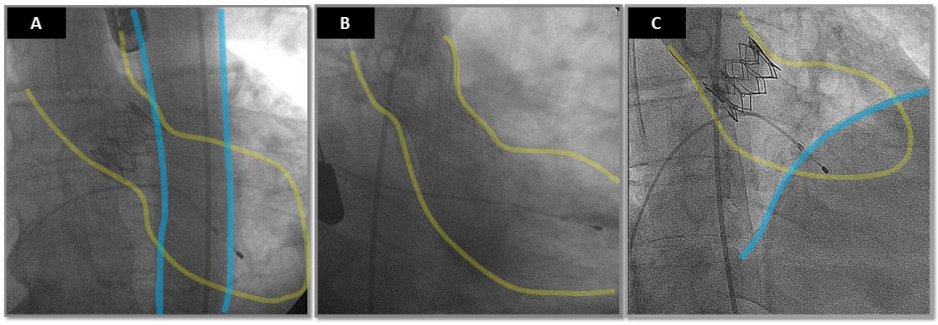

Figure 2. Post-transcatheter aortic valve implantation aortography for quantitation of aortic regurgitation. (A) The contrast-filled descending aorta overlaps the left ventricle interfering with proper assessment of contrast leak. (B) The left ventricular apex is not included in the view. (C) The diaphragm overlaps the left ventricle.

Recently, relative AUC and quantitative regurgitation assessment index have been described as feasible and reproducible markers of AR severity after TAVI.[14] Both parameters correlated well with Sellers' grading and improved inter-rater agreement. Another advantage of these parameters over the categorical Sellers' grades is their continuous nature.[14,36] Video-densitometric methods could be applied to the entire ventricle or to any LV segment separately. Interrogation of the entire LV is, however, subject to several limitations, including the inability to visualize the apex and overlap by background structures such as the contrast-filled descending aorta[14] (Figure 2). Furthermore, penetration of AR jet towards LV apex is influenced by eccentricity of the jet, LV compliance, and high velocity jets from concomitant mitral stenosis.[38] Left ventricular outflow tract (LVOT)-AR is another method of VD angiography that confines the ROI to the sub-aortic segment of the LV (Figure 3). Limitations, such as inability to visualize the apex or super-

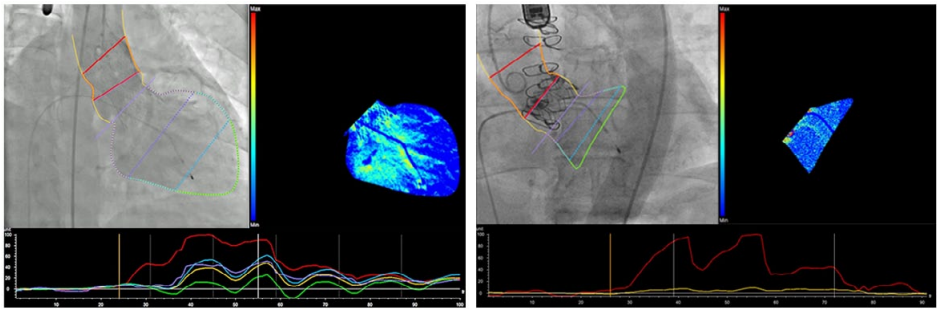

Figure 3. Two video-densitometric methods of aortic regurgitation assessment. On the left, the entire left ventricle is interrogated as a region of interest, while the aortic root serves as the reference region (between the two red lines). On the right, the sub-aortic segment of the ventricle is isolated as a region of interest (left ventricular outflow tract-aortic regurgitation). In both methods, time–density curves can be generated (the lower panels) along with the colour-weighted contrast time–density maps (the upper right panels).

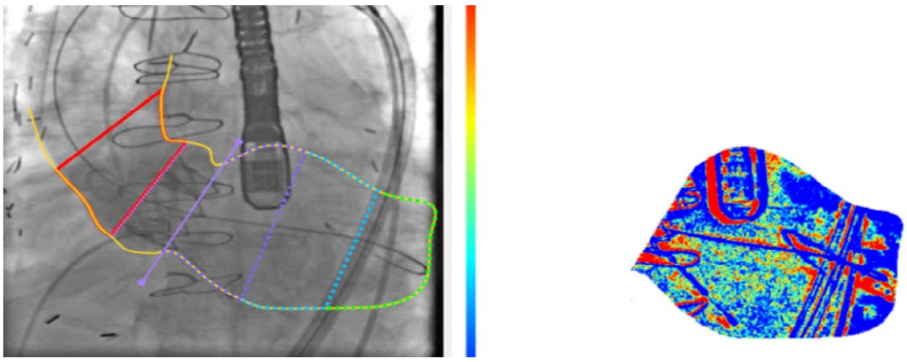

Figure 4. A 'forest' of dense objects (surgical wires, guidewires, catheters, pacemaker lead, and transesophageal echocardiography probe) overprojecting on the reference region and the region of interest as shown in the density colour map (the right panel).

imposition of the descending aorta, could be avoided, and feasibility of analysis could, thus, be improved with this method. Prognostic implications of this parameter has been demonstrated at intermediate and long terms.[39]

Video-densitometric angiography is, however, not without limitations. A forest of dense objects (guidewires, catheters, pacemaker lead, surgical wires, TEE probe, and electrocardiogram electrodes) is a frequent scene during TAVI procedure (Figure 4). These dense objects might confound automatic density weighing and make VD an imprecise method. Video-densitometric angiography is also sensitive to patient/table motion. Schultz et al. checked the feasibility of AR assessment by VD in 285 retrospectively collected post-TAVI aortograms. The majority of aortograms were not appropriate for accurate assessment. Among 32 prospectively collected aortograms (after the adoption of adequate acquisition), only 22 (69%) were yet appropriate for accurate analysis (mostly due to breathing motion or over-projection of the descending aorta on the LV).[14] Standardization of image acquisition and quality is likely to solve these issues. Among the parameters that need standardization are the volume of contrast (that provides adequate opacification at the least contrast-related hazards), the catheter position (that effectively delivers contrast without artificially disrupting the valve competence), contrast injection rate and timing (that interferes least with the physiological flow), and the fluoroscopic projection (with the least over-projection of background structures). A straightforward rule to define a patient-specific overlap-free fluoroscopic projection has recently been developed and is awaited to overcome one of the main remaining technical hurdles to a standardized high-quality aortography (G.Y. Justin Teng and C. Schultz, unpublished data).

HEMODYNAMIC PARAMETERS

Given their availability in the cath lab and potential prognostic value, haemodynamic indices can be an integral part of the peri-procedural assessment of PVL, especially when its severity by angiography/echocardiography is intermediate.40 Even the outcome of patients at either side of the classic none–mild and moderate–severe PVL echocardiographic spectrum can be further stratified by haemodynamic indices.[41] Several haemodynamic indices have been increasingly described but tended to be used as prognostic rather than diagnostic tools. This is primarily due to their inability to differentiate transvalvular from paravalvular regurgitation and due to being used as binary qualitative rather than quantitative markers. Furthermore, these indices are likely to also incorporate other markers of adverse prognosis that are not related to the degree of PVL per se (e.g. impaired LV systolic or diastolic function, aortic stiffness, and/or pathological vasodilatation due to a systemic inflammatory response).

Aortic regurgitation index

The end-diastolic pressure gradient across aortic valve (diastolic arterial blood pressure 2 left ventricular end-diastolic pressure) is a simple index of AR severity. The adjustment of this gradient to the respective systolic blood pressure gives a dimensionless AR index (ARI) that could predict clinical outcomes.[41,42] An ARI of <25 was independently associated with a 2.9-fold increase in 1 year mortality.[41] However, the frequency of an ARI <25 among TAVI patients is very high, ranging from 34 to 57%,[40-42] and an ARI of <25 often coexists with no/trivial AR, particularly in the presence of relative bradycardia (Figure 5).[40]

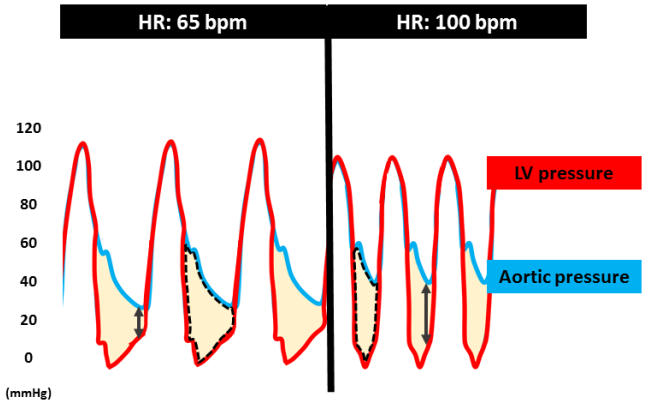

Figure 5. Impact of heart rate variation on diastolic pressure gradient across aortic valve. The instantaneous pressure difference (aortic regurgitation index) is markedly influenced by heart rate changes and for the same degree of aortic regurgitation, a significantly different aortic regurgitation index (double-headed black arrows) can be found due to different heart rates. The time-integrated aortic regurgitation index (traced yellow areas) accounts for the influence of heart rate changes.

While the difference between ARI value before and after the procedure could reflect AR severity, a single ARI measurement might rather reflect a pre-existing elevation of LV end-diastolic pressure. An underlying LV diastolic dysfunction, a well-known poor prognostic marker,[43] can reduce ARI regardless of AR severity. At baseline, patients with lower ARI tended to have more pulmonary hypertension, lower ejection fraction (EF), and more severe mitral regurgitation,[41,44] conditions that can raise LV diastolic pressure and impact patients' outcomes as well.

Peri-procedural myocardial ischaemia is another confounder that may further complicate the interpretation of haemodynamic indices just after valve implantation. Transcatheter aortic valve implantation is systematically associated with myocardial ischaemia even in the absence of overt coronary obstruction or embolism.[45] It has been shown that even transient ischaemic injury can lead to a prolonged rise in myocardial stiffness and LV diastolic pressure.[46]

Other haemodynamic indices

The modified, time-integrated ARI (Figure 5) had a better sensitivity and specificity for AR severity compared with the instantaneous ARI.[47] The heart rate-adjusted diastolic delta (the end-diastolic transvalvular pressure gradient/heart rate × 80) is another haemodynamic index that accounts for the effect of heart rate on pressure gradient and has a greater discriminatory value for 1-year mortality than ARI (Figure 6).[40] The prognostic value of the heart rate-adjusted diastolic delta was further supported by the better prediction of percentage increase in LV dimensions and serum natriuretic peptide levels.[40] All of the aforementioned haemodynamic methods are readily feasible, quick

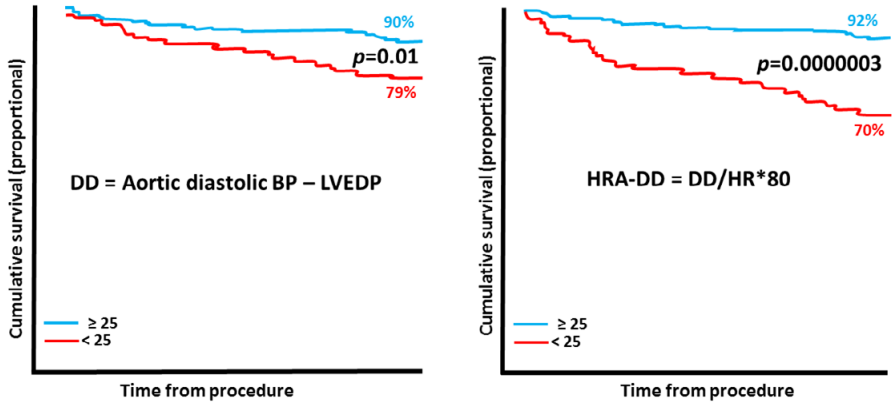

Figure 6. Kaplan–Meier survival curves according to immediate post-transcatheter aortic valve implantation diastolic delta (DD) and the heart rate-adjusted diastolic delta (HRA-DD). Heart rate (HR) adjustment improves the stratification of survival by the gradient across the aortic valve. Reproduced with modification from Jilaihawi et al.,[40] with permission from Europa Digital & Publishing. BP, blood pressure; LVEDP, left ventricular end-diastolic pressure.

with robust reproducibility, but are calculated with the catheter passing through the prosthetic valve disrupting its competence. The measurement of LV diastolic pressure at the beginning of the procedure can serve as the denominator for ARI calculation, clearly at the expense of losing the advantage of simultaneous measurement with aortic pressure. In spite of doubtful practicality, the use of a micromanometer pressure guidewire instead of a catheter to measure LV diastolic pressure is an option[48,49] and should induce less AR. However, some types of surgical prosthetic aortic valves became incompetent when crossed by a pressure wire in an ex vivo study.[50] The effect of these micro wires on the competence of transcatheter aortic valves is not known.

The relative amplitude index is another haemodynamic parameter that compares the ratio of aortic pulse pressure to systolic pressure before and after TAVI. It was shown to define the haemodynamic significance of AR and to predict mid-term mortality. Obviously, it does not need a catheter passing through the valve and can be measured non-invasively allowing for repeat follow-up measurements.[51]

ECHOCARDIOGRAPHY

Echocardiography is a readily available, safe, and convenient tool that provides a real-time information on the severity and the mechanism of AR and is thus the preferred method for post-TAVI surveillance. Since the introduction of Doppler echocardiography to clinical practice, tens of parameters have been proposed to assess AR severity, and the majority were validated against aortography as a reference standard. This report will, however, give more attention to the key parameters adopted by the Valve Academic Research Consortium (VARC)[52] for the assessment of PVL, the most common form of AR after TAVI.

Clinical utility of the currently proposed echocardiographic criteria of post-transcatheter aortic valve implantation aortic regurgitation

For a diagnostic test to be clinically useful, it needs to be feasible, precise (i.e. reproducible on rerating), and accurate (i.e. representative of the true disease severity). Data on how far the VARC echocardiographic criteria comply with these three conditions are scarce. On the basis of the so far available data, a multi-parametric approach that combines multiple indices derived from multiple windows is preferred over reliance on a single criterion. Evidence supporting this approach is derived from the PARTNER trial data. The core lab used a multi-parametric approach (basically based on the American Society of Echocardiography (ASE)/European Association of Echocardiography (EAE) recommendations for AR evaluation[53,54]) with the colour Doppler parasternal short-axis (PSAX) view weighted more heavily than other parameters.[44] Mild (HR: 1.37) and moder-

ate–severe (HR: 2.18) PVL as defined by this approach independently predicted all-cause mortality at 1 year.[44] A multi-parametric approach was further supported by a better, yet modest, agreement with CMR-based RF than a single parameter.[55] From a feasibility perspective, even when performed under core lab proctoring, up to 13% of post-TAVI echocardiograms are of inadequate quality to be reliably adjudicated according to the VARC-recommended multi-parametric approach.[56] The majority of patients in clinical practice have adequate colour Doppler images for semi-quantitative analysis. However, suprasternal and subcostal views of the aortic flow as well as PSAX view of the right ventricular outflow tract (RVOT) are not consistently of adequate quality for diastolic flow reversal (DFR) and quantitative Doppler (QD) analysis.[55] This was shown in a large core lab series (1255 echocardiograms) where the majority (68%) of cases had only one or two of the VARC parameters reliably assessable. Colour Doppler from long-axis views was analyzable in almost all acquisitions (96%) and from PSAX in the majority of them (90%). Other Doppler parameters [DFR in 68%, QD in 65%, and effective regurgitant orifice area (ROA) in 41%] were less reliably analysable (A. Abdelghani et al., unpublished data).

While the VARC recommends a three-class (mild–moderate–severe) grading scheme, which is generally well aligned with other techniques including angiography and CMR, some authors suggest a more granular (five-class) scheme to improve reproducibility of grading.[56,57] The latter benefit was, however, modest (weighted kappa improved from 0.48 to 0.52), and cut-points of the added classes (mild–moderate and moderate–severe) are yet to be validated. This more granular scheme would be especially useful in the research and clinical trials setting. A simpler grading scheme would always suffice for most diagnostic and prognostic purposes, is more familiar to clinicians, and is easier to unify among different techniques in the setting of a multimodality imaging strategy. One important advantage of the recently proposed granular scheme is its 'collapsibility' into the original three classes. Table 1 summarizes the accuracy, reproducibility, and feasibility characteristics of echocardiographic parameters commonly used for PVL assessment.

Colour Doppler parameters

The VARC-recommended multi-parametric approach emphasized the role of PSAX view colour Doppler.[52] Likewise, large TAVI trials and registries heavily weighed the circumferential extent (CE) of PVL in PSAX view.[56] An adjacent wall distorts the regurgitant jet extent and profile. In in vitro models, a wall-impinging jet (such as a PVL) appears smaller than a free jet of the same ROA when viewed from a vertical long-axis view.[58] A paradoxical overexpansion of the wall-impinging jet could be seen when viewed from a horizontal perspective[58] (similar to the short-axis view) (Figure 7). Tendency of CE from SAX view, when used alone, to overestimate AR has been demonstrated in comparison with a multi-parametric echocardiographic scheme[56] and with CMR-determined RV and RF.[55,59] This tendency for 'overestimation' might support the VARC's cut-points (CE, ≥30%)

Table 1. Summary of the accuracy, reproducibility and feasibility profile of echocardiographic parameters proposed to quantify AR after TAVI[§].

Parameter	Accuracy	Reproducibility	Feasibility*
2D Color Doppler:	The main tool to define the number and location of PVLs and to differentiate paravalvular from transvalvular regurgitation.		Provides quick online diagnosis without the need for offline Analysis. Feasible in the majority (.90%) of cases.
PSAX views	Mild or greater AR, as defined by CE, is associated with reduced survival, functional capacity, and reverse remodelling[44] (TAVI). More-than-mild AR, as defined by VC area, is associated with increased mortality[92] (TAVI). PVL jets of multilevel origin cannot be adequately adjudicated from a single level and a single tilting angle of the imaging plane. A too low/too high/tangential imaging plane can lead to false negative or overestimated assessment. Caution has to be exercised as to include the sum of the separate jets, not the paravalvular arc that includes the non-regurgitant space between jets.	CE has an excellent intra-observer agreement.[56] Kappa coefficient of inter-observer variability for CE-based classification ranges from 0.6[55] to 0.78[133] (TAVI). ICC for VC area (TEE) is 0.96 (intra-observer) and 0.95 (inter-observer)[92].	VC area planimetry (TEE) is feasible in 76% of cases[92] (TAVI).
Long axis views	Apical five- and three-chamber views are superior in visualizing posterior jets (might be obscured in parasternal views). Care should be exercised to differentiate posterior jets from mitral inflow. Assessment largely qualitative and subjective and standardized cut-off values are lacking. Qualitative assessment of jet breadth at its origin correlates with RF[59]. The maximal longitudinal jet extent (compared with the location of the tip of the anterior mitral leaflet) correlates with the VC area[92] (TAVI).	Excellent inter-observer agreement on PVL grade when based on visual assessment of jet width (kappa coefficient = 1.0)[55] (TAVI). ICC for jet length is 0.93 for intra-observer and 0.94 for inter-observer readings[92] (TAVI).	The maximal longitudinal jet is measurable by TEE in 80% of cases[92] (TAVI).
3D color Doppler	Guarantees a perpendicular imaging plane to the jet origin enabling accurate measurement of its CE and planimetry of its VC area.	Inter-observer variability of VC area planimetry in TAVI patients averaged 12.4+11.5%[62] (TAVI).	Offline cropping is time-consuming

Table 1. (*continued*)

Parameter	Accuracy	Reproducibility	Feasibility*
	3D VC area correlated well with RV[62] (TAVI).	3D colour Doppler-based estimate of RV is more reproducible than PWD-based RV[63] (TAVI).	Adequate quality of images cannot be achieved in at least 10% of TAVI cases[66] (due to low spatial and temporal resolution and stitching artefacts from breathing and/or rhythm irregularity).
	Can provide an estimate of RV (3D ROA multiplied by AR VTI) that correlated with CMR-based RV better than PWD-based RV[63] (TAVI).		
Quantitative Doppler *(LVOT-RVOT PWD)*	Formula for calculation of RV/RF is based on invalid geometric assumptions (assuming the LVOT[161] strictly circular).	Intra-observer variability was 73.5+52.2% for RV and 75.2+55.9% for RF[63] (TAVI). Inter-observer variability was 108+64.7% for RV and 120.3+62.3% for RF[63] (TAVI).	Calculations are tedious and time-consuming.
	Errors of potentially inexact measurements—especially RVOT diameter, which is highly dynamic, anteriorly located, and usually off-axis—are inflated due to multiplying and squaring. Accuracy is diminished in the presence of outflow obstruction (e.g. stenotic valvular lesions).	Direct CSA planimetry on 3D echocardiography and contrast-enhanced endocardial border definition could improve reproducibility of RVOT measurements.	QD using the RVOT–LVOT method is feasible in 75% of cases with native AR[74].
	Cannot be used in case of significant comparison-valve (pulmonary or mitral) regurgitation or in the presence of intra-cardiac or extra-cardiac shunts.		In post-TAVI patients, reliable measurement of RVOT stroke volume is feasible in only two-thirds of patients.
DFR			Limited utility because of the noisy signal from suprasternal and subcostal views particularly in the elderly. In post-TAVI echocardiograms, reliable analysis is feasible in 57% of cases.
Duration of DFR:	HDFR is sensitive for detecting moderate–severe AR but could be seen in patients with only mild AR[86] and could not be confirmed by velocity-encoded CMR[87] in a significant proportion of patients.		

Table 1. (*continued*)

Parameter	Accuracy	Reproducibility	Feasibility*
	Reduced aortic compliance with advancing age may prolong, the normally brief, diastolic flow reversal in the absence of a significant AR[54,88].		
VTI ratio:	Correlates with RF measured by CMR[86] and cardiac catheterization[76] better than the isolated presence of holodiastolic flow reversal. VTI ratio is not significantly influenced by advanced age[88].		
EDFV:	EDFV has a good specificity but low sensitivity to detect severe AR[91].	EDFV shows a small inter- (4.4+3.2%) and intra-observer (5.6+3.6%) variability[83].	
End-diastolic to peak-systolic velocity ratio:	The ratio[89] minimizes Doppler insonation angle problem, as forward (the denominator) and backward (the numerator) flow occur in the same axis. Accuracy influenced by the presence of concomitant aortic stenosis (r = 0.89 in the absence of AS, r = 0.61 in the presence of AS, and r = 0.81 overall)[89].		
PHT	Influenced by haemodynamic factors including increased ventricular and aortic stiffness, acuteness of AR, heart rate changes, and rhythm irregularity. Sampling usually interrogates a single jet, and PVLs are often multiple.	Excellent inter- and intra- observer grade agreement[162]. Average variability of absolute measurements <10%[163,164].	Feasibility is limited in milder grades of AR (38–54% in trace–mild AR)[75,94]. A clear envelop could be obtained in 56% of TAVI patients.

[§]Data derived from native AR studies (unless otherwise stated).

*Data on feasibility of Doppler parameters in TAVI patients are generally derived from a large core lab series (A. Abdelghani et al., unpublished data), unless otherwise cited.

Abbreviations: AR, aortic regurgitation; CE, circumferential extent; CMR, cardiac magnetic resonance; CSA, cross-sectional area; DFR, diastolic flow reversal; EDFV, end-diastolic flow velocity; HDFR, holodiastolic flow reversal; ICC, intra-class correlation coefficient; LVOT, left ventricular outflow tract; PHT, pressure half time; PSAX, para-sternal short-axis view; PVL, paravalvular leakage; PWD, pulsed wave Doppler; QD, quantitative Doppler; RF, regurgitation fraction; ROA, regurgitant orifice area; RV, regurgitant volume; RVOT, right ventricular outflow tract; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography; VC, vena contracta; VTI, velocity time integral.

defining severe PVL, which is higher than the ASE-recommended value (≥20%) defining severe surgical para-prosthetic leak.[53] Notably, according to the experts' opinion, both cut-points are 'not well validated',[60] and they can be used only as an 'approximate guide'.[53] Long-axis views could better visualize some jets, particularly posterior ones,[57] and jet width from long-axis views correlated better than CE with CMR-RF in one study.[59] In contrast to typical acquisition guidelines, off-axis views may be helpful in localizing regurgitant jets and determining their origin.[53] Therefore, adopting a multiwindow (parasternal and apical), multiplane (short and long axes) assessment of the jet(s) width at its origin could compensate for the relative deficiency of each, if used separately.

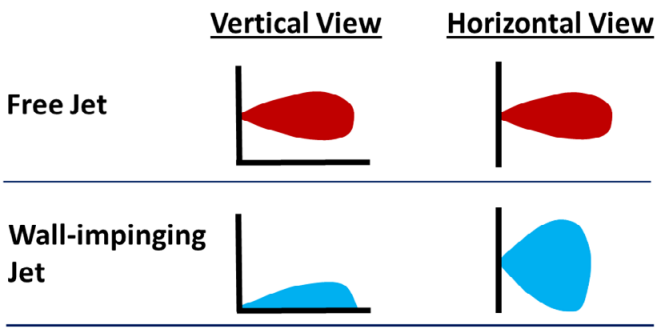

Figure 7. When compared with a free jet of the same regurgitant orifice shape and size, wall-impinging jet tends to be underestimated when imaged by colour Doppler from a long-axis vertical view. The reverse occurs when the jet is viewed from a horizontal view. Modified from Cape et al.[58]

Role of three-dimensional colour Doppler:

Accurate assessment of CE extent of a PVL jet can be technically challenging. The best utility of this parameter is achieved only if a careful scan of multiple cranio-caudal planes is performed. This is because PVLs are often multiple stemming at different levels. A single-plane scan cannot detect and accurately represent the extent of all jets. A too-ventricular plane will cut through the 'spraying' distal jet (especially if originating at a commissure), frequently leading to overestimation, while a too-aortic plane would totally miss a considerable leak originating at a lower level. Cropping of 3D echocardiography data sets could ensure that the imaging plane is perpendicular to the jet origin enabling accurate measurement of its CE and planimetry of its ROA.[61,62] In one study, the planimetered ROA from PSAX view by 3D echocardiography correlated well with Doppler-based RV.[62] This rather small study highlighted the potential role of this technology that needs to be confirmed in larger series. In another study, the planimetered ROA by 3D echocardiography was multiplied by velocity time integral (VTI) of the regurgitant jet to estimate RV.[63] Three-dimensional-based RV was more reproducible and correlated with CMR-based RV better than 2D-based RV.[63] The colour 3D assessment

of ROA is promising but requires meticulous and time-consuming offline reconstruction and is presently not adequately standardized. Among the various 3D echocardiographic acquisition and display modes,[64] x-plane colour Doppler (which allows customizable simultaneous visualization of two 2D planes) and 3D full-volume colour Doppler (which permits construction of an en face view of the regurgitant orifice in relation to the valve) are two modes that can provide extra data on the accurate location and the ROA of the PVL jet. The low spatial and temporal resolutions are still important limitations[65] of 3D echocardiography (especially 3D colour Doppler), leading to inadequate quality of images in at least 10% of studies.[66] It should be acknowledged, however, that the most common reason for failure of 3D imaging is frequently a technically inadequate 2D image rather than an inferior resolution and that technological improvements in processing are likely to improve the resolution of 3D images.

Multiple-beat acquisition improves temporal and spatial resolution but may be limited by 'stitch artefacts' from irregular rhythm or respiration and is not suitable for real-time diagnosis. Multiple beat acquisition is a prerequisite for the full-volume mode, which has a reasonable spatial and temporal resolution and a wide interrogation sector[64,67] that could cover the entire ROI. Live-mode 3D imaging is possible with the single-beat technique. This mode, however, displays a narrow pyramidal volume, which is useful to focus on a specific suspicious sector but is often inadequate to visualize the entire valve perspective.[64] Sometimes incorporating the entire annulus is possible, but at the expense of a drop in the volumetric frame rate, which drops even more when colour Doppler is activated. Three-dimensional TEE full-volume colour Doppler imaging usually provides a better resolution and a higher volumetric frame rate than 3D transthoracic imaging.[68] Considering the currently available technology, 3D TEE should be complementary but not an alternative to 2D colour Doppler[65] in the assessment of PVL, particularly when the latter cannot provide accurate diagnosis.

Other echocardiographic parameters for paravalvular leakage assessment

Quantitative Doppler:

Aortic RV can be calculated as the difference between forward stroke volume across the LVOT and across any non-regurgitant orifice [RVOT or mitral valve (MV)][54,69] and could independently predict clinical outcomes in patients with native valvular AR.[70] However, as listed in Table 1, erroneous calculations lead to a stroke volume difference that is translated to a spurious RV and RF.[71,72] In the absence of any clinically significant AR, 'spurious' RFs of up to 30% (mean: 15.7+7.6%) have been reported when the flow rates across the LVOT and MV are compared.[73] When RVOT flow is used instead of the MV, the 'spurious' difference is <10% (mean: 2.4+5%).[71] Right and left ventricular outflow tract method correlated better with RF measured by cardiac catheterization and with aorto-

graphic visual grading than MV-LVOT method.[71,73,74] As previously mentioned, images of the RVOT diameter and VTI are frequently of inadequate quality limiting the utility of QD.

Aortic diastolic flow reversal:

While a brief diastolic retrograde flow could normally be detected in the aorta, a prolonged DFR in the absence of a peripheral fistula or a patent ductus arteriosus indicates AR.[54,75,76] With significant AR, DFR could be detected in ascending aorta,[77] left subclavian,[78] carotid,[79,80] and coronary arteries.[81] The two locations most often used in clinical practice for detecting DFR are descending thoracic[82-84] and abdominal aorta.[84,85] Holodiastolic flow reversal (HDFR) of aortic flow could, however, be seen in the absence of a significant AR, especially in elderly patients[54,86-88] (Table 1). Therefore, the reliance on the mere presence of HDFR to define AR severity is inadequate. A more detailed analysis of DFR (Figure 8 and Table 1) could improve the utility of this parameter in AR adjudication. End-diastolic reversed-flow velocity (EDFV) could be utilized for AR adjudication,[89] provided that a clear Doppler signal is available, and correlates with angiographic AR grades and RF measured by cardiac catheterization[83] and CMR.[90] An EDFV of ≥15.6 cm/s provided the best sum of sensitivity (which was only modest) and specificity to define severe AR.[91] Given its low sensitivity and negative predictive value, severe AR should not be excluded on the basis of this parameter alone. Admittedly, data on the utility of aortic DFR are derived from native AR where aortic and ventricular compliance and pres-

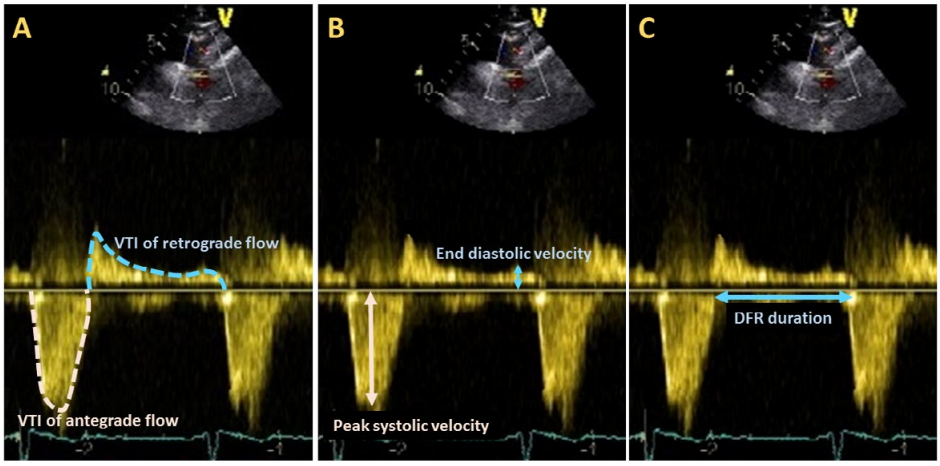

Figure 8. (A) The velocity time integral (VTI) of descending aortic diastolic flow reversal can be compared with the antegrade flow velocity time integral to estimate aortic regurgitation fraction. (B) A prominent reversed-flow end-diastolic velocity indicates a significant aortic incompetence and can be compared with the peak systolic velocity to represent regurgitation fraction. (C) Diastolic flow reversal duration and its ratio to the diastolic time are markers of aortic regurgitation severity.

sure are different from TAVI patients. In the latter, the pattern (persistent/intermittent/absent) of DFR (by TEE) was shown to modestly correlate (r = 0.61) with the ROA with a significant overlap between AR classes.[92] Significant AR (ROA ≥ 0.10 cm^2) was present in all cases with a persistent HDFR, in 50% of those with intermittent HDFR and in 22% of those with no HDFR.[92]

Pressure half time:

The inherent limitation of pressure half time (PHT) as a marker of AR severity is the sensitivity to pressure changes on either side of the aortic valve. This is particularly relevant in the setting of increased LV and aortic stiffness, typically seen in elderly aortic stenosis patients undergoing TAVI.[93] Paravalvular leakage jets are often multiple, and continuous wave Doppler signal is often interrogated from a single jet. The latter fact could, however, be argued by the haemodynamic nature of PHT making it theoretically representative of the total volume overload rather than the interrogated jet. The practical utility is especially limited in smaller jets as a well-defined complete modal velocity envelop cannot be acquired in 46% of mild AR.[75,94] On the other hand of those limitations, having a non-invasive haemodynamic index of AR load is an appealing option. This should stimulate a more rigorous investigation of PHT, possibly yielding specific cut-points of severity (reflecting the different haemodynamics of PVL from chronic native valvular AR).

Left ventricular haemodynamic and geometric changes as surrogate markers of paravalvular leakage severity

Changes in LV diameters, volumes, mass, and EF reflect the volume burden of a chronic AR.[54] Figure 9 demonstrates the confusion that can be encountered when we look at the haemodynamic and geometric changes of the LV exposed to a PVL. Acutely, haemodynamic changes are indistinguishable from pre-existing (increased ventricular pressure) and normal post-implantation changes (increased filing and stroke volume). In the long term, when negative cardiac remodeling from volume overload is awaited, neither the normal response to successful TAVI nor the natural history of LV subjected to PVL is certain. Diastolic dysfunction often persists, and LV hypertrophy incompletely regresses even several years after successful surgical aortic valve replacement.[95]After TAVI, CMR showed that LV mass, end-diastolic volume, and EF improve unless TAVI is complicated by more-than-mild AR,[9] where these parameters remain unchanged. Echocardiographic data from the PARTNER trial revealed that in more-than-mild AR complicating TAVI, LV mass, and EF still improve, LV end-systolic volume does not change, and LV end-diastolic volume increases.[44]

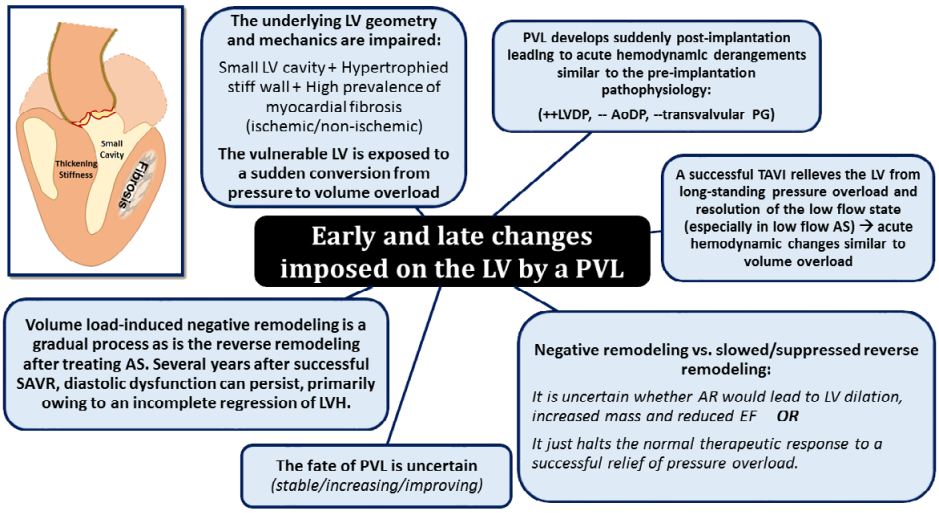

Figure 9. The complexity of left ventricular changes after successful transcatheter aortic valve implantation and transcatheter aortic valve implantation complicated with paravalvular leak. AoDP, aortic diastolic pressure; AS, aortic stenosis; EF, ejection fraction; LV, left ventricle; LVDP, left ventricular diastolic pressure; LVH, left ventricular hypertrophy; PG, pressure gradient; SAVR, surgical aortic valve replacement.

Specific methodology for post-transcatheter aortic valve implantation aortic regurgitation assessment

As shown in Table 1, data on most of the currently available echocardiographic parameters used for PVL adjudication are largely extrapolated from native/surgical prosthetic AR experiences. Many of the currently recommended echocardiographic parameters in the ASE/EAE guidelines[53,54,96] for native valvular/surgical prosthetic AR assessment were initially validated on the basis of their agreement with angiography. This holds true for the jet width/LVOT width, jet cross-sectional area (CSA)/LVOT CSA,[97] proximal isovelocity surface area,[98] and PHT.[99] This agreement between echocardiographic and angiographic parameters in native AR has been extrapolated to the post-TAVI setting, and agreement between echocardiographic and angiographic grading is intuitively assumed in clinical practice. In the post-TAVI setting, however, echocardiographic and angiographic agreement on PVL grade is achieved in only 56% of cases (inter-technique kappa, 0.14[100]–0.20[92]). Similarly, echocardiographic grading of PVL is often at odds with CMR assessment.[55,59,100,101] This contrasts with the good agreement between both methods in the assessment of native AR[59,102] and surgical prosthetic[102] AR. These observations denote that the extrapolation of native or surgical prosthetic AR diagnostic rules to post-TAVI AR might not always be accurate. Development of a PVL-specific strategy is anticipated to answer the following questions: what is the best combination of criteria, the relative weight of each of the component parameters, and the cutpoints defining the severity grades? The target should be a scheme that correlates with hard clinical

endpoints and provides the best degree of feasibility and consistency (intra- and inter-technique).

How necessary intra-procedural transesophageal echocardiography is

The increasing trend of performing TAVI under sedative rather than GA has been shown to reduce procedural time and hospitalization without increasing procedural morbidity or mortality.[103,104] Data from the FRANCE2 registry gave important insights into this trend.[2] The ratio of local anaesthesia (LA) to GA increased from 0.16 to 1.4 over 22 months. Transesophageal echocardiography was used in 17% of cases in the LA group and in 76% in the GA group. Significant AR was more common in the former (19%) than in the latter (14%, p = 0.015). After propensity matching, including TEE usage, the difference in AR became non-significant (GA, 13% vs. LA, 16%; p = 0.19). The authors considered their results supporting the importance of TEE during TAVI to reduce PVL. However, three points are worth mentioning before any conclusion can be based on such findings. First, the difference in AR in the un-matched analysis resulted in no difference in procedural success, incidence of VARC-defined complications, and 30-day or 1-year survival rates. Second, matching for TEE usage improved but did not eliminate the difference in AR. Third, matching also included other predictors of AR that were more frequent in the LA group (CoreValve usage and more AR at baseline). In a pilot study, TTE-guided TAVI under sedative anaesthesia was shown to be feasible and safe compared with TEE-guided procedure.[105] Procedural time was shorter with no difference in procedural success, severity of paravalvular regurgitation, need for additional valve implantation or peri-procedural complications (including stroke and death). Notwithstanding, TTE image quality is suboptimal in supine position, and TTE imaging interferes with fluoroscopy and cannot provide continuous guidance (as it interrupts the procedure).[106] Intra-cardiac echocardiography (ICE), which is compatible with sedation and local anaesthesia, can be considered another alternative to TEE for intra-procedural guidance and causes less interference with fluoroscopy with much less need for repositioning during the procedure. Intra-cardiac echocardiography assessment of paravalvular AR is generally comparable to conventional TEE imaging[106,107] but is somewhat limited by shadowing in the LVOT when imaged from the right atrium. This limitation can be addressed by advancing the ICE catheter into the right ventricle to image the LVOT through the interventricular septum.[108] Disadvantages of ICE guidance include the need for insertion of a second venous sheath; potential interference with the pacemaker lead; the risk of inducing atrial or ventricular arrhythmias; additional learning curve for the imaging and the interventional cardiologists; and the higher cost compared with TEE.[106]

Calculation of RF based on quantitation of flow in the ascending aorta is not affected by PVL-specific shortcomings occurring at both the valve level as well as the ventricular level. These shortcomings include multiplicity and eccentricity of jets and their origination at multiple level, poor acoustic window, and artefacts from stent frame and /or calcification. Quantitation of forward and backward aortic flow is feasible by CMR velocity-encoded phase contrast mode (or simply, CMR velocity mapping)[109,110] and has been shown to correlate with clinical outcomes in patients with native and post-TAVI AR.[55,111] Cardiac magnetic resonance velocity mapping comprises a set of cross-sectional cine images of ascending aorta and their respective velocities. The 'through-plane' flow is measured from CSA multiplied by the velocity. A flow/time curve of the entire cardiac cycle is generated with the systolic flow represented by area under the forward part of the curve, and area above the backward diastolic part, when present, indicates the retrograde-regurgitant flow volume (Figure 10).[112] Compared with echocardiography, CMR has lower intra- and inter-observer variability for RV, suggesting that CMR may be superior for serial measurements.[113] Better reproducibility of CMR-based RV and RF has also been shown in comparison with angiographic grading.[20] Non-invasiveness, freedom from exposure to ionizing radiation, and the relatively shorter time of scan when velocity mapping alone is performed are all relative advantages of CMR-based AR adjudication.[114] In addition to quantitative evaluation of regurgitation, CMR cine imaging could accurately and precisely assess LV volumes, mass, and systolic function.[115,116]

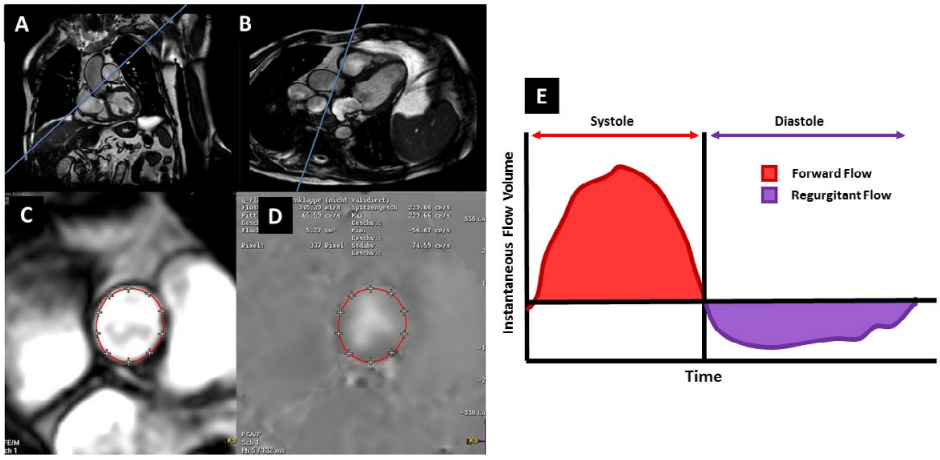

Figure 10. (A and B) Steady-state free precession cardiac magnetic resonance images (blue lines, imaging planes for velocity mapping). (C and D) Magnitude image and phase velocity map. (E) The time–velocity curve of aortic flow over one heart cycle obtained from the magnetic resonance velocity mapping (violet part represents regurgitant flow). This curve represents an aortic regurgitant fraction of 45%. Reproduced and modified with permission from Orwat et al.[101]

Limitations of cardiac magnetic resonance in aortic regurgitation grading

Patients with implanted cardiovascular electronic devices:

As shown in Figure 11, many patients planned for TAVI have at baseline an implanted cardiovascular electronic device (ICED), and another 13%[117] sustain an indication for pacemaker implantation after the procedure. In the 2007 statement on the safety of magnetic resonance imaging (MRI) in patients with ICEDs, MRI was designated as contraindicated.[118] However, more recent studies showed no major adverse events in patients with pacemakers[119] and implanted cardioverter defibrillators (ICDs)[120] who underwent a MRI scan, suggesting that CMR might be an option when there are no alternatives, provided that the scan be performed in sufficiently experienced and equipped centres.[121] Affection of the device function was, however, reported in some cases in those studies and this risk might even be higher when the scan is applied to the chest region.[122] As of 2008, the modern MRI 'conditional' pacemakers, approved as MRI-safe under certain precautions,[123] became commercially available. In addition to the classical triad of mechanical, electromagnetic, and thermal hazards, imaging artefacts represent another limitation of CMR in patients with ICEDs including the modern MRI-conditional devices.[123] This phenomenon is most pronounced when an ICED is implanted in the left pectoral region[124] and in cases with ICD systems.[125] Therefore, with the newer MRI-conditional devices implanted in the right pectoral region, CMR may be an option, provided that the manufacturer's recommendations are strictly adhered to. Otherwise, the risk–benefit ratio is unfavorable, and CMR should be avoided.

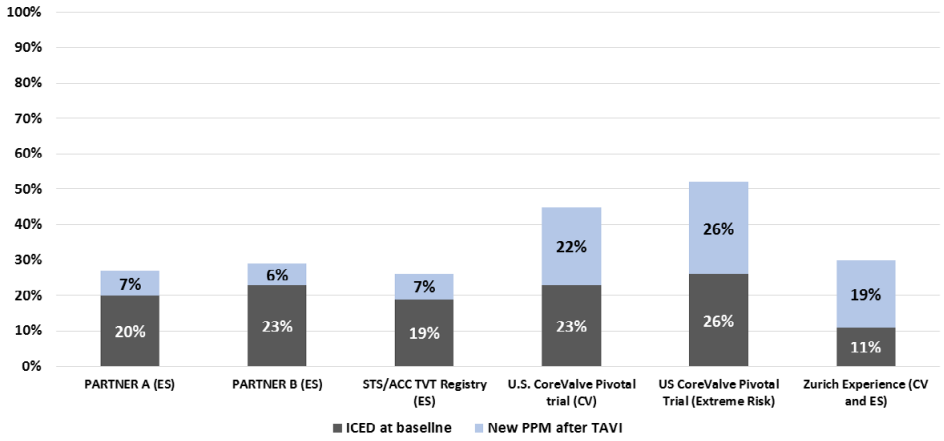

Figure 11. The prevalence of implanted cardiovascular electronic devices in transcatheter aortic valve implantation patients. ICED, implanted cardiovascular electronic devices; CV, CoreValve; ES, Edward Sapien valve; PPM, permanent pacemaker.

Inconsistent severity definitions:

Few data are available on what CMR-based RF is predictive of clinical outcomes in patients with AR. Regurgitation fraction of >33% could predict the development of symptoms or other indications for valve replacement in patients with native AR.[111] In one, rather small size, study of 23 post-TAVI patients, a RF of >20% was associated with reduced survival free of the composite of all-cause death, heart failure hospitalization, and intractable symptoms necessitating repeat invasive therapy.[55] On the other hand, many studies compared AR severity by CMR vs. echocardiography. The aim of those studies was to define what percentage of CMR-based RF corresponds to mild, moderate, and severe grades, using echocardiographic definition as a reference standard. As shown in Table 2, the cut-off values for AR grades are variable, possibly reflecting the variability of the reference parameters to which CMR was compared. The reference standard in these studies ranged from pure qualitative through semi-quantitative to pure quantitative echocardiographic parameters. As a result, marked heterogeneity exists among the definitions of AR severity used in post-TAVI CMR studies. As shown in Table 3, grading schemes differed both in the number of classes and in the RF range that defines each class. The RF representing none–trace AR varied from <1 to <10% and that representing a severe AR ranged from >30 to >50%. No distinction between none, trace, and mild AR is defined in some schemes. Consequently, the reported rates of more-than-mild AR in

Table 2. The definition of AR severity grades by CMR-based regurgitation fraction compared with reference methods.

Study	Reference standard	Mild	Moderate	Moderate-to-severe	Severe
Gabriel et al[130]	Qualitative and semi-quantitative echocardiography	< 8%	8-19%	20-29%	≥30%
Gelfand et al[165]	Qualitative echocardiography	≤ 15%	16–25%	26–48%	> 48%
Globits et al[166]	Echocardiography (qualitative and quantitative) + Catheterization (angiography and quantitative)	0-15%	16-30%	31-50%	> 50%
Honda et al[114]*	Qualitative echocardiography	2.1%	8.8%		39.5%
Ley et al[167§]	Clinical + Electrocardiography + Qualitative echocardiography	6 ± 8%	17 ± 11%		30 ± 11%
Altiok et al[63§]	Multiparametric approach combining qualitative and quantitative VARC criteria	20.7 ± 14.9%	11.4 ± 7.6%		41.2 ± 14%
Salaun et al[133]	Multiparametric approach combining qualitative and quantitative VARC criteria	< 14%			

*Data presented as the mean regurgitation fraction corresponding to each echocardiographic grade.
§Data presented as mean ± standard deviation of regurgitation fraction corresponding to each echocardiographic grade.

Table 3. CMR-based AR severity schemes used in different studies and reported rate of significant regurgitation based on each scheme.

Study	Transcatheter heart valve	CMR Regurgitation Fraction (%) Defining Each Severity Class					Reported prevalence (%) of > mild AR
		None-trace	Mild	Moderate	Moderate-severe	Severe	
Frick et al[20]	Edwards SAPIEN XT and CoreValve	< 8		9-19	19-29	>30	62
Orwat et al[101]	Edwards SAPIEN	< 10	10-20	20-40		>40	27
Sherif et al[100]	CoreValve	<15		16-30	31-50	>50	38
Altiok et al[63]	Edwards SAPIEN XT and CoreValve	< 20		20-30		> 30	18
Ribeiro et al[59]	Edwards SAPIEN, SAPIEN XT and SAPIEN 3	< 5	5-19	20-29		>30	26.2
Merten et al[9]	Edwards SAPIEN XT and CoreValve	< 1	2-15	16-30	31-50	> 50	18
Crouch et al[102]	Edwards SAPIEN XT	< 8	9-20	21-39		>40	35
Abdel-Wahab et al[31]	Edwards SAPIEN XT CoreValve	≤15		16-30%	31-50%	>50%	1.8 18.2

post-TAVI patients varied in CMR studies from 1.8 to 35% for Edwards SAPIEN XT, from 18.2 to 38% for CoreValve, and from 18 to 62% for mixed cohorts. Notably, the whole scale for mixed cohorts (18–62%) is far greater than the rate of 11.7% reported in pooled data from clinical trials and large TAVI registries,[4] which is based mainly on angiographic and echocardiographic definitions. Inability to characterize mild degrees of aortic regurgitation. Mild AR is increasingly identified as a risk marker of poor outcomes in post-TAVI patients,[1,4] and its identification, thus, became an important clinical objective. Newer valve iterations could effectively reduce moderate–severe, but mild PVL is still frequent.[126-129] Cardiac magnetic resonance velocity mapping cannot precisely identify mild AR. In some CMR studies, RF did not significantly differ between patients with mild AR (as defined by echocardiography) and healthy subjects.[114,130] A small 'physiological' reflux through the normal aortic valve has been described.[131] This tiny RV might not be appreciable by Doppler echocardiography but could still be detectable by the more sensitive CMR velocity mapping. Another source of small fallacies is the coronary flow, which averages 1.5–3 mL/beat.[132] Both factors might account, at least partially, for the inability to distinguish mild AR from normal flow by CMR velocity mapping.

Technical limitations of cardiac magnetic resonance velocity mapping:

Cardiac magnetic resonance-based RF differs significantly when measured at different (proximal vs. distal) levels of the ascending aorta, being significantly greater at the sino-tubular junction than at the distal ascending aorta especially at milder degrees of AR.[130]

Measurements best correlated with echocardiographic AR grading when made in the proximal ascending aorta.[130] Turbulent flow causes signal loss, and capability of accurate velocity mapping may be limited. This phenomenon is most pronounced when aortic stenosis or aortic aneurysm coexist[114] or flow is interrogated inside the prosthetic valve stent (e.g. when the transcatheter valve frame is long).[133] Correct flow rate calculations require an exact 'double-oblique' positioning of the cross-section and its orthogonal flow vector, which is subject to potential errors, especially with aortic root dilatation.

Other limitations: Cardiac magnetic resonance is costly and demanding in terms of logistics and expertise. The severity of AR after TAVI may vary over time[12] and often requires repeated follow-up, which is impractical in terms of cost and availability of CMR. TAVI patients are typically elderly with multiple co-morbidities and may not tolerate a complete CMR scan, which typically takes a long duration. Up to 10% of TAVI patients ask for early termination of the scan due to anxiety and/or physical discomfort,[101] refuse the scan, or have claustrophobia.[133] CMR is not available in the cath lab (where the diagnosis of PVL is most critical), cannot differentiate transvalvular from pravalvular regurgitation, and cannot localize a PVL. This differentiation has important therapeutic implications.

Other cardiac magnetic resonance parameters of aortic regurgitation severity

Estimation of regurgitation volume from ventricular stroke volume:
In the absence of concomitant valve incompetence or intra-cardiac shunt, the difference between right and left ventricular stroke volumes is equal to aortic RV and can be measured by CMR. However, pooled data from clinical trials and large TAVI registries refer to a prevalence of concomitant significant mitral regurgitation of 19–34% and of significant tricuspid regurgitation of 15–25%.[12,134-137]

Imaging of regurgitant jet in the left ventricle:
The turbulence created by AR can be visualized as a loss of signal (signal void) on cine gradient-echo CMR.[137] The area of diastolic LV signal loss correlates with RV measured by echocardiography.[138] The area of regurgitant jet, however, depends not only on RV or ROA but also on the pressure gradient, orifice shape, and proximity of the regurgitant orifice to adjacent walls[58,139,140] and is sensitive to changes in acquisition parameters.[141]

Imaging of proximal isovelocity in aortic root:
Aortic regurgitation produces a zone of proximal isovelocity that can be visualized by CMR as a semi-circular signal void in aorta. Area of proximal isovelocity has a good specificity to define significant AR but only modest sensitivity to characterize different grades of AR.[142]

MULTISLICE COMPUTED TOMOGRAPHY AND ROTATIONAL ANGIOGRAPHY

Multislice computed tomography (MSCT)-based sizing of the aortic valve annulus played a pivotal role in reducing the incidence of PVLs.[143,144] Multislice computed tomography also helped understanding PVL mechanism and relation to the host's characteristics (such as aortic valve calcification[145,146] and annular eccentricity[147]). However, the role of MSCT in the diagnosis and quantification of PVL is less well established and is associated with additional irradiation and contrast-related hazards. The additional irradiation from an MSCT scan in a typical elderly TAVI patient may not carry any considerable additional risks, but would become more relevant as TAVI is used in younger and lower-risk patients. In some laboratories, prosthetic valve stent abnormalities such as eccentricity and suboptimal depth of implantation (which could be precisely quantitated by MSCT[148-150]) are included as 'structural' qualitative parameters for PVL grading.[57] Multislice computed tomography-based RV and RF can be estimated through the comparison of the stroke volumes of left and right ventricles[151,152] and correlates well with CMR-based RV and RF[117] and with echocardiographic grading.[151,152] The diagnostic accuracy was best when the anatomic ROA was added to the MSCT scheme.[151] Although planimetry of the ROA is feasible by MSCT,[153-156] manual tracing of the area(s) of malapposition between the valve stent and the host's landing zone is problematic because of the signal loss caused by dense calcification adjacent to the metal frame. Instead of manual tracing, a computer simulation model that 'predicts' the valve frame deformation could be applied. The 'virtual' model combines the patient-specific anatomic and tissue characteristics (derived

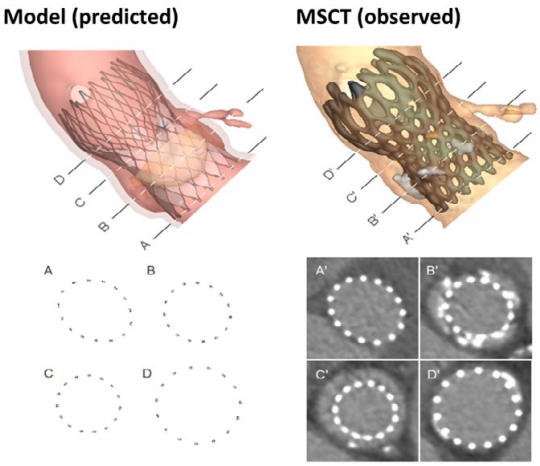

Figure 12. Predicted (model, left) and observed (multislice computed tomography, right) geometry of transcatheter heart valve frame at the ventricular end (A and A'), nadir (B and B'), central coaptation (C and C'), and commissures (D and D') of the prosthetic valve leaflets. Reproduced and modified from Schultz et al.[157] with reproduction permission from Europa Digital & Publishing.

from MSCT) with the valve frame geometry and expected radial force (based on ex vivo bench tests) to predict their interaction. An initial report on this technology has been recently released and referred to a good agreement between 'predicted' and 'observed' valve frame geometry and also between the predicted and observed displacement of aortic leaflet calcification by the valve frame[157] (Figure 12). Adequacy of apposition and extent of malapposition between the valve stent and adjacent tissues could, thus, be predicted. The extent of malapposition should correlate with the severity of PVL (Figure 13), a relation that is currently under investigation. If under-expansion or deformation of

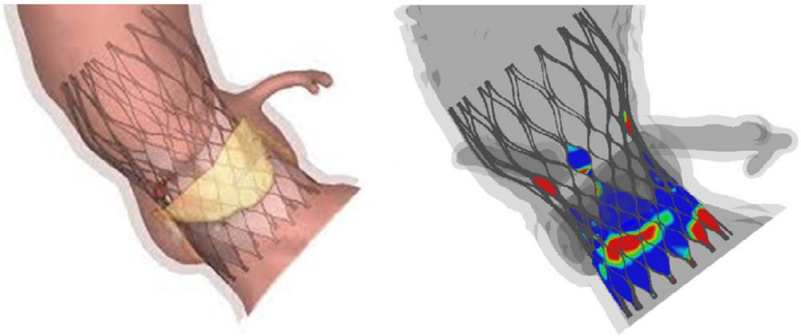

Figure 13. Prediction of frame deformation (left) and apposition (right). Areas of malapposition represented by red colour (indicating the path of leakage) and perfect apposition represented by dark blue.

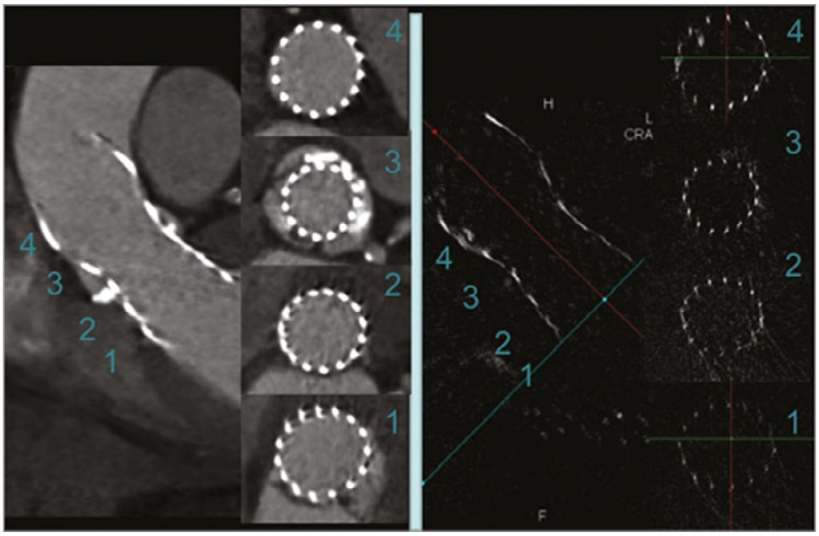

Figure 14. Prosthetic frame geometry shown with multislice computed tomography (left panel) and rotational angiography with motion-compensated three-dimensional reconstruction (right panel) from the same patient. Short-axis cuts are made at the level of the inflow (1), the leaflet nadirs (2), leaflet central coaptation (3), and the leaflet commissures (4). Reproduced from Schultz et al.[159] with permission from Europa Digital & Publishing.

the prosthetic frame is detected during the procedure, effective corrective measures can be performed. Prosthetic frame expansion and deformation could be evaluated using rotational angiography.[158] A novel motion compensating 3D reconstruction (precluding the need for rapid pacing) produces MSCT-like image (with a small inter-modality difference[159]) (Figure 14). Prosthetic frame expansion and eccentricity could be evaluated, and significant AR could be predicted being associated with greater prosthesis eccentricity[159] relative to the annular eccentricity.[160] Good quality 3D reconstruction is, however, not possible in ~15% of cases[159,160] because of over-projection of radio-dense objects or obesity of the patient.

CONCLUSION AND CLINICAL PERSPECTIVE

All currently available technologies and parameters used for the assessment of AR severity after TAVI suffer from significant limitations. Reproducible, accurate, and feasible methods are needed but are difficult to validate in the absence of a reference gold standard. Looking into near future, multi-modality imaging could be a reasonable approach. Putting this in mind, clinical researchers and scientific bodies should guarantee the highest degree of homogeneity of the schemes used by different modalities. Ideally, clinicians should have a unified scheme where one grade as defined by a certain technique would be interchangeable with a similar grade defined by another method. For immediate post-implantation diagnosis, the combination of transthoracic echocardiography, quantitative angiography, and a haemodynamic index is often feasible. The haemodynamic index should account for the effect of heart rate and be measured before implantation as a reference to compare the post-implantation value with. This approach could provide adequate diagnostic and prognostic information without the need for GA necessary for TEE. To get the best benefit from angiography, which routinely subjects the patient to extra irradiation and nephrotoxic dye, a standardized image acquisition should be defined and integrated into the routine clinical practice. For follow-up imaging, echocardiography is the most convenient. To provide acceptable accuracy, combining multiple parameters of high-quality images is necessary. Unlike what has been adopted in many clinical trials, selective heavy weighting of certain parameters should be discouraged, and considering as much as possible of technically 'reliable' parameters is preferred, likely at the expense of reduced reproducibility. Adherence to strict acquisition protocol is necessary to compensate for the generally low feasibility of most of Doppler parameters. Priority in future research should be given to validating quantitative parameters (e.g. 3D-based vena contracta area) tested in the specific post-TAVI setting. Clinical utility of CMR velocity mapping is, currently, limited due to intrinsic demands of the technology, the high rate of ICED in TAVI patients, and the lack

Table 4. Cut-points of PVL severity that are linked to worse prognosis.

Technique	Parameter, cut-point	Risk of 1-year mortality, HR (95% CI)
Angiography	LVOT-AR[39] ≥0.18	3.82 (1.50-9.75)
Hemodynamic indices	Aortic regurgitation index[41,168] <25*	2.9 (1.3-6.4)
	Relative amplitude index[51] ≥14	3.39 (1.6-7.19)
Echocardiography	Jet arc[§] ≥10% of the annulus circumference[44]	2.18 (1.57–3.02)
	Jet arc <10% of the annulus circumference[44]	1.37 (1.14–1.90
	Vena contracta[§] area[92] ≥10 mm²	2.4 (1.3-4.5)

*The same cut-off value applies to the heart-rate adjusted diastolic delta.

[§]Cut-points of jet arc circumferential extent and vena contracta area are useful quantitative metrics but should be supported by other qualitative/semiquantitative parameters.

of unified diagnostic definitions of AR severity. For guidance of corrective measures (e.g. post-dilation), cutpoints that determine the threshold for intervention are not clear. Relying on the classic mild vs. moderate–severe classification, the interventionist tends to intervene in moderate–severe PVL, but how do we know that 'mild' PVL might not benefit from a more aggressive strategy? A more mechanistic use of numerical cut-points linked to worse outcome is, therefore, advisable (Table 4).

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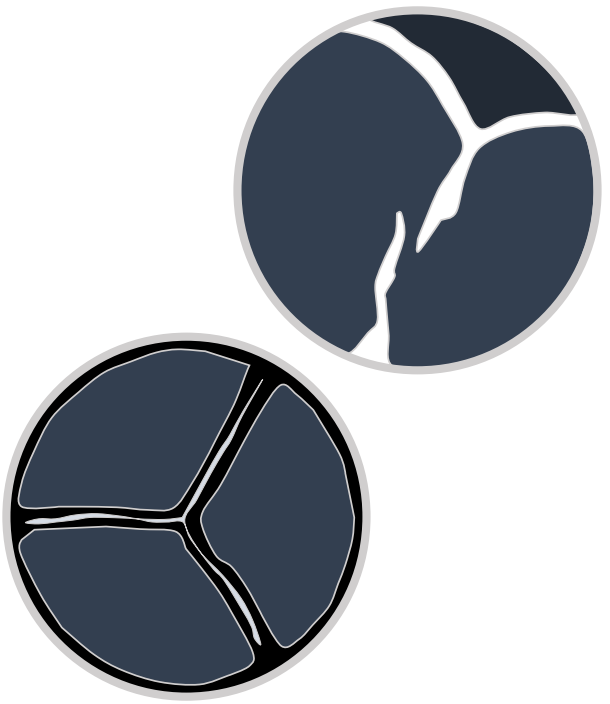

Chapter 5

Echocardiographic and angiographic assessment of paravalvular regurgitation after TAVI: optimizing inter-technique reproducibility

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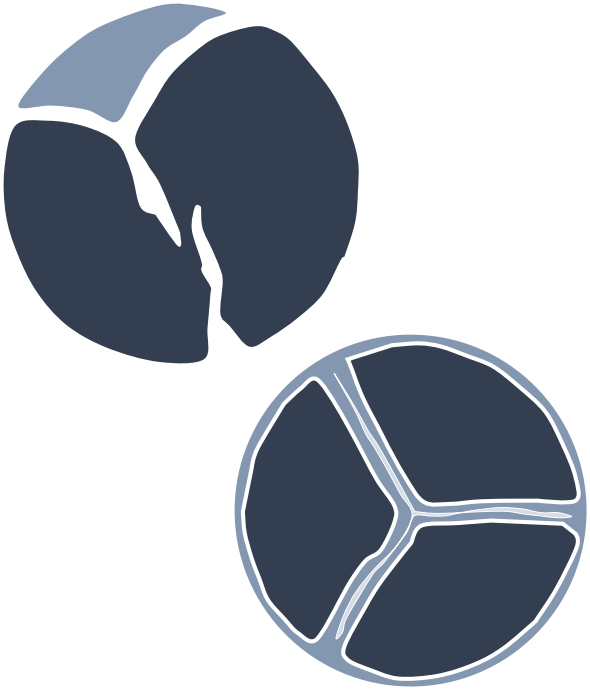

ABSTRACT

Aims:

Aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI) is often first diagnosed by angiography and then confirmed and followed-up by transthoracic echocardiography (TTE). Consistency between both methods is important for follow-up. We sought to determine inter-technique reproducibility of the assessment of paravalvular AR after TAVI.

Methods and results:

The study included 165 patients treated with a self-expanding bioprosthesis and had angiography and TTE performed at a median interval of 4 days. TTE parameters of AR severity included VARC score (the average AR grade determined by the echocardiographic VARC-II criteria), pressure half time (PHT), regurgitation jet features in long axis views (LAX score) and color Doppler (CD) score (= paravalvular AR jet circumferential extent (%) + LAX score). Using ROC curves, the cut-points that best defined an angiographic >mild AR were identified.

On TTE, AR was paravalvular in all cases, multi-jet in 28%, and predominantly (64%) detected in the commissural region between the right and left coronary sinuses. Using VARC-II criteria (combining at least two), TTE agreed with angiographic classification in 53% of cases (k=0.14). Greater than mild AR could better be defined by one of the following combinations of criteria: a) LAX score >4.25 and VARC-II score >1.33; b) CD score >11.5 and PHT <400 msec. The combination of the CD score with PHT gave the best sum of sensitivity, specificity, positive and negative predictive values.

Conclusions:

Agreement between angiography and TTE (using the VARC-II criteria) in the grading of post-TAVI AR is modest, and this might have contributed to the inconsistency of data on the rate and fate of paravalvular AR. Inter-technique reproducibility can be improved using a combination of color Doppler and hemodynamic parameters.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) irreversibly changed the profile of the valve disease therapeutic armamentarium. Post-TAVI aortic regurgitation (AR), often paravalvular, is common[1] and was shown to adversely affect morbidity, mortality and reverse cardiac remodeling[2,3] after TAVI.

There are important inconsistencies of data on the rate and fate of post-TAVI AR and its relation to patients' outcomes[1]. Intra-technique (transthoracic echocardiography-TTE) reproducibility is suboptimal and is thought to have contributed to those inconsistencies[4]. Inter-technique reproducibility is another source of discrepancies[5,6] unless systematically optimized.

Aortic root angiography, typically using Seller's visual grading[7], is the first screening tool used in most laboratories for detection of post-implantation AR and guidance of timely corrective measures (e.g. post-dilation, valve-in-valve and, most recently, retrieval and reposition of the valve). A widespread trend is to perform TAVI without general anesthesia[8] making it as quick and simple as typical cardiovascular interventions[9,10]. Angiography might, thus, become the only intraprocedural technique to detect AR or be combined with TTE under conscious sedation[11,12]. Angiography is, however, inappropriate for longer-term follow up where TTE is the standard imaging method. Therefore, post-TAVI AR is often first diagnosed by angiography and then confirmed and followed-up by TTE. Both methods should provide an acceptable degree of consistency.

In the present study, we sought to investigate the consistency between echocardiographic and angiographic assessment of post-TAVI AR.

METHODS

The study included patients with symptomatic severe aortic stenosis, who underwent TAVI based on the decision of a multidisciplinary team after providing written informed consent. Two hundred five consecutive patients were initially included in the present study. Out of those patients, 12 were excluded due to the final angiographic acquisition performed while a catheter or a guide-wire was left passing through the implanted valve. Further 28 patients were excluded due to incomplete TTE data, defined as < two reliably-analyzable parameters of AR severity. In those patients, AR severity was defined, with modest confidence, as moderate in one patient, as mild in nine patients and as none-trace in the remainder based on color Doppler data (n=13), quantitative Doppler data (n=9), continuous wave Doppler data (n=5) or descending aortic flow profile (n=1). Final analysis included 165 patients who were alive until hospital discharge and had both angiography and TTE performed at a median interval of 4 days (range: 2-7 days).

Prosthesis sizing was based on the multislice computed tomography (MSCT)-based annular sizing in all cases. The cover index was calculated as; 100 x ([prosthesis area – MSCT annular area]/prosthesis area[13].

Angiography:

Aortography was performed at least 10 minutes after final valve implantation (or after post-dilation, if applicable) thus allowing for any spontaneous regression of paravalvular AR to occur prior to final assessment[14]. The pigtail catheter was positioned in the upper third part of the frame of the self-expanding valve and at least 20 ml of contrast were injected at a rate of 20 ml/sec into the aortic root. A single experienced investigator blinded to echocardiographic data (HT) visually graded the severity of AR according to the Sellers' method[7]. The same observer reanalyzed 20 randomly selected angiograms at a median interval of 60 days. Intraobserver reclassification occurred in 4 cases (20%) with no > one class reclassification (kappa coefficient = 0.62, indicating a good agreement[15,16]). Sellers' grade I was defined as mild AR and Sellers' grade ≥II was defined as >mild AR.

Echocardiography:

Echocardiographic analysis was performed by two cardiologists (OS and MA) blinded to angiographic data.

The following parameters were measured according to the recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging[17-20]: paravalvular AR jet circumferential extent (CE), AR jet pressure half time (PHT), duration and end-diastolic velocity of aortic diastolic flow reversal (DFR), regurgitation volume and fraction (RV/RF) and effective regurgitant orifice area (EROA). RV was calculated as the difference between the stroke volumes at the left and right ventricular outflow tracts (LVOT and RVOT) using pulsed wave Doppler. RF was calculated as the RV divided by the LVOT stroke volume.

CE from the color Doppler parasternal short axis (PSAX) view was measured in the frame that shows high velocity mosaic color that is continuous and not significantly different from preceding and following frames measuring the angle that contains the jet as an absolute value (degrees) and as a fraction (percentage) of the 360° face-of-a clock (figure 1). Caution has been exercised to include the sum of the separate jets, not the paravalvular arc which includes the non-regurgitant spaces between jets[21].

Grading of AR severity:

VARC-II criteria:

Categorical grading of AR severity was based on integrating available valve academic research consortium (VARC-II) criteria[22], namely: CE, DFR, RV/RF and EROA (table 1). AR

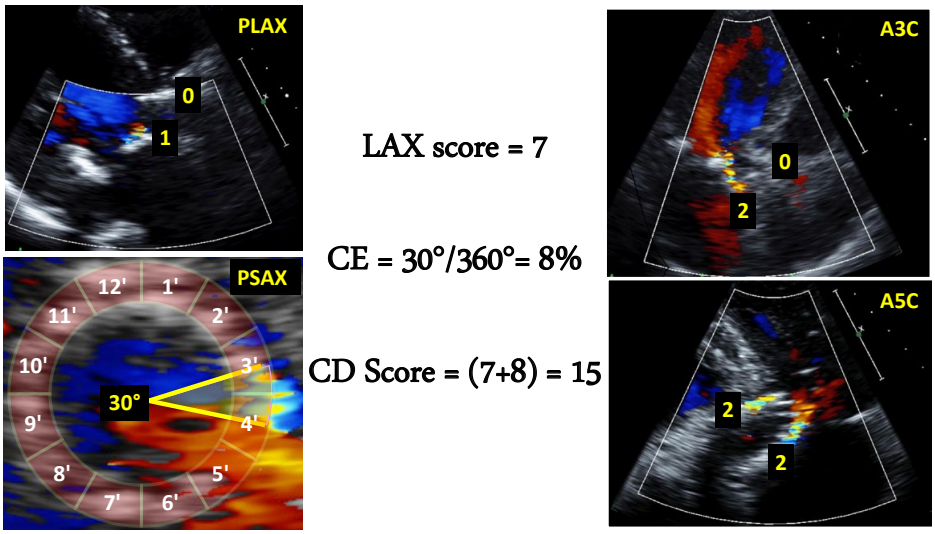

Figure 1. Color Doppler parameters of paravalvular AR assessment. Diagrammatic representation of the face-of-a clock model of parasternal short axis view (left lower panel) with a color Doppler scan. A paravalvular leak is seen circumferentially extending for 30° (from 3'and 4'). Low velocity (laminar) flow is not considered as regurgitation. Long axis (LAX) score is generated as the sum of the qualitative assessment of the regurgitant jet from the parasternal long axis (PLAX), apical-five chamber (A5C) and apical-three chamber (A3C) views. Color Doppler (CD) score is the sum of the circumferential extent (CE) of the PVL and the LAX score.

Table 1. The Valve Academic Research Consortium-II criteria for quantification of transcatheter aortic valve regurgitation.

		Mild	Moderate	Severe
1.	**Diastolic flow reversal in the descending aorta—PWD**	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
2.	**Circumferential extent (CE) of prosthetic valve paravalvular regurgitation (%)**	<10%	10-29%	≥30%
3.	**Regurgitant volume (ml/beat)** **Regurgitant fraction (%)**	<30 ml <30%	30-59 ml 30-49%	≥60 ml ≥50%
4.	**Effective regurgitant orifice area (cm^2)**	0.10 cm^2	0.10-0.29 cm^2	≥0.30 cm^2

PWD=pulsed-wave Doppler

grade was based on the class agreed by all/the majority of available criteria. In case of discrepancy of available criteria, CE was always heavily weighted unless negative (due to a relatively high rate of false negative results of this parameter).

A continuous metric was generated to represent the average rank (0=none-trace, 1=mild, 2= more than mild) of all available AR severity criteria assuming an equal weight of all criteria (VARC score). If all four criteria are measurable, a maximum total score of 8 could be obtained.

Color Doppler-based AR grading:

Four color Doppler views were used to scan for AR; the PSAX view and 3 long axis (LAX) views (parasternal long axis, apical 5-chamber and apical 3-chamber views). From the 3 LAX views, 6 different locations around the transcatheter valve can be identified (figures 1 and 2)[23].

LAX score: For each of the 6 LAX locations, a qualitative score was given for paravalvular AR jet features; 0=no visible regurgitant flow, 1=ill-defined turbulence within the stent that is not quantifiable, 2=significant well-defined jet with the jet path visible from its origin until the valve stent inflow edge. This gives a theoretical range of 0-2/LAX location and a theoretical range of 0 (no visible jets in any of the 6 locations) to 12 (significant jets seen in the 6 locations) for all locations combined (figure 1).

Color Doppler (CD) score (figure 1): CD data from LAX and PSAX views were combined to generate a CD score (=CE% + LAX score). The maximum CD score possible is 112 although severe AR would typically have a score of ≥ 30 to 42.

Interobserver variability of echocardiographic AR assessment: In randomly selected cases, echocardiographic analysis was performed by both observers (n=30) and by the same observer (at a median interval of 49 days, n=15) to test inter- and intra-observer reproducibility. Weighted kappa coefficient for AR grade (based on the VARC-II criteria) was 0.51 (consistent with a moderate agreement[15,16]) for inter-observer comparison

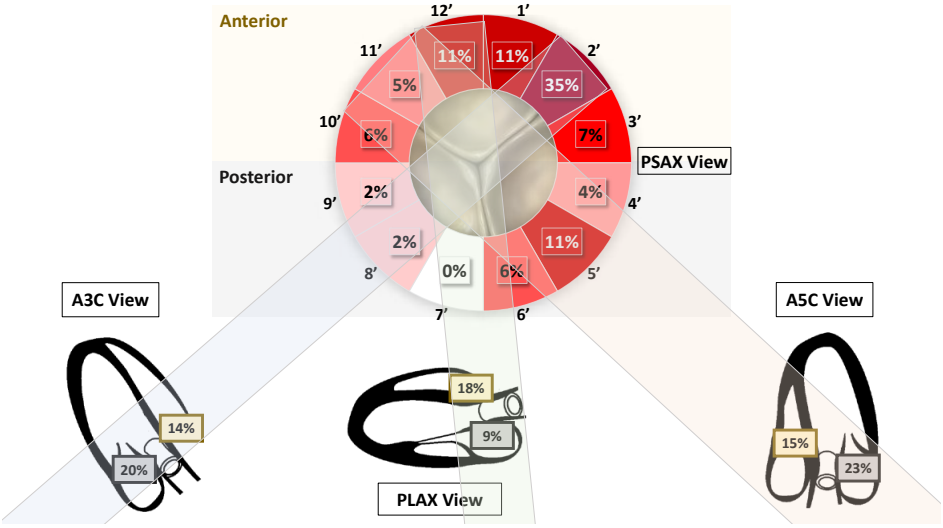

Figure 2. Location of paravalvular AR jets determined by color Doppler in parasternal short axis (PSAX) view and long axis views. Jet originating at the non-coronary sinus region (posterior location in apical 3-chamber view) are under-represented in PSAX view. While 20% of jets seen in long axis views are present in that region, only 4% of those depicted on PSAX are located in that sector. The overlay of the orientation of long axis views on the clock-face model of the PSAX view is modified from Schultz et al, 201145. Part of the figure has been reproduced with permission from Gonçalves et al. J Am Soc Echocardiogr. 2012; 25(1):47-5546.

and 0.83 (consistent with an excellent agreement[15,16]) for intra-observer comparison ($p<0.005$ for both). The intraclass correlation coefficient (ICC) for paravalvular AR jet CE was 0.91 (95% confidence limits, 0.82-0.96) for inter-observer comparison and 0.95 (95% confidence limits, 0.86-0.98) for intra-observer comparison ($p<0.001$ for both).

Statistical methods:

For numerical variables, visual inspection (of histograms) and Shapiro-Wilk test were used to determine normality of distribution. When nonparametric statistical methods were used, we summarized data as median and quartiles instead of means and standard deviations (SD). Categorical variables were summarized as frequencies and percentages.

Baseline patient characteristics were descriptively summarized. Differences between groups with different angiographic grades of AR were assessed by Kruskal-Wallis and Mann-Whitney U tests for continuous variables and by chi-square test for categorical variables. A kappa (k) statistic was used to determine the agreement on grading of AR severity between TTE and aortography. Receiver-operating characteristics (ROC) curves were generated for the diagnosis of >mild AR by multiple quantitative echocardiographic parameters. The cut-points were defined using ROC curves on the basis of the highest sum of sensitivity and specificity for the definition of significant AR.

Statistical analysis was performed with SPSS 23 (IBM, Armonk, NY, USA). All probability values were two-tailed, and a value of $P<0.05$ was considered significant.

RESULTS

One hundred sixty five patients (age, 82±5 years; 94 males) were included. All patients received a CoreValve bioprosthesis (Medtronic, Minneapolis, MN, USA), via a transfemoral (n=138), trans-subclavian or direct aortic access. The valve size was 29 mm in 45%, 31 mm in 32%, 26 mm in 20% and 23 mm in only 3% of patients, with an average cover index of 14.7±4.9%. On post-implantation angiography, AR was graded as none-trace in 15 (9%), mild in 111 (67%) and >mild in 39 (24%) patients. Postdilation was performed in in 21.7% and another valve (in-valve) was implanted in 5.2% of cases. Apart from male gender (76.3% vs. 52.4%, p=0.007), there were no differences in baseline characteristics (table 2) between those with and without >mild AR.

Table 2. Baseline demographic, clinical and echocardiographic characteristics.

Variable	All patients (n=165)
Age (years)	82.1±5.2
Male	94 (57)
Logistic EuroSCORE (%)	14.8±9
Body mass index (kg/m^2)	28.9±5.3
Diabetes mellitus	55 (33)
Hypertension	153 (93)
Chronic lung disease	58 (35)
Cerebrovascular disease	31 (19)
Renal dialysis	1 (0.6)
Previous CABG	42 (25)
Previous PCI	22 (13)
NYHA class	
II	71 (43)
III	89 (54)
IV	5 (3)
AVA (cm^2)	0.68±0.16
AVA index (cm^2/m^2)	0.37±0.11
Mean pressure gradient (mmHg)	48.7±13.8
LVEF (%)	59.9±10
Aortic annulus diameter (mm)	22.7±2.8

Data presented as mean±SD or n (%).
AVA=aortic valve area, CABG=coronary artery bypass grafting, Logistic EuroSCORE=Logistic EuroSCORE predicted risk of mortality at 30 day, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, PCI=percutaneous coronary intervention.

ECHOCARDIOGRAPHIC ASSESSMENT OF AR:

Number and location of AR jets:

On PSAX color Doppler (n=146), at least one paravalvular AR jet was seen in 101 patients (69%). A single jet was present in 73 (72%) and multiple jets in 28 (28%) patients (two jets in 24, three jets in 2 and four jets in 2 patients). Two thirds (64%) of jets were detected in the sector of the 360° face-of-a clock that extends from11' to 3' (figure 2).

In those with PSAX showing no AR (45 cases), AR was revealed on LAX color Doppler in 25 (false negative PSAX). Figure 2 shows the location of paravalvular AR jet(s) in PSAX and in LAX views. Jets originating at the non-coronary sinus (posterior location in PLAX and apical 3-chamber views) were more likely to be missed in the PSAX view.

AR grading according to the VARC-II criteria:

As shown in table 3, although median values of the individual parameters (CE, RV, RF and EROA) increased numerically with increasing angiographic severity of AR, there was a marked overlap (P>0.05 for RV, RF and EROA).

Table 3. Distribution of the numerical VARC-II parameters across the three angiographic grades of AR.

Parameter*	Angiographic			P value§
	None-trace AR	Mild AR	>Mild AR	
Circumferential extent *(%)*	1(4)	7(10)	9(8.5)	0.008
Regurgitation volume *(ml)*	16(17)	18(21)	24(22)	0.51
Regurgitation fraction *(%)*	27(21)	30(31)	31(36)	0.783
Effective regurgitant orifice area *(cm^2)*	-	0.12(0.11)	0.14(0.08)	0.185
VARC score *(≥2 criteria)*	1.0 (0.5)	1.33(0.75)	1.5(0.83)	0.03

*Data presented as median (IQR).
§Non-parametric Kruskal-Wallis test
VARC= the Valve Academic Research Consortium.

CE% differed significantly (p=0.008) between the classes (median[interquartile range-IQR]; 1[4], 7[10] and 9[8.5] % in none-to-trace, mild and >mild angiographic AR). When AR grading was based only on CE% (n=121), grade agreement with angiography was achieved in 43% of cases (kappa statistic= 0.13) (table 4.A).

Table 4. Aortic regurgitation grade agreement between echocardiography (VARC-II criteria) and angiography.

A.

n=121			CE%-based grading			Total
			None-trace	Mild	>Mild	
Angiographic grading	**None-trace**	n (%)	**7 (70.0%)**	2 (20.0%)	1 (10.0%)	**38/121 (31%)**
	Mild	n (%)	23 (28.4%)	**30 (37.0%)**	28 (34.6%)	**52/121 (43%)**
	>Mild	n (%)	5 (16.7%)	10 (33.3%)	**15 (50.0%)**	**31/121 (26%)**

CE=circumferential extent of the paravalvular AR jet.

B.

n=101			VARC-II grading (≥ two criteria)			Total
			None-trace	Mild	>Mild	
Angiographic grading	**None-trace**	n (%)	2 (18.2%)	8 (72.7%)	1 (9.1%)	**32/101 (32%)**
	Mild	n (%)	6 (9.1%)	37 (56.1%)	23 (34.8%)	**53/101 (53%)**
	>Mild	n (%)	1 (4.2%)	9 (37.5%)	14 (58.3%)	**16/101 (16%)**

VARC=the Valve Academic Research Consortium.

Overestimation vs. angiography
Agreement with. angiography
Underestimation vs. angiography

The average AR grade determined by the VARC II-parameters (VARC score), significantly differed between the AR angiographic grades (1[0.5] vs. 1.33[0.75] vs. 1.5[0.83], p=0.03) but only when at least 2 criteria were combined (n=101). Grade agreement with angiography was, however, achieved in only 53% of cases (kappa statistic= 0.14). Inter-technique agreement was lowest for none-trace (18%) AR (table 4.B). Extreme misclassification (i.e. from none-to-trace to >mild or vice versa) occurred only in 2 cases (2%).

AR grading using other criteria:

PHT (n=71) tended to be higher in patients with angiographic mild or less AR (450 [102] ms) than in those with >mild AR (398 [149] ms, p=0.057). Based on the cut-point (500 msec) set per-guidelines[18] for discriminating mild or less from >mild AR, agreement with angiographic grading was achieved in only 42% of cases (in 79% of cases with angiographic >mild and in only 23% of cases with mild or less AR). Using the ROC curve to better define a cut-point, 403 msec had the best sum of sensitivity (75%) and specificity (52%) to define >mild AR (area under the curve-AUC, 0.63) and improved agreement with angiography to 68%.

LAX color Doppler view(s) were available in almost all cases (n=164, 99%). LAX score showed a stepwise increase with increasing angiographic severity of AR (3[4] in none-trace, 4[4] in mild, and 6.5[2.8] in >mild AR, p< 0.001). CD score was available in 130 cases (79%) and increased significantly with increasing angiographic severity of AR (2[8.5] in none-trace, 11[14] in mild and 18[10] in >mild AR, p<0.001).

Using ROC curves, the cut-points of the VARC score, LAX score, CD score and PHT that best defined an angiographic >mild AR were identified (Table 5, Figure 3). Using those cut-points, the combination of LAX score and VARC score improved the specificity and the negative predictive value of identifying angiographic >mild AR to 78% and 87%, respectively (Figure 4.A). The combination of the CD score with PHT gave the best sum of sensitivity (69%), specificity (91%), positive (85%) and negative (81%) predictive values (Figure 4.B).

Table 5. ROC-curve statistics of the VARC, long-axis and color Doppler scores and PHT to define angiographic >mild AR (n=101).

Index	Angiographic >Mild AR				
	C-statistic (95% confidence limits)	p	Cut-point	Sensitivity (%)	Specificity (%)
VARC score	0.63 (0.51-0.75)	0.057	1.29	75	52
LAX score	0.79 (0.69-0.88)	<0.001	4.25	92	58
CD score*	0.76 (0.65-0.88)	<0.001	11.5	91	56
PHT	0.66 (0.5-0.82)	0.058	403	75	62

*CD score = LAX score + CE (%).

CD=color Doppler, CE=circumferential extent of the paravalvular regurgitation jet, LAX=long-axis, PHT=pressure half time, VARC=the Valve Academic Research Consortium.

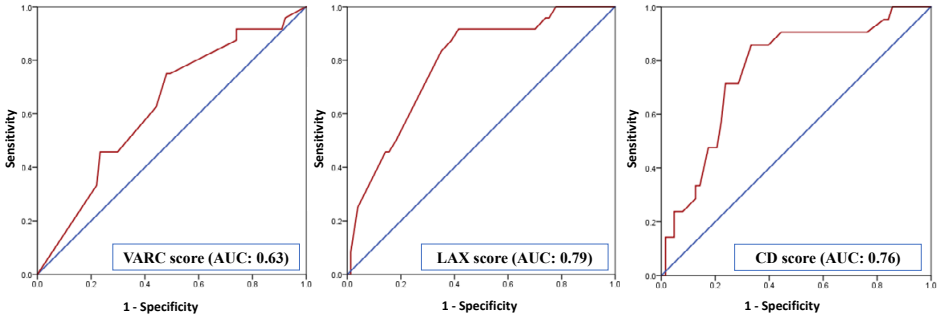

Figure 3. Receiver operating characteristics (ROC) curves of the VARC, long axis (LAX), and color Doppler (CD) scores used to define an angiographic >mild AR.

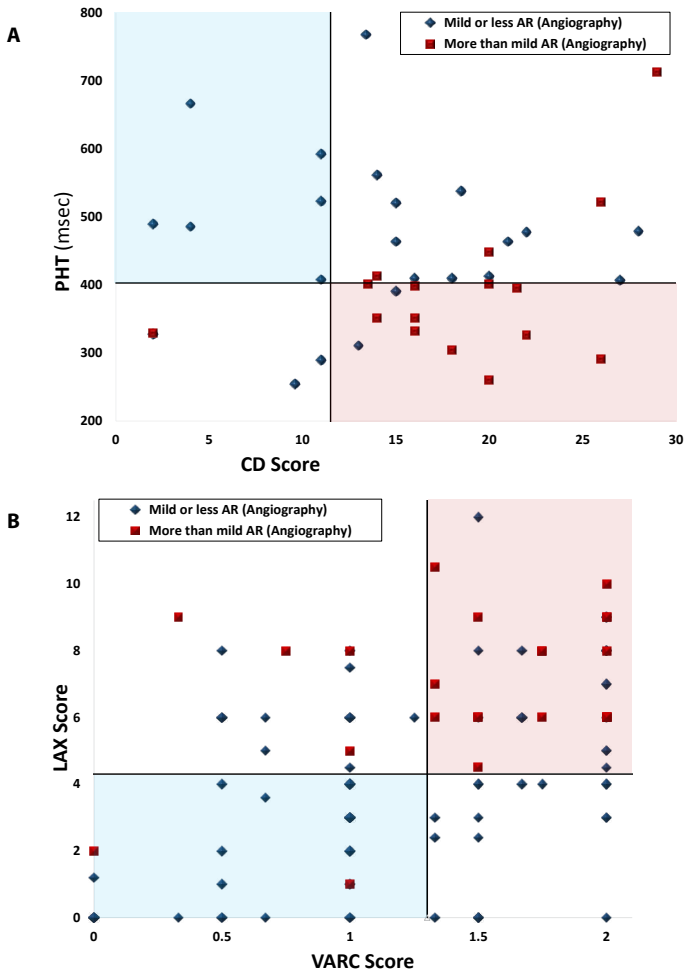

Figure 4. Combining different echocardiographic parameters (A: long-axis score and VARC score; B: Color-Doppler score and pressure half time) to define angiographic >mild AR.

DISCUSSION

The main findings of the present study are that (1) echocardiographic grading of post-TAVI AR (based on VARC II criteria) is frequently at odds with angiographic grading, especially when a single echocardiographic parameter is used, (2) combining more echocardiographic criteria and adding LAX color Doppler to the current VARC criteria improve inter-technique agreement, and (3) greater than mild AR can be defined by one of the following combinations of criteria: a) LAX score >4.25 and VARC score (using at least 2 criteria) >1.33; b) CD score >11.5 and PHT <400 msec.

Paravalvular AR is a frequent complication of TAVI that contributed to eroding its clinical benefit and limiting its extension into lower risk patients. Very important data on the natural history of post-TAVI AR are still, however, inconsistent. The reported rate of incidence ranged from 40% to 67% for trivial to mild and from 7% to 27% for moderate to severe AR[1,24]. The fate of AR has been described as "improving"[25], "deteriorating"[26], "stable"[27] and "variable"[28] in different reports. The reported association with clinical outcomes ranged from "no relation"[29] to "a strong relation" of even mild AR[2].

Many echocardiographic parameters used for quantitating native transvalvular AR are inherently unreliable in paravalvular leakage. This might, at least partially, explain the heterogeneity of data on post-TAVI AR and the discrepancy in AR grading between echocardiography and other methods (e.g. cardiac magnetic resonance-CMR).

While there was no difference between CMR and echocardiography in native AR[30,31] or in post-surgical replacement AR[30] quantification, important differences were reported in post-TAVI AR[5,6,30-32]. Kappa statistic of agreement between CMR and echocardiographic AR grading (based on the VARC-II criteria) was 0.33-0.36, consistent with a fair agreement[5,16]. The rate of detection of >mild AR (as defined by CMR) by echocardiography (using VARC criteria, especially DFR and CE) was reported to be 19%[5].

Agreement between angiography and echocardiography has a special importance as they are the standard techniques for periprocedural and follow-up assessments, respectively. In a study by Sherif et al, angiographic and CMR grading of post-TAVI AR showed a substantial agreement (k = 0.72)[6]. Echocardiographic grading was, on the other hand, discordant with CMR (k=0.20) and angiography (k=0.14)[6]. Small sample size, relatively long interval between angiographic and echocardiographic studies (4 weeks) and using PLAX view as a sole echocardiographic view for AR assessment are, however, important limitations of that study. In another study by Mihara et al[24], AR grading on color Doppler transesophageal echocardiography was discordant with that determined by angiography in 44% of cases (kappa statistic = 0.20). In the present study, discordance between echocardiographic and angiographic grading of post-TAVI AR is further confirmed.

Color Doppler criteria:

LAX color Doppler (combining parasternal and apical views) was available in 99% of cases in the present study and was shown to be the most concordant echocardiographic parameter with angiography. LAX color Doppler has been previously shown to better correlate with aortic regurgitation volume and fraction (as defined by CMR) than short axis CE[31].

Using angiography and LAX color Doppler as a reference, we found a relatively high false negative rate (17%) of PSAX observations. Multiple LAX views on the other hand, allow a nearly complete evaluation of the circumference of the stented valve[23]. Complementing the PSAX color Doppler with the more sensitive LAX views would reduce the rate of false negative observations and might explain the improved agreement with angiography when this parameter was added (to the VARC score or in the CD score).

The high false negative rate of the PSAX view is likely due to two factors; the level of the imaging plane being too aortic thus missing regurgitation at the lower edge of the valve stent, and the acoustic shadowing of the posterior paravalvular region by the stented valve apparatus and native valve calcification[20,23]. The present study supports this latter theory since jets originating at the non-coronary sinus (posterior location in PLAX and apical 3-chamber views) were more likely to be missed in the PSAX view.

Even after consideration of the low sensitivity of PSAX view to detect jets at the non-coronary sinus, there seems to be a preferential vulnerability of the commissural region between the right and left coronary sinuses (RLC) to the development of paravalvular leaks after TAVI. In the present study, 64% of leaks were detected in only one third of the 360° perspective that extends from11' to 3' (mainly involving the right coronary sinus and the RLC) (figure 2). This spatial distribution contrasts with the preferential development (~70%[33,34]) of post-surgical paraprosthetic leaks at the commissural region between right and non-coronary sinuses opposite the membranous interventricular septum (from 8' to 11'). This finding may be due to the asymmetric calcification of the aortic valve with more heavily calcified non-coronary and right coronary cusps[35] but possibly also to the deployment angle and depth of the self-expanding CoreValve[36,37].

Although quantitative grading of AR is recommended by both echocardiographic guidelines[20] and the VARC-II document[22], the present study showed a significant overlap in quantitative grading when compared to angiographic grading. Rather than a pitfall of echocardiography, this finding may be due to the known inconsistent correlation of quantitative assessment of AR with angiographic classification and the significant overlap between angiographic grades[38,39].

Hemodynamic criteria:

Adding a hemodynamic index to the instantaneous color Doppler parameters is an appealing approach. Invasively-measured diastolic pressure gradient across the leaking

bioprosthesis was shown to accurately represent the severity of AR and predict clinical outcomes[40,41]. In the present study, PHT improved the agreement of echocardiography with angiography when added to a color Doppler-based scheme. The proposed cut-point differentiating mild or less from >mild AR (400 ms instead of 500 ms) needs yet to be validated but reconciles with the hemodynamic context of post-TAVI AR. Small, stiff and concentrically-hypertrophied left ventricles[42] with concomitant abnormal aortic compliance may lead to flow characteristics of the AR jet that are quite different from chronic AR[43].

Limitations:

Angiographic assessment of AR cannot distinguish central from paravalvular jet and provides a subjective qualitative grading that inconsistently correlates with quantitative assessment of AR[38,39]. Those shortcomings limit its consideration as a "gold standard", but rather emphasize the need for combination with echocardiography and the importance of inter-technique consistency. Alternative options are, nevertheless, limited. Cardiac magnetic resonance is a more precise and quantitative means of assessing chronic AR but correlates poorly with echocardiography in the post-TAVI setting[31]. Furthermore, the inconsistency of definitions of AR severity[44] and the inability to distinguish mild AR (common and likely harmful after TAVI) from normal flow[44] are important limitations of AR assessment by CMR after TAVI.

The performance of aortography shortly after valve implantation might have limited the accuracy of AR assessment, because the nitinol frame of the CoreValve may continue to expand after implantation. However, early postimplantation angiography is the routine method in the majority of laboratories and at least 10 minutes were mandatorily left before final aortographic acquisition in the present study. When is the most appropriate time-point to assess AR after TAVI? This is a critical question given the conflicting data on the fate of PVLs, with the answer being yet awaited.

Angiographic and echocardiographic studies were performed sequentially (rather than simultaneously) under different hemodynamic circumstances. As Doppler data are impacted by the driving pressures, this might have introduced some variability to the results of both techniques.

In fact, all Doppler parameters, especially continuous wave Doppler ones, are sensitive to LV filling characteristics which are subject to acute changes after TAVI. This could be, on one hand, considered a limitation of those parameters but can be, on the other hand, considered as an advantage. An index that accounts for the hemodynamics on either side of the aortic valve (e.g. LV compliance) should more accurately reflect not only the hemodynamic significance of an AR jet but also the underlying hemodynamic vulnerability. We think that one of the approaches to delineate the significance of mild PVLs (a matter of continuing debate) could be the use of those "hemodynamic" parameters.

All cases received a single device type (self-expanding), and generalization of the results to other devices should be cautious.

Finally, the studied group of patients is not a truly-consecutive series given the common existence of exclusion criteria (inadequate angiographic and/or echocardiographic studies). Adequacy of echocardiography demanded good-quality images of at least 2 of the parameters of AR severity (color Doppler, quantitative Doppler, aortic flow criteria and/or PHT of AR jet). The rate of >mild AR in the present series is higher than usually reported for this type of transcatheter aortic valves, reflecting the selection bias by excluding cases with inadequate angiographic and/or echocardiographic study.

CONCLUSION

There is only a modest agreement between angiography and the individual echocardiographic parameters in the grading of AR severity after TAVI. This might account, at least partially, for the inconsistency of data on the incidence and fate of post-TAVI AR. Integrating multiple parameters (instead of relying on a single criterion) and adding more parameters (color Doppler and hemodynamic) to the VARC-II criteria improve inter-technique reproducibility. Combination criteria for determining the severity of AR, such as those proposed in the present study, should be validated in in terms of their association with clinical endpoints.

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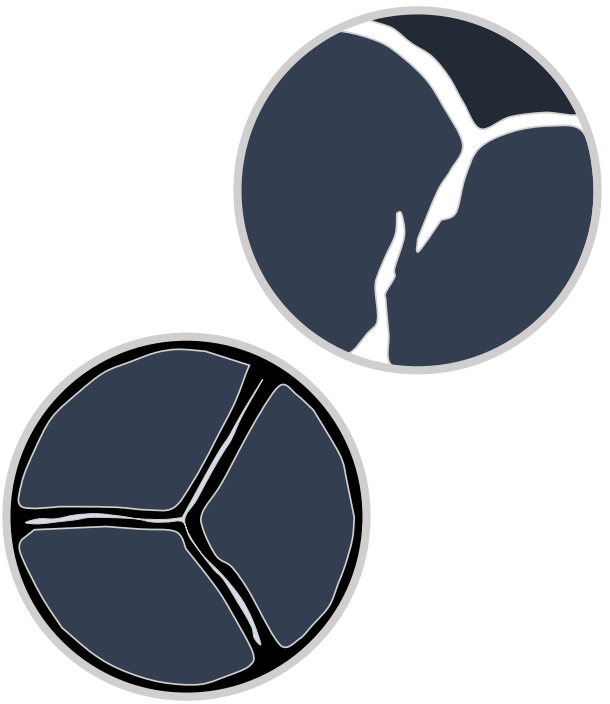

Chapter 6

Videodensitometric quantification of paravalvular regurgitation of a transcatheter aortic valve: in-vitro validation

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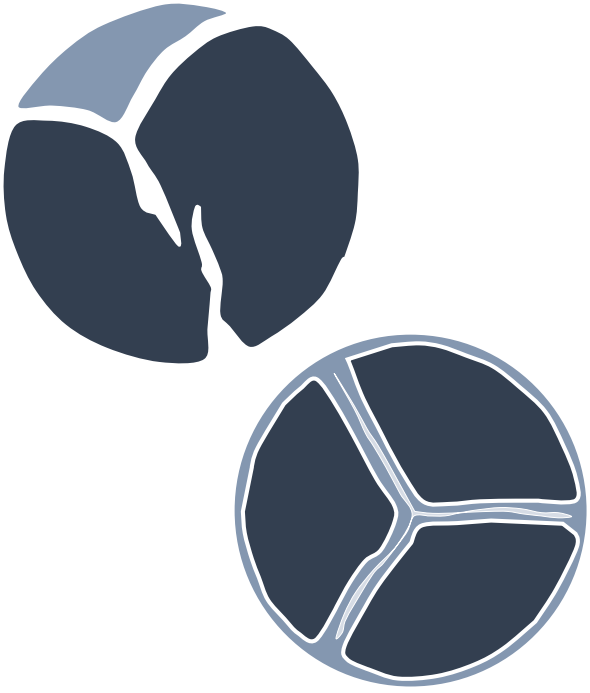

ABSTRACT

Aims:

Videodensitometric assessment of aortography provides a periprocedural quantitation of prosthetic valve regurgitation (PVR) after transcatheter aortic valve implantation. We sought to compare the videodensitometric parameters of PVR severity to the regurgitation fraction (RF) in a controlled in-vitro setting.

Methods and results:

In a mock circulation system, a transcatheter balloon-expandable valve inserted at the aortic valve position was gradually deformed to induce different grades of paravalvular leakage and the RF was measured with a transonic flow probe. Contrast aortography was performed and the following videodensitometric parameters were generated: left ventricle-aortic regurgitation (LV-AR), LV outflow tract–AR (LVOT-AR), quantitative regurgitation assessment (qRA) index, relative maximum density (Relative Max), and Maximum Upslope of the LV time-density curve.

The correlation was substantial between videodensitometric parameters (LV-AR, LVOT-AR, qRA index, Relative Max, and Maximum Upslope) and RF (r^2=0.96, 0.96, 0.93, 0.87, and 0.93; $p<0.001$ for all). LV-AR (region of interest-ROI=entire LV) and LVOT-AR (ROI=LVOT) were not different (p=0.51) and were strongly correlated (r^2=0.99) with a mean difference of 1.92 [95% limits of agreement: ±2.83] %.

The correlations of LV-AR and LVOT-AR with RF were stronger when more than one cardiac cycle was included in the analysis (1 cycle: r^2=0.85 and r^2=0.83; 4 cycles: r^2=0.96 and r^2=0.96, for LV-AR and LVOT-AR, respectively). Including more cycles beyond 4 did not improve accuracy.

Conclusion:

Quantitative assessment of PVR by videodensitometry of aortograms strongly correlates with the actual RF in a controlled in-vitro setting. Accuracy is improved by including more than one cardiac cycle in the analysis.

INTRODUCTION

Since prosthetic valve regurgitation (PVR) after transcatheter aortic valve implantation (TAVI) is related to mortality[1-3], accurate assessment of its severity is needed during the procedure when there is still a chance to avert it. Quantification of PVR, typically and most commonly paravalvular, is challenging[4]. Transesophageal echocardiography (TEE) and aortography are the standard tools for the assessment of PVR during the procedure. However, echocardiography has a low reproducibility[5] and a low sensitivity to detect paravalvular leaks in certain sectors of the device circumference[6], and the Sellers' method[7] of aortographic assessment is qualitative and subjective[4].

Quantitative aortographic assessment of PVR after TAVI by video-densitometry is reported to overcome the limitations of the Sellers' method[4,8,9]. In the first application of this technique to TAVI patients by Schulz et al[10], the entire left ventricle (LV) was considered the region of interest (ROI) and the contrast density in the LV was compared to that in the aortic root to yield the quantitative regurgitation analysis (qRA) index. However, this method of analysis was not feasible in the majority of cases due to the influence of background structures overlapping the ROI (e.g. the contrast-filled descending aorta). In order to avoid this shortcoming, our group developed a modified method that restricts the analysis to the left ventricular outflow tract.

In the minimalist TAVI approach, which is becoming the default TAVI approach[11,12], since general anesthesia is replaced by sedation and TEE is seldom an option, quantitative aortographic assessment can serve as the first screening technique to determine the severity of PVR during the procedure. However, this technology is yet to be validated. In a mock circulation system, an artificial PVR was created in a balloon-expandable transcatheter heart valve (THV) and the videodensitometric aortographic assessment was compared to the actual regurgitation fraction measured by a transonic probe.

METHODS

The mock circulation system:

The mock circulatory system, shown in Figure 1, consists of three components: 1) an elastic silicone tube corresponding to the aortic root, 2) a THV module (a 25 mm diameter plastic tube in which a THV was deployed), and 3) a rigid polycarbonate tube including a servomotor-operated piston pump acting as the LV[13,14]. The system was submerged in a 30 Liter water bath heated to 37 degrees Celsius. A pulsatile cardiac output of 5.0 (L/min) was generated at a rate of 75 /min with a corresponding ISO 5840-compliant flow curve (35% systole and 65% diastole per cycle).

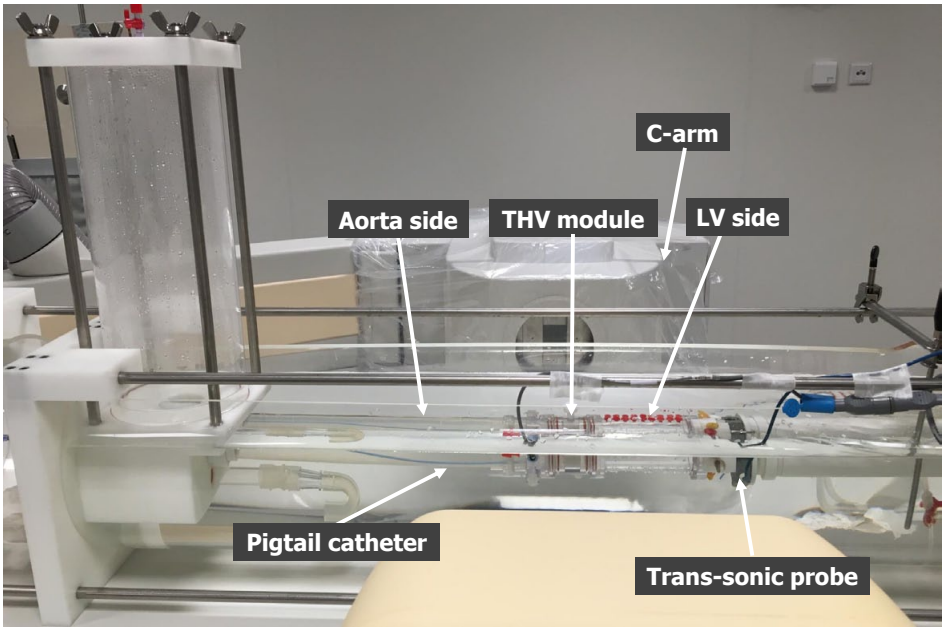

Figure 1. The mock circulation system.
The mock circulation system was set in the cath-lab with a C-arm angulation of LAO 90/CRA 0. The system consists of: 1) Aorta side: an elastic tube corresponding to the aortic root seen on the left-hand side of the figure, 2) Transcatheter heart valve (THV) module: a balloon-expandable THV within a plastic tube seen in the middle, and 3) Left ventricle (LV) side: a tube including a servomotor-operated piston pump seen on the right-hand side of the figure.

The PVR model:

To mimic the asymmetric underexpansion of a THV by a calcium chunk in the landing zone, a radiolucent screw was inserted radially into the THV module and pushed to deform the stent of a 26 mm Sapien XT device (Edwards Lifesciences, Irvine, CA) from the outside (Figure 2). The screw was advanced gradually to create an increasing amount of paravalvular leakage. The device used was clinically-discarded and transvalvular regurgitation (regurgitation fraction: 12%; see Figure 3) was present at baseline before creating paravalvular leakage. The flow rate was measured with a transonic flow probe (Transonic 28PAU, with TS 410 flowmeter) positioned between the outlet of the pump and the aortic valve. The regurgitation volume for each heart beat was calculated as the difference between forward stroke volume and reverse flow volume. The regurgitation fraction (RF) was calculated by dividing the regurgitation volume by the forward stroke volume% (Figure 3). The aortic valve closing volume[15,16] was taken into account as a component of the reverse flow that does not represent an actual regurgitant flow (i.e. subtracted from the reverse flow).

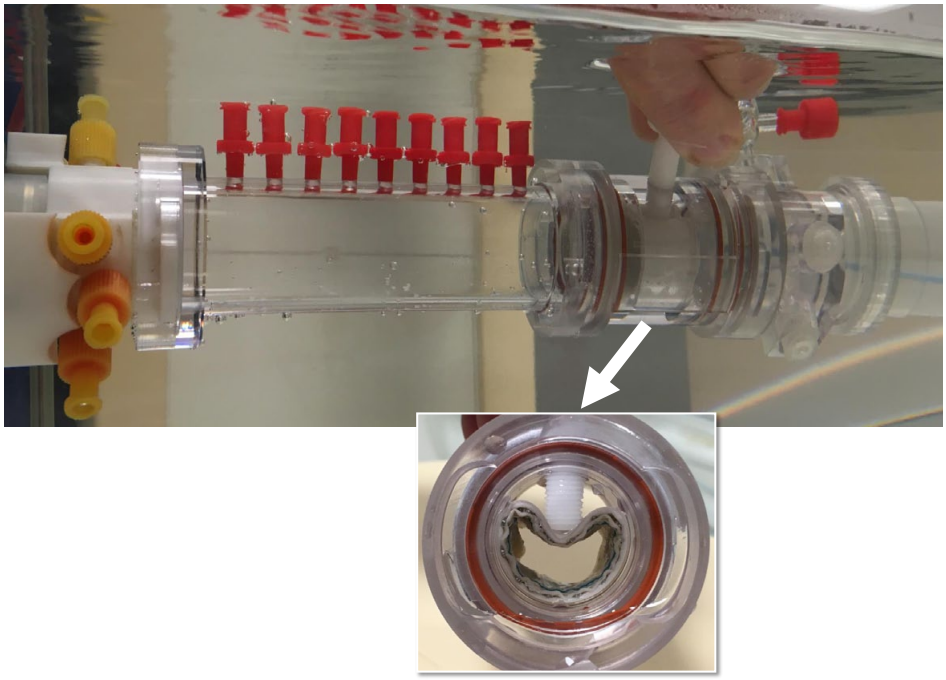

Figure 2. Paraprosthetic valve regurgitation model.
The radiolucent screw was gradually advanced to create a controlled deformation of the prosthetic valve stent, producing increasing paravalvular leakage. The extent of device deformation depicted in this figure was the maximum deformation (yielding a regurgitation fraction of 65%).

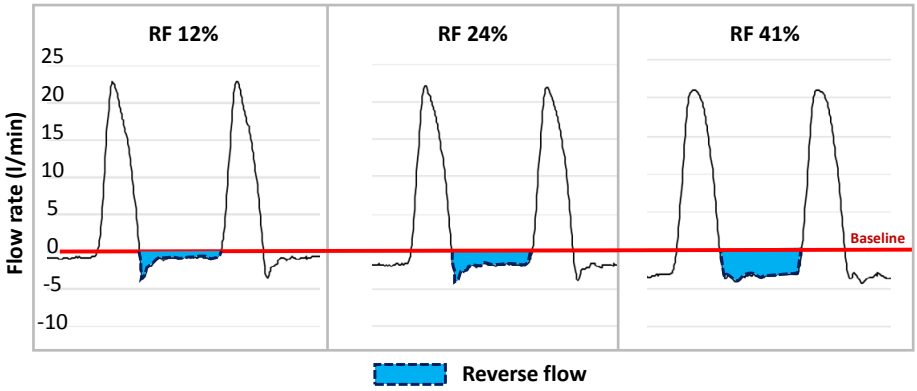

Figure 3. Flow rate curves generated from the readings of a trans-sonic probe.
Prosthetic valve regurgitation fraction (RF) was calculated as the regurgitation volume (below the base line, blue tracing) excluding the closing volume divided by the forward stroke volume (above the baseline). Please note that the lowest RF was 12% because a transvalvular regurgitation existed before deforming the valve stent.

Contrast aortography:

Fluoroscopic images were acquired in the cath-lab (Catharina hospital, Eindhoven, The Netherlands) at a C-arm angulation of LAO 90/CRA 0 (Figure 1). Contrast was injected through a 6 Fr pigtail catheter whose tip was located 2 cm above the upper edge of the THV stent. The distance between the catheter tip and the THV stent edge was confirmed by offline measurement using a quantitative angiographic software (CAAS 5.11, Pie Medical Imaging, Maastricht, The Netherlands).

Contrast (Isovue-370, Bracco Diagnostics Inc., NJ, USA) injection was performed using ACIST CVi® contrast delivery system (ACIST Medical Systems, MN, USA). The set volume, rate, and pressure limit of contrast injection were 20 mL, 22.5 mL/s, and 700 psi, respectively. The mock circulation was heated to body temperature, to bring contrast solubility to physiological levels.

Quantitative videodensitometric analysis of contrast aortography:

A dedicated videodensitometry software (CAAS A-valve 2.0.2; Pie Medical Imaging, Maastricht, The Netherlands)[8-10] was used to analyze the contrast aortograms. For descriptive purposes, the three segments of the mock circulation system were labeled as "aortic root", "THV module" and "LV" (Figure 1). Contrast density in the "aortic root" served as a reference, to which the density in the region of interest (ROI; the entire LV [LV-AR] or the basal third of the LV [LVOT-AR]) is compared (Figure 4-A and B and Online Video 1). The moment of contrast injection is indicated so that all static background radiodensities are subtracted from any further analysis. Using a semi-automatic algorithm, contrast time-density curves (TDC) were generated for the reference region (the aortic root) and for the ROI. The area under the curve (AUC) is automatically calculated as the time-density integral and the relative area under the curve (RAUC) is calculated as the AUC of the ROI divided by the AUC of the reference region% (theoretical range: 0 to 100%). In addition to the RAUC for the entire LV and for the LVOT, the quantitative regurgitation analysis (qRA) index was also calculated. In qRA algorithm, not only the density and the duration of opacification of the LV, but also increasing apical depth of the leaking contrast are considered as markers of PVR severity (figure 4-C). The qRA index, which reproduces the concept of Sellers' method[7] (appreciating density, duration, and depth of LV opacification), yields a continuous severity scale ranging from 0 (indicating no contrast leakage into the LV) to 4 (indicating contrast filling of the entire LV with a greater density than the aortic root). From the cardiac cycle that shows the maximum contrast density value in the reference region, two other parameters were automatically calculated; the Relative Max (= the maximum time-density value of the ROI divided by the reference maximum time-density value %) and the Maximum Upslope (= the maximal slope during upstroke of time-density curve of the ROI) (Figure 4).

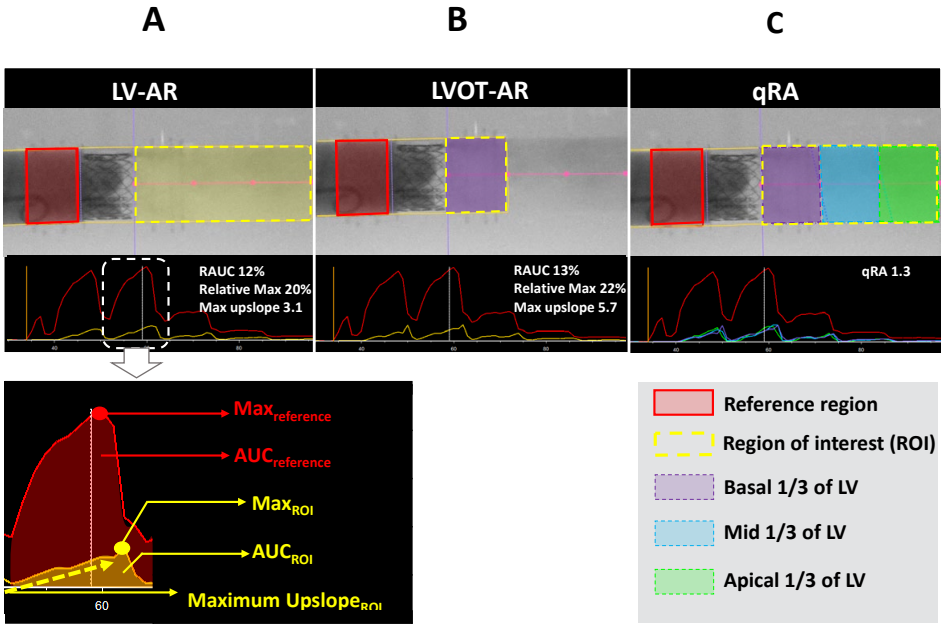

Figure 4. Videodensitometry parameters (LV-AR, LVOT-AR, qRA, Relative Max, and Maximum Upslope). Representative figures for the assessment of LV-AR (A), LVOT-AR (B) and qRA index (C) are shown. Contrast density in the aortic root served as the reference density (red rectangle), to which the density in the region of interest (ROI; enclosed by the yellow dotted line) is compared. The ROI can be the entire left ventricle (LV-AR), the basal third of the LV (LVOT-AR) or the entire LV applying the quantitative regurgitation analysis (qRA) index concept. In the qRA algorithm (C), three time-density curves are generated for the three segments of the LV (basal [violet], mid [blue], and apical [green]). The time-density values for the apical segment are more heavily weighted than the mid and basal, and the values for the mid segment are more heavily weighted than the basal segment.
Abbreviations: AUC=area under the time-density curve, RAUC=relative AUC

Statistical analysis

For numerical variables, when non-parametric statistical methods were used, we summarized data as median and inter-quartile range [IQR]. Otherwise, numerical data were summarized as mean ± standard deviation (SD). The relationship between continuous parameters of PVR severity was tested using Spearman correlation. The sample size for correlation was estimated to be at least 10 data pairs (for an α-level of 0.05, a β-level of 0.20 [power = 80%], and a hypothesized correlation coefficient r=0.80 [denoting a strong correlation]). The reproducibility of videodensitometric assessment was assessed by calculating the intraclass correlation coefficient (ICC) presented with its 95% confidence interval (CI) and the difference between paired observations (bias) was displayed using the Bland-Altman method. The 95 % limits of agreement (95 % LOA) were estimated as ±1.96 × SD of the bias. Wilcoxon signed-rank test was performed to compare LV-AR and LVOT-AR.

RESULTS

Twelve in-vitro experiments were performed at different degrees of RF (mean±SD: 35.6±21.5%; range: 11.8% to 65.3%). The actual contrast injection volume and rate were (median [IQR]) 19.4[19.2-19.9] ml and 21.1[20.8-21.9] ml/sec.

Videodensitometric parameters vs. RF of PVR:

The mean±SD (range) for videodensitometric parameters were as follow: LV-AR, 24.1±18.3 (3.0-49.0)%; LVOT-AR, 26.0±17.7 (6.0-50.0)%; qRA index, 1.71±0.79 (0.70-2.60); Relative Max, 30.8±23.9 (5.0-63.0)%; and Maximum Upslope, 6.73±6.29 (0.80-16.30).

The correlation was substantial between LV-AR and RF (r^2=0.958, y=0.845x - 6.011; Figure 5.A), between LVOT-AR and RF (r^2=0.964, y=0.816x - 3.049; Figure 5.B), between qRA index and RF (r^2=0.933, y=0.036x +0.417; Figure 5.C), between Relative Max and RF (r^2=0.874, y=1.094x -8.130; Figure 5.D), and between Maximum Upslope and RF (r^2=0.931, y=0.286x -3.462; Figure 5.E), p<0.001 for all.

LV-AR and LVOT-AR were not different (p=0.514) and were strongly correlated (r^2=0.992, p<0.001, y=0.967x + 2.718). The mean difference between LVOT-AR and LV-AR was 1.917 [95% LOA: ±2.828] %.

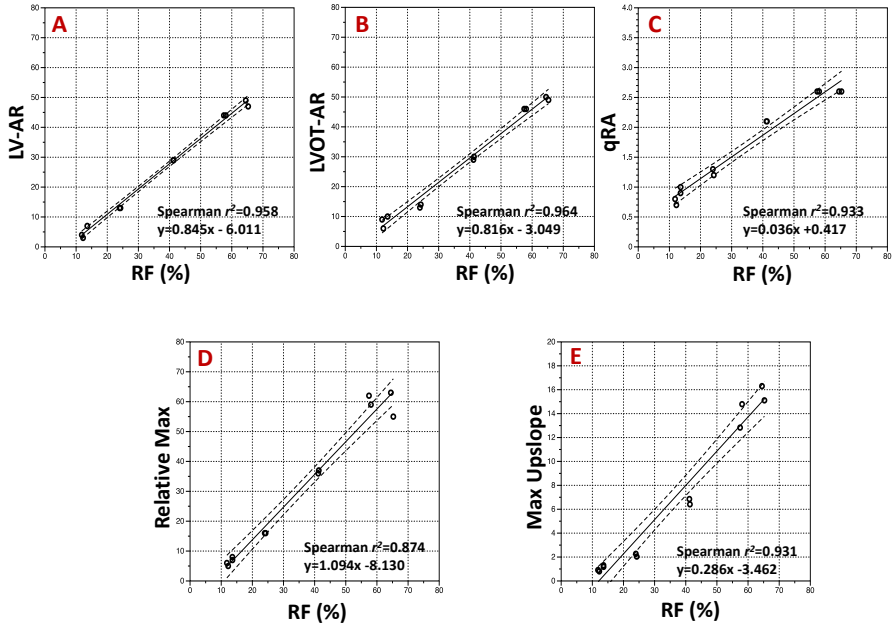

Figure 5. Correlation between videodensitometric parameters of PVR severity and RF. Scatter plots with the line of best fit and the 95% confidence interval lines displaying the relation between the regurgitation fraction (RF; on the horizontal axis) and videodensitometric parameters of regurgitation severity on the vertical axis: LV-AR (A), LVOT-AR (B), qRA index (C), Relative Maximum (D), and Maximum Upslope (E).

How many cardiac cycles to include in videodensitometric analysis:

As shown in Figure 6, the correlations of LV-AR and LVOT-AR with RF were stronger when more than one cardiac cycle was used for the analysis. The correlation coefficient increased stepwise with increasing number of cardiac cycles included, from 1 cycle (LV-AR: r^2=0.854, LVOT-AR: r^2=0.830) to 4 cycles (LV-AR: r^2=0.962, LVOT-AR: r^2=0.962). Including more cycles beyond 4 did not seem to add any meaningful accuracy to the analysis.

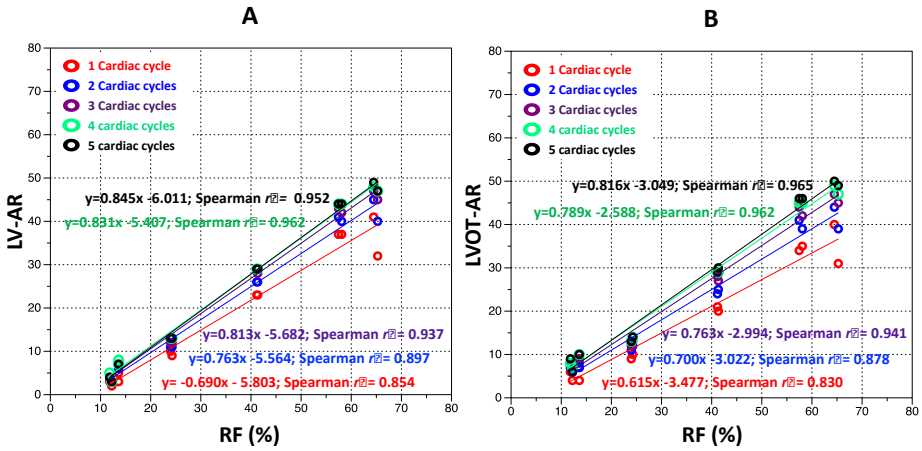

Figure 6. Correlation between LV-AR and LVOT-AR and RF using different numbers of cardiac cycles. Scatter plots with the lines of best fit displaying the correlations of LV-AR and LVOT-AR with RF when 1, 2, 3, 4 or 5 cardiac cycle(s) is/are included in the analysis.

Reproducibility of videodensitometric parameters:

To investigate the inherent variability of the method, videodensitometric assessment was repeated for each RF level by the same analyst. The ICC was 0.999 (95%CI: 0.998-1.000) for LV-AR and 0.999 (95%CI: 0.998-1.000) for LVOT-AR. The average intra-observer difference was -0.67% for LV-AR and -0.25% for LVOT-AR while the 95% LOA was ±1.27% and ±1.22%, respectively (Supplementary Figure 1).

DISCUSSION

Quantitative videodensitometric assessment of AR severity is based on the concept of comparing opacification of the LV to that of the aortic root after aortic root angiography[17-19]. The present study provides an in-vitro validation of this concept in a THV module through comparison with the gold standard (actual controlled RF of AR). The strong correlation between videodensitometric parameters and RF further supports

the results of previous clinical studies which showed a significant correlation between videodensitometric parameters of PVR severity and clinical outcomes after TAVI[8,9,20].

In the minimalist TAVI era, the majority of procedures are performed without transesophageal echocardiographic (TEE) guidance. A combination of transthoracic echocardiography (TTE) and a hemodynamic index (like aortic regurgitation index-ARI) can serve as a substitute for TEE when TAVI is performed without general anesthesia. However, the frequency of an ARI <25 (reported to correspond to significant PVR and to portend a worse prognosis[21]) among TAVI patients is very high, ranging from 34 to 57%[21-23] and an ARI of <25 frequently co-exists with no/trivial AR, particularly in the presence of relative bradycardia[22]. When TTE is technically adequate (in patients with a good acoustic window), it remains subject to limited reproducibility and qualitative and overlapping severity grades[5,24,25]. On the other hand, aortography is a practical tool as it is already a routine part of all procedures and gives a direct assessment of regurgitation severity without any inferences or assumptions. On the other hand, ARI utilizes pressures as a surrogate for regurgitation severity and assumes that a rise of LV pressure is the result of PVR, although it might rise due to periprocedural myocardial ischemia[4]. Doppler echocardiography also utilizes mainly color Doppler measurements at a certain jet level as a surrogate for PVR severity and assumes that this level is the neck of the jet, although the jets are often multiple and multi-level[4]). The limitations of aortography are, however, well-acknowledged and are basically related to the subjective qualitative assessment[26]. Videodensitometric technique aims at addressing these limitations. Notwithstanding, videodensitometric methods are not without limitations. An overlap of the contrast-filled descending aorta on the LV and/or aortic root is an important technical challenge to videodensitometric analysis[4]. The definition of a patient-specific overlap-free fluoroscopic projection is, however, possible using computed tomographic planning[27,28].

Videodensitometric methods; accuracy vs. practicality:

Although aortographic assessment of AR has long been based on the visual assessment of the extent of opacification of the entire LV as compared to the aortic root (Sellers' method), we hypothesized that interrogating only the basal one-third of the LV (LVOT-AR) would be adequate. This is based on the fact that any contrast that leaks from the aortic root, has to go through the LVOT, but does not necessarily reach the mid and apical segments. This is even more relevant in the setting of PVR, where regurgitation is most commonly paravalvular. Paravalvular leak typically follows an eccentric, wall-impinging course[29] limiting its free penetration towards the LV apex. Moreover, LVOT-AR has been shown to be less influenced by background radiodensities (e.g. the contrast-filled descending aorta and the diaphragm) and variability of the LV size and function[9,10,18] than the entire-LV interrogation method (LV-AR and qRA). In the present study, the concept of

LVOT-AR which was previously shown to correlate with clinical and surrogate endpoints after TAVI[8,9], is further supported by an excellent correlation with the RF.

Overall, the correlation between videodensitometric parameters of PVR severity and RF was very strong. Moreover, the difference between LV-AR and LVOT-AR was very small and clinically-irrelevant, implying that both parameters can be used interchangeably. Therefore, in the clinical setting when the LV apex is not within the fluoroscopic view or is overlapped by the diaphragm, by gastric air, or by lung shadow, LVOT-AR is a practical and accurate alternative to LV-AR.

We found that the accuracy of the concept of the RAUC (applied in LV-AR and LVOT-AR) is influenced by the number of cardiac cycles included in the analysis. Averaging the values of the RAUC over four cardiac cycles seems to be the ideal setting, with more than 4 cycles adding very little to accuracy, yet prolonging the acquisition and exposing the patient and the physician to needless irradiation. Moreover, with too long acquisition in the clinical setting, contamination of the ROI by coronary opacification and myocardial blush becomes more likely. Although less important in older patients, a higher dose of irradiation can be an issue for younger individuals in whom TAVI seems to be a promising option and in whom accurate assessment of PVR is even more crucial. Therefore, an ideal PVR assessment method should not expose the patient to increased irradiation. Reassuringly, a single cine run of 3-5 cardiac cycles was shown in the present experiment to be sufficient for an accurate videodensitometric analysis.

The importance of the Relative Max and the Maximum Upslope is that both parameters are less influenced by the number of cardiac cycles analyzed and can, thus, be calculated from a single cardiac cycle. We found that these two parameters yield their best accuracy when derived from the cardiac cycle in which the contrast density in the aortic root reaches its peak (results not shown). We observed that this takes place in the second cardiac cycle after contrast injection. It turns out that operators are recommended to acquire a fluoroscopic run of at least four cardiac cycles after contrast injection. In case when this rule is fulfilled but the LV mid- or apical third cannot yield a reliable analysis (e.g. overlapped by background structures), LVOT-AR is a good alternative. In case less than 4 cardiac cycles are available for the analysis, Maximum Upslope can be measured from the second cardiac cycle after contrast injection.

Like other quantitative methods of AR assessment (e.g. magnetic resonance imaging- and Doppler-based RF), the sum of all regurgitant jets (irrespective of their level/number/mechanism) is represented. Notwithstanding, significant PVR after TAVI is most commonly paravalvular and visual angiography is also unable to differentiate para- from trans-valvular regurgitation. However, inability to differentiate para- from trans-valvular regurgitation remains a limitation of the videodensitometric assessment, as the mechanism of regurgitation should be confirmed before a corrective measure (e.g. post-dilation) is performed. So, in an ideal scenario, videodensitometric assessment

should replace visual assessment as the first post-deployment screening test followed, in case of significant PVR, by an ad-hoc transthoracic echocardiographic confirmation of the regurgitation mechanism.

Limitations and advantages of the mock circulatory system and the PVR model:

The settings of the experiment have taken into account the clinical setting in the cath lab (e.g. physiologic cardiac output and heart rate, catheter type and size, as well as type, volume and rate of contrast injection), and more importantly, used a model of THV paravalvular regurgitation for testing.

The mock circulatory system has a 30 Liters container which provides a good dilution of contrast. Therefore, we could ignore the accumulating contrast during the successive experiments. Moreover, the software subtracts background radiodensities present in the field of analysis.

The LV chamber was represented by a rigid cylindrical tube, which obviously lacks the geometry and the physiologic compliance of a human ventricle, but facilitates the measurement of the flow rate which is easier to quantitate in a rigid cylindrical than in a compliant globular chamber[13,30]. An elastic tube was used to substitute the aortic root while exhibiting a physiologic-like distensibility. It is noteworthy that aortic root elasticity was previously reported to be associated with the severity of AR[31]. However, two important differences between the aortic root tube used in the model and the human aortic root existed: 1) The lack of coronary arteries and 2) the lack of coronary sinuses. In a clinical setting, coronary artery opacification and myocardial blush are background radiodensities that interfere with videodensitometric assessment of aortograms and might interfere with the accuracy of analysis. This interference is basically seen when analysis involves long fluoroscopic runs (allowing coronary contrast filling and myocardial blush to take place).

The aortic valve closing volume, which contributes together with the regurgitant flow to the reverse flow, is a confounder to the calculation of regurgitation volume and fraction, especially in sinus-less systems[15]. Although the closing volume typically amounts to ≤10% of the stroke volume, this volume can reach up to 25% of the stroke volume in sinus-less systems[15]. Although we attempted to account for the closing volume and to segregate it from the actual regurgitation volume, the closing volume might still have led to RF overestimation and, hence, to the apparent tendency of the videodensitometric RAUC to give lower absolute values than the RF. Moreover, this "overestimation" might have contributed the relatively large regurgitation at baseline (RF: 12%).

Although it is well-acknowledged that paravalvular leakage jets have peculiar characteristics that limit extension of the rules of assessment of transvalvular regurgitation[4,29], dedicated paravalvular leakage models are scarce. To the best of our knowledge, this is the first in-vitro model that uses an actual commercially-available THV to validate a

PVR assessment method. It should be noted, however, that before creating the artificial paravalvular leakage, a RF of 12% was recorded and, accordingly, smaller RF than 12% were not possible to test. This regurgitation measured before THV deformation can be explained by a combination of a transvalvular regurgitation of the clinically-discarded THV and the "overestimation" effect of the valve closing volume. In the present study, a cobalt-chromium balloon-expandable THV with annular leaflet position was used. Although the reaction of different THV platforms to the screw-induced deformation might vary, the videodensitometric analysis is minimally influenced by these differences. This is because the origin of the paravalvular leak (at the device deformation point) is excluded from the analysis. The regions of interest include the subvalvular segment of the LV (LVOT) and the supravalvular segment of the aortic root. Therefore, the analysis is minimally influenced by the morphology of the regurgitation orifice.

CONCLUSION

Quantitative assessment of PVR by videodensitometry of aortograms is very well correlated with the regurgitation fraction. The restriction of the videodensitometric analysis to the subaortic segment can be more suitable for the assessment of PVR compared to the entire LV interrogation, as it is more feasible in the clinical setting and is accurate in the in-vitro setting.

IMPACT ON DAILY PRACTICE

Quantitative assessment of PVR by videodensitometry of aortograms is an accurate and a reproducible method that can be used to guide TAVI procedures.

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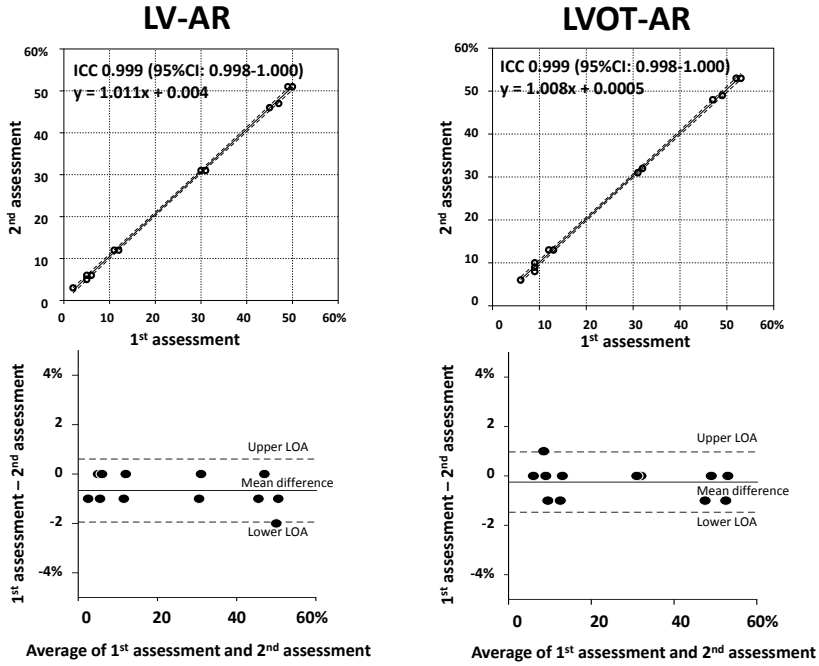
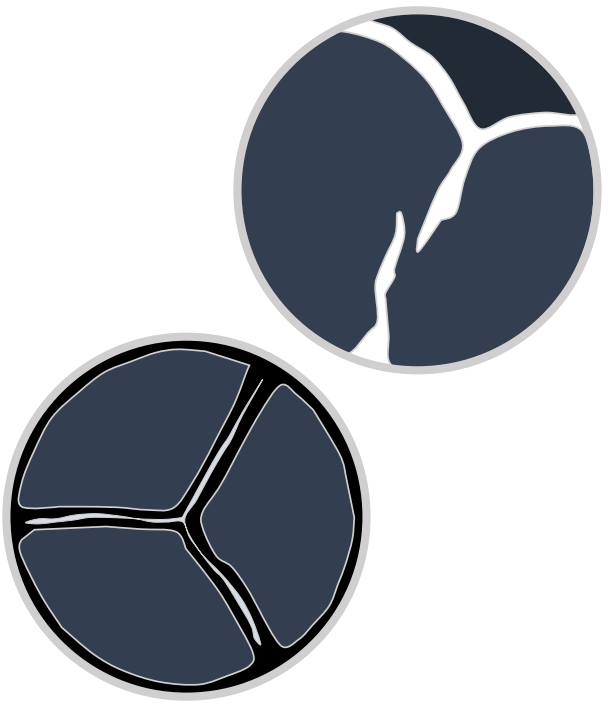
SUPPLEMENTARY FIGURE



Supplementary figure 1. Reproducibility of LVOT-AR and LV-AR.
Upper panels: Scatter plots displaying intraobserver reproducibility of LV-AR (left) and LVOT-AR (right). Lower panels: Intraobserver variability of LV-AR (left) and LVOT-AR (right) displayed on Bland-Altman plots.



Chapter 7

A Novel Angiographic Quantification of Aortic Regurgitation after TAVR Provides an Accurate Estimation of Regurgitation Fraction Derived from Cardiac Magnetic Resonance Imaging

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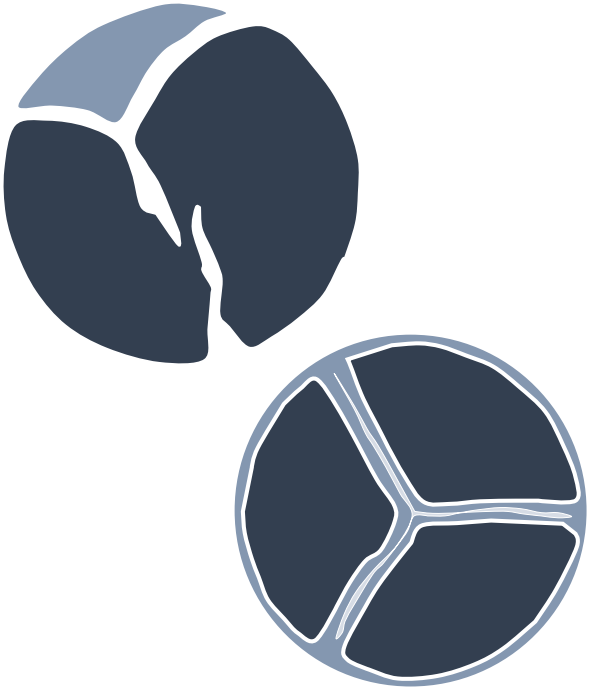


ABSTRACT

Objectives:

We aimed at comparing a new quantitative angiographic technique to cardiac magnetic resonance-derived regurgitation fraction (CMR-RF) for the quantification of prosthetic valve regurgitation (PVR) after transcatheter aortic valve replacement (TAVR).

Background:

PVR after TAVR is challenging to quantify, especially during the procedure.

Methods:

Post-replacement aortograms in 135 TAVR-recipients were analyzed off-line by videodensitometry to measure the ratio of the time-resolved contrast density in the left ventricular outflow tract to that in the aortic root (videodensitometric aortic regurgitation % - VD-AR). CMR was performed within an interval of ≤30 days (mean±SD, 11±6 days) after the procedure.

Results:

The average CMR-RF was (mean±SD) 6.7±7.0% while the average VD-AR was 7.0±7.0%. The correlation between VD-AR and CMR-RF was substantial ($r=0.78$, $p<0.001$). On receiver operating characteristics curves, an VD-AR ≥10% corresponded to ≥mild PVR as defined by CMR-RF (area under the curve-AUC: 0.94, $p<0.001$; sensitivity: 100%; specificity: 83%), while a VD-AR ≥25% corresponded to moderate-to-severe PVR (AUC: 0.99, $p=0.004$; sensitivity: 100%; specificity: 98%). Intra-observer reproducibility was excellent for both techniques (intraclass correlation coefficient: 0.91, $p<0.001$ for CMR-RF and 0.93, $p<0.001$ for VD-AR). The difference on re-rating was -0.04±7.9% for CMR-RF and -0.40±6.8% for VD-AR.

Conclusions:

The angiographic videodensitometric AR provides a surrogate assessment of PVR after TAVR that correlates well with the CMR-RF.

INTRODUCTION

Since the introduction of transcatheter aortic valve replacement (TAVR) as a minimally-invasive alternative to surgery[1], significant improvements have been introduced to this technology. Currently, TAVR outperforms surgery in many aspects[2], but prosthetic valve regurgitation (PVR) still occurs at a higher rate than after surgery and portends worse prognosis[3]. The quantification of PVR is challenging[4]. Although long-term surveillance is typically based on echocardiography, recent data supports a more reliable prognostic value of cardiac magnetic resonance-derived regurgitation fraction (CMR-RF)[5,6]. This superior prognostication is added to some other well-known advantages of CMR over echocardiography; including more reproducible and quantitative assessment[4]. CMR can, therefore, be considered as an ideal tool to quantify PVR but is limited by a number of logistic constrains. The high cost, the limited availability, the technical demand, and the incompatibility with some implanted cardiac rhythm devices all make CMR a less practical tool for routine PVR assessment compared to echocardiography[4].

Recently, the minimalist TAVR approach is increasingly adopted by large TAVR centers. In this approach, general anesthesia is replaced by sedation and transesophageal echocardiography (TEE) is seldom an option. In this setting, angiographic assessment, which currently serves as the first screening tool in most laboratories, is becoming even more crucial in determining the severity of PVR during the procedure. Angiographic assessment using the classic visual (Sellers') method[7] bears many limitations, including subjectivity and lack of precise quantification[4]. Quantitative videodensitometric aortic regurgitation (VD-AR) assessment was recently reported to overcome the limitations of the Sellers' method[4,8,9]. In this study, we sought to compare two quantitative modalities for PVR assessment; a well-established modality that cannot be used in the cath-lab (CMR-RF), and a novel one which has the potential to be applied in the cath-lab for PVR quantification and decision-making guidance (VD-AR). The primary objective was to estimate the correlation between these two modalities, while the secondary objective was to compare their reproducibility.

METHODS

Study population

All patients who were treated with TAVR and had a CMR study performed after the procedure at the Heart Center, Segeberger Kliniken GmbH, Bad Segeberg, Germany were screened for inclusion in this study. The flow chart of the study is displayed in Supplementary Figure 1. The main reason for exclusion was VD-AR non-analyzability (principally due to overlap of the regions of interest by the contrast-filled descending

aorta [83%] or breathing motions [9%]). A total of 135 consecutive patients treated with TAVR who had quantitative angiographic and CMR assessments of PVR performed within an interval of ≤ 30 days constituted the study population. Data collection was approved by the institutional review board, and all patients signed an informed written consent.

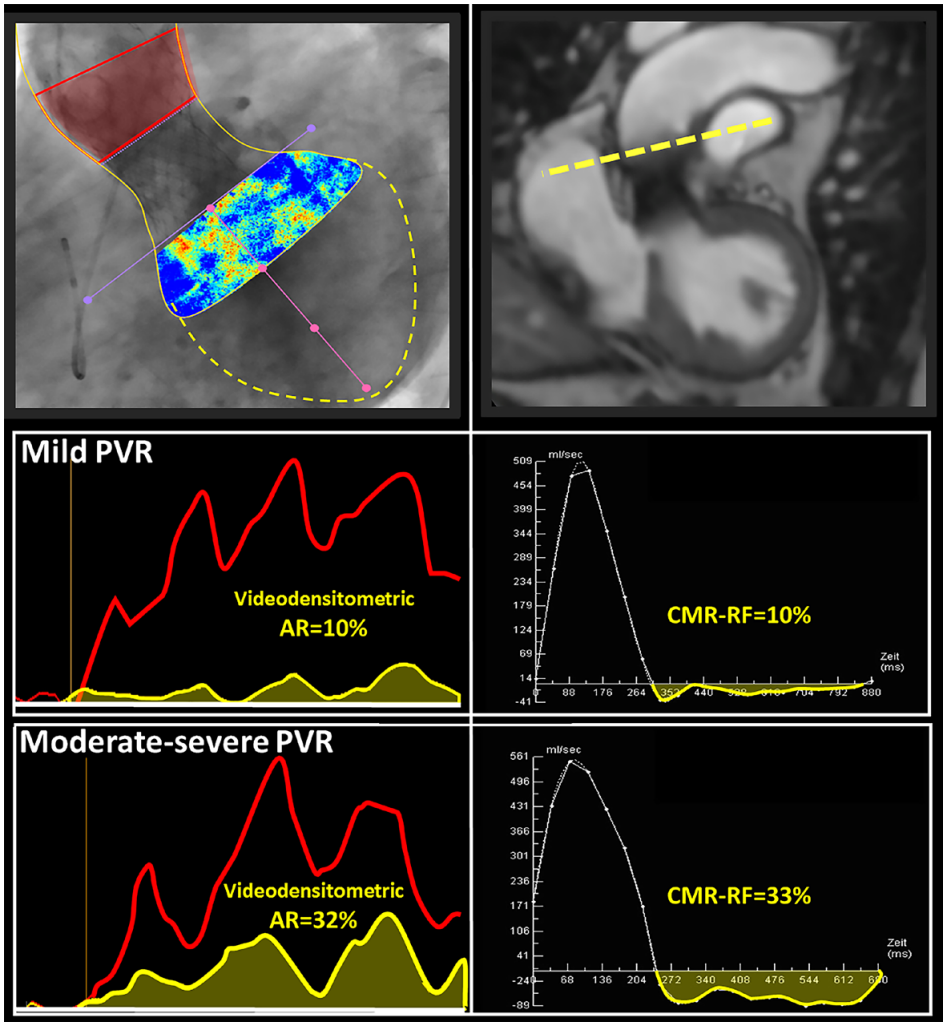
Quantitative aortic root angiography using videodensitometry

Aortic root angiography was performed after valve replacement using a non-ionic contrast (25-30 ml) injected through a pigtail catheter positioned above the prosthetic valve (in case of a balloon- or mechanically-expandable device) or within the distal third of the prosthetic valve (in case of a self-expanding device). A dedicated software (CAAS A-Valve 2.0.2; Pie Medical Imaging, Maastricht, The Netherlands) was used for off-line analysis of the angiograms. The details of this technique have been described elsewhere[9,10]. Briefly, the aortic root and the subaortic (basal) one third of the left ventricle (LV) are manually traced, and the aortic valve annular plane is indicated to define the distal end of the LV region of interest. Contrast time-density curves (TDCs) are generated for both the region of interest (in the LV) and the reference region (the aortic root) from at least three cardiac cycles after contrast injection. From these TDCs, the area under the curve (AUC) is automatically calculated to represent the time-density integral. VD-AR corresponds to the relative AUC, which is automatically calculated by dividing the AUC of the LV region of interest by the AUC of the aortic root (Central Illustration). VD-AR was analyzed by an independent core laboratory (Cardialysis Clinical Trials Management and Core Laboratories, Rotterdam, The Netherlands) and observers were blinded to all baseline, procedural, and CMR data. Rerating by the same observer was performed in 75 cases to test the intrinsic variability of the method.

CMR imaging protocol and data analysis

All patients were investigated by electrocardiogram-gated CMR in the supine position with a 5-element cardiac phased-array coil using a 1.5 Tesla whole body scanner (Magnetom Espree, Siemens AG, Erlangen, Germany). The flow signal at the level of the stent of the prosthetic valve could be safely interrogated by CMR as previously described[11,12].

For flow measurements, a breath-hold velocity-encoded phase contrast magnetic resonance sequence was used ("through plane", segmented fast low-angle shot 2-dimensional sequence, repetition time/echo time 46/2.7 ms, velocity encoding 150-300 cm·sec-1, scan in expiration, scan duration around 10 seconds). The slice was positioned perpendicular to the long axis of the ascending aorta closely beneath the upper margin of the stent of self-expanding prostheses or at a corresponding distance from the aortic annulus for all other shorter TAVR prostheses. This position was chosen as it had been proven to be less susceptible to artefacts caused by the valve and stent compared to a lower position, and a perpendicular cut through the ascending aorta could be achieved



Central illustration. Quantitative assessment of PVR by videodensitometric aortography and by CMR:

Upper panels:

Left: A post-TAVR aortogram with videodensitometric analysis. A color-weighted contrast time-density map is superimposed on the sub-aortic segment of the ventricle, while the reference region (aortic root) is highlighted with red color. Right: Steady-state free precession CMR image (yellow dotted line=imaging plane for velocity mapping).

Middle and lower panels:

Two examples of post-TAVR patients with mild and moderate-to-severe PVR. On videodensitometric angiographic analysis (left), the area under the contrast time-density curve of the left ventricular outflow tract (yellow) is divided by that of the aortic root (red) to yield videodensitometric AR. On CMR (right), the backward flow (below the baseline) is divided by the forward flow (above the baseline) to yield the regurgitation fraction (CMR-RF).

more accurately. In fact, no visible artefacts of the valve or the stent were seen on the analysed images. Contrast administration was not necessary for both cine imaging and flow measurements. Consequently, no patients were excluded because of impaired renal function.

CMR data were analysed by two independent and experienced observers. No formal blinding was performed, but observers had no access to the results of echocardiography or angiography data at the time of CMR evaluation. Rerating by the same observer was performed in 75 randomly-selected cases to test the intrinsic variability of the method.

For the assessment of the aortic regurgitant fraction (RF), the cross-sectional area of the ascending aorta was defined and manually corrected for motion artefacts that occurred during the breath hold scan. Using a standard software (Argus WIP 2.3, Siemens AG, Erlangen, Germany), the forward and reverse volumes within this region of interest were determined, and the RF was calculated as follows: (regurgitant volume/total forward volume) × 100 (Central Illustration). CMR-RF of ≤15% was graded as trace-mild, and >30% as moderate-to-severe PVR according to criteria used in previous TAVR studies[11-13].

Statistics

When nonparametric statistical methods were used, we summarized data as median and quartiles instead of mean and standard deviation (SD). Categorical variables were summarized as frequencies and percentages. The distribution of CMR-RF and VD-AR across the angiographic visual Sellers' grades was compared using Mann–Whitney U test. The relationship between continuous parameters of AR severity was tested using Pearson correlation while the relation between quantitative and qualitative parameters was tested using Spearman correlation. For the correlation between VD-AR and CMR-RF, the sample size was estimated to be at least 19 data pairs (for α-level of 0.05, a β-level of 0.20 [power = 80%], and a hypothesized correlation coefficient r=0.60 [denoting at least moderate correlation]). Fisher r-to-z transformation was used to assess the significance of the difference between two correlation coefficients. Receiver-operating characteristics (ROC) curves were generated for the VD-AR values that correspond to mild and moderate-to-severe PVR as defined by CMR-RF. The area under the ROC curve was calculated and the cut-points were defined on the basis of the highest sum of sensitivity and specificity. The reproducibility of CMR-RF and VD-AR was assessed by calculating the intraclass correlation coefficient (ICC) presented with its 95% confidence interval (CI). The difference on re-rating was displayed using the Bland-Altman method and the 95 % limits of agreement (95 % LOA) were estimated as ±1.96 × SD of the difference. Statistical analysis was performed with SPSS 23 (IBM, Armonk, NY, USA). All probability values were two-tailed, and a value of $P<0.05$ was considered statistically significant.

RESULTS

The study included 135 patients who underwent TAVR principally through a transfemoral approach (97%) and were treated either with a balloon-expandable (60.5%), self-expanding (32%), or mechanically-expanding (7.5%) bioprosthesis. The baseline characteristics of the study population are summarized in Table 1.

Table 1. Baseline characteristics of the study population.

n=135 patients	
Age (year)	81±6
Male	57 (42%)
BMI (kg/m^2)	27±5
Logistic EuroSCORE	23.2±16.7
STS score	6.2±6.7
Hypertension	125 (93%)
Diabetes mellitus	36 (27%)
Dyslipidemia	68 (50%)
NYHA III-IV	88 (65%)
Atrial fibrillation	52 (39%)
Chronic obstructive pulmonary disease	20 (15%)
Coronary artery disease	93 (69%)
Previous PCI	48 (36%)
Previous CABG	28 (21%)
Previous SAVR	8 (6%)
Cerebrovascular disease	20 (15%)
Peripheral arterial disease	20 (15%)
Chronic kidney disease	30 (22%)
LV ejection fraction (%)	54±13
Transaortic mean PG (mmHg)	44±18
Aortic valve area (cm^2)	0.64±0.28
Aortic annulus diameter (mm, on TEE)	23.1±2.2
sPAP (mmHg)	46.5±15.9
Mitral regurgitation, moderate-severe	34 (25%)
Aortic regurgitation, moderate-severe	23 (17%)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; LV, left ventricle; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PG, pressure gradient; SAVR, surgical aortic valve replacement; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TEE, transesophageal echocardiography.

Assessment of PVR

PVR severity was assessed by procedural angiography and by CMR performed within 30 days (mean±SD, 11±6 days) after the procedure. During CMR, 83 patients (62%) were in sinus rhythm with an average heart rate of 67 ± 12 beats/min. The remainder had atrial fibrillation (AF) with an average heart rate of 69 ± 12 beats/min. The average CMR-RF was (mean±SD, 6.7±7.0%; median [IQR], 4.7 [1.6-9.2%]) while the average VD-AR was (mean±SD, 7.0±7.0%; median [IQR], 5.0 [2.0-9.0%]). Supplementary Figure 2 displays the cumulative curves of PVR severity as assessed by both techniques. On pre-discharge transthoracic echocardiography (TTE), PVR was graded as none-trace in 77 patients (57%), as mild in 54 patients (40%), and as moderate in 4 patients (3%).

Quantitative vs. qualitative assessment of PVR by CMR and angiography

The visual (Sellers') grades of PVR severity on post-implantation angiography were: none (Sellers'0) in 39 patients (28.9%), mild (Sellers' I) in 74 patients (54.8%), moderate (Sellers' II) in 15 patients (11.1%), and moderate-to-severe (Sellers' III) in 8 patients (5.9%). The distributions of CMR-RF and VD-AR across the Sellers' grades are shown in Figures 1.A and 1.B. Spearman's coefficient of correlation between Sellers' grades and CMR-RF was 0.25 and between Sellers' grades and VD-AR was 0.55 (p<0.001).

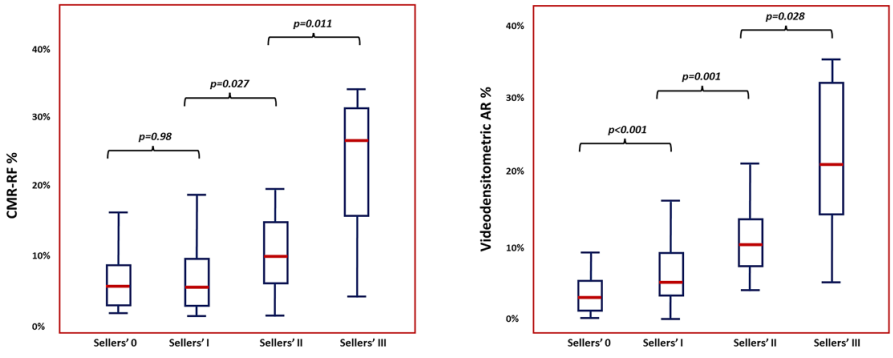


Figure 1. The distribution of CMR-RF (A) and videodensitometric AR (B) across the angiographic Sellers' grades of PVR severity. A) There has been an overlap between CMR-RF and Sellers' grades of AR, especially between Sellers' 0 and Sellers' I (p>0.05). B) The overlap between videodensitometric AR and Sellers' grades was less remarkable.

Intermodality agreement in the quantitative assessment of PVR

The correlation between VD-AR and CMR-RF was substantial (Pearson r=0.78, p<0.001; Figure 2). The correlation remained significant in the following patient subgroups: patients with AF (n=52, r=0.77), patients who received a self-expanding device (n=42, r=0.86), patients in whom balloon post-dilatation was performed (n=24, r=0.82), and patients in whom aortographic acquisition projection was LAO (n=96, r=0.73); p<0.001 for all.

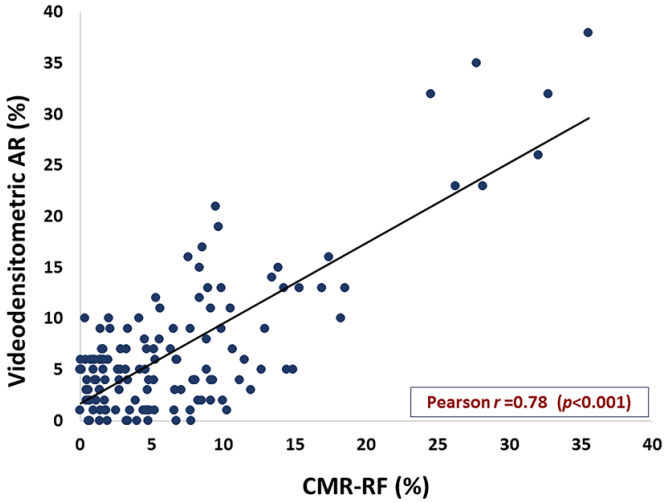


Figure 2. Linear correlation between CMR-RF and videodensitometric AR.
The scatter plot shows that the linear relationship is weaker at the lower CMR-RF values (< 5%).

On ROC curves, a VD-AR ≥10% corresponded to ≥mild PVR as defined by CMR-RF (AUC: 0.94, p<0.001; 95% CI: 0.90-0.98; sensitivity: 100%; specificity: 83%), while a VD-AR ≥25% corresponded to moderate-to-severe PVR (AUC: 0.99, p=0.004; 95% CI: 0.98-1.00; sensitivity: 100%; specificity: 98%).

Reproducibility of the two quantitative techniques of PVR assessment

To investigate the inherent variability of the method, CMR-RF was re-rated by the same analyst in the same session in 75 randomly selected cases. The ICC was 0.91 (95% CI: 0.86-0.95, p<0.001). As shown in Supplementary figure 3.A, the average bias on re-rating was -0.04% while the 95% limits of agreement were ±7.9%.

In Supplementary Figure 4, patient-dots were labeled to indicate the cardiac rhythm (AF vs. sinus rhythm) during CMR acquisition. The average bias was similar regardless of the cardiac rhythm, but the limits of agreement were wider apart in patients with AF (±10.6%) than in patients in sinus rhythm (±6.7%).

VD-AR was also re-rated by the same analyst in the same 75 cases. The ICC was 0.93 (95% CI: 0.88-0.95, p<0.001). As shown in Supplementary Figure 3.B, the average bias on re-rating was -0.40% and the 95% limits of agreement were ±6.8%.

DISCUSSION

In the present study, VD-AR was shown to provide a surrogate assessment of the regurgitant fraction (as defined by CMR) with a comparable reproducibility. Therefore, VD-AR has a two-fold advantage: 1) It is angiography-based, and hence is available in all procedures; 2) It provides a reproducible quantitative assessment of PVR severity.

VD-AR has been shown to be feasible[10] and reproducible[9,10] and to correlate with echocardiographic assessment[8] and with clinical outcomes[8,9]. Additionally, in an in-vitro validation (n=29 observations) in a PVR model of a balloon-expandable device implanted in a mock circulation system[14-16], VD-AR was shown to closely correlate (r^2=0.964, y=0.816x - 3.049) with the regurgitation fraction measured by a transonic flow probe. In the present study, in-vivo accuracy and precision of this technique were further confirmed.

The incidence of PVR after TAVR has dramatically improved thanks to improved valve design and size range and, most importantly, to proper sizing[4]. However, the incidence of mild PVR remains high –albeit with controversial prognostic relevance[17-20]- and the extension of TAVR indications to patients with bicuspid and/or predominantly-regurgitant aortic valves is expected to increase the potential for PVR[4]. PVR remains, therefore, an important limitation of TAVR as compared to surgery and its timely detection, accurate quantification, and effective elimination remain of crucial importance. For this target to be achieved, a reliable intra-procedural tool to detect and quantify PVR is required. TEE, which has long been the standard intra-procedural tool for PVR assessment, is now progressively less utilized in the era of "minimalist TAVR"[21]. Although TTE was reported to be an efficient alternative for procedural guidance[22], its intra-procedural use is complicated by important technical constraints[23]. The invasively-measured AR index was shown to define the severity of PVR and an ARI of <25 correlated with clinical outcome after TAVR[24]. However, the specificity of ARI is modest and an ARI of <25 often co-exists with no/trivial AR, particularly in the presence of relative bradycardia[25].

Aortic root angiography is the first screening tool for PVR in most laboratories and is a quick and friendly tool to the interventionists. However, the visual (Sellers') assessment is subjective, qualitative, and non-validated in the post-TAVR setting[4]. It has been previously reported that native aortic valve regurgitation volume and fraction measured by magnetic flowmetry[26] and by cardiac catheterization (using Fick's method and left ventriculography)[27-29] markedly overlap between the Sellers' grades. In the setting of TAVR, comparison of the Sellers' grades with PVR volume and fraction revealed that there is only a moderate correlation with a significant overlap between the Sellers' grades and PVR volume/fraction[30]. In the present study, this overlap was further confirmed (Figures 1A and 1B).

Implementation of the VD-AR technology into routine clinical practice

There are currently three main issues that need to be dealt with, in order to allow for the routine use of VD-AR (Figure 3). First, the limited analyzability rate, ranging from 43% (in the present study) to 65-68% (in previous studies)[8,9], is a major shortcoming of this new angiographic technique when applied retrospectively to aortograms that have not been acquired following a standardized acquisition protocol. The limited yield is principally (>90%) due to technical operator-dependent factors, mostly involving an overlap of the contrast-filled descending aorta on the LVOT and/or aortic root (Figure 3A)[31]. The definition of a patient-specific overlap-free fluoroscopic projection is now possible, thanks to computed tomographic planning, and is reliable in 98% of cases[32]. As shown in Figures 3B and C, an overlap-free projection can be predicted using computed tomography well in advance of the procedure. An alternative simplified rule is to choose an angulation of ≥35-40 degrees towards the same side as the descending aorta relative to a vertical line that hemisects a diagonal line extending from LV apex to the ascending aorta (Figures 3D and E).

Second, one further step to optimize the accuracy and reproducibility of the results of this new technique, is angiographic acquisition standardization. This includes standardization of the volume, rate, and timing of contrast injection as well as the position of the catheter tip. Based on an in-vitro validation model, injection of 20 ml of contrast at a rate of 20 ml/sec with the catheter tip positioned ≤20 mm above the aortic (prosthetic) valve leaflets seem to provide excellent accuracy and reproducibility[16]. A short diastolic injection synchronized to an electrocardiographic trigger can also help reduce the contrast volume to 8 ml/injection[16]. Due to the observation seen in some TAVR cases, that PVR shows a marked improvement within few minutes after valve implantation (likely due to the interaction of the external sealing skirt with the landing zone, which probably needs few minutes to be established), it is recommended to delay the final aortographic acquisition to 10 minutes after final valve deployment. It is also important not to overlook the influence of "Automatic Exposure Control" characteristic built into most of angiographic acquisition systems. This mode implies a dynamic adjustment of the X-ray exposure, and hence change of pixel darkness, to maintain a constant image quality at the expense of oscillating brightness. Such a property can influence the automatic videodensitometric assessment of contrast density, and should thus be inactivated when videodensitometric assessment is intended.

Third, enabling a real-time on-line use of VD-AR within the cath-lab helps guide the decision making as whether a corrective measure is required and judging its effectiveness. Currently, off-line analysis entails a manual contour tracing. Although this tracing typically requires less than one minute, it can be made even faster and more reproducible through the overlay of the pre-loaded computed tomographic contours of the heart and aortic root on the flouroscopic images. This can potentially enable instant

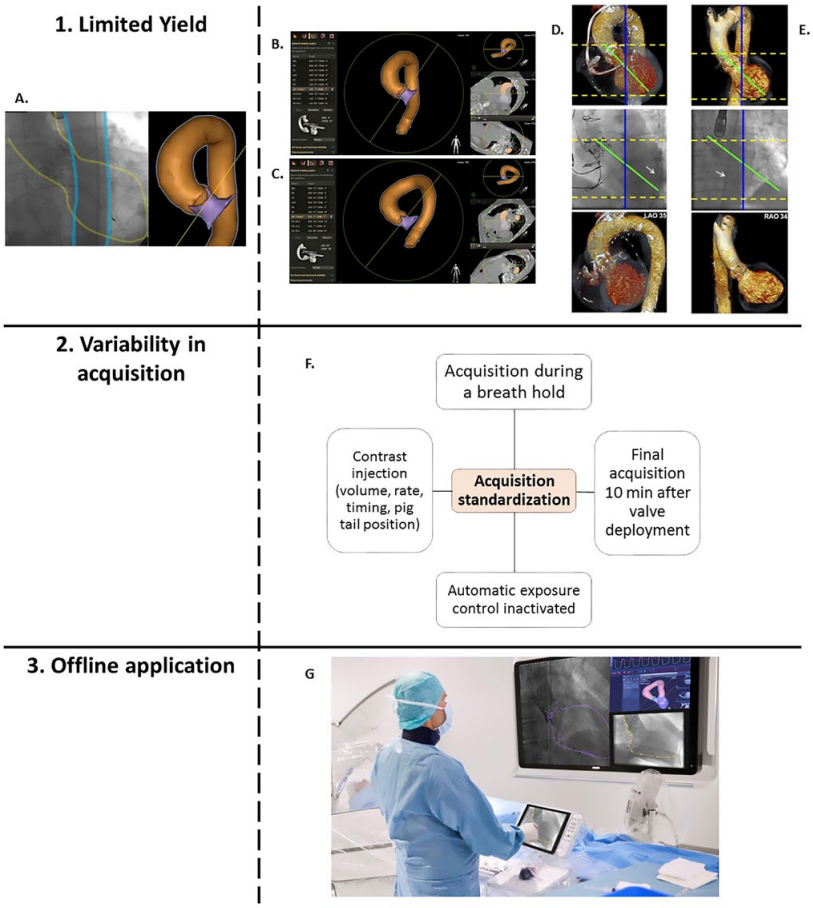


Figure 3. Technical limitations of videodensitometric AR and the respective practical solutions.
The three major technical limitations of VD-AR technology are listed in the left-hand side column and their respective ongoing/proposed solutions listed in the respective cells of the right-hand side column. The limited yield (analyzability) is principally due to an overlap of the contrast filled descending aorta on the regions of interest (Figure A). An overlap free-projection can be predicted using baseline computed tomography (Figure B and C). Another option to get an overlap-free projection has been proposed by Teng et al[32] and is displayed in Figures D and E: The posterior-anterior projection on fluoroscopy (middle row) and on computed tomography (upper row) as well as an overlap-free fluoroscopic projection (lower row) of two patients (D and E) are shown. A diagonal green line extending from LV apex to ascending aorta is hemisected by a blue vertical line. The catheter path in the descending aorta is indicated by the white arrows. For patient D, the descending aorta is predominantly to the left side of the blue line, and an LAO 35° projection was overlap-free. For patient E, the descending aorta is predominantly on the right side of the blue line, and an RAO 34° projection was overlap-free. Figure F summarizes the main elements of a standardized aortographic acquisition protocol to improve accuracy and reproducibility of VD-AR. Figure G shows how the integration of the VD-AR technology into an on-line workflow in the cath lab can be helped by the HeartNavigator technology (Philips Healthcare, Eindhoven, the Netherlands) to impose the cardiac contours over the fluoroscopic images precluding the need for manual tracing.
Some parts of the figure are reproduced from Sahyoun[31] and Teng et al[32] (with permission from Europa Organization).

analysis of VD-AR within few seconds, instead of the current method which requires, in average, 3 minutes per analysis. A feasibility study of the on-line implementation of the technology is currently underway with the results being anticipated in 2018[31]. Figure 3 summarizes the current technical limitations of the technology and the respective ongoing/proposed solutions to help its clinical implementation.

Overall, one intrinsic limitation of aortography in assessing PVR, is the inability to discriminate transvalvular from paravalvular regurgitation. Although significant post-TAVR PVR often paravalvular, confirmation of the mechanism of regurgitation is still important before performing a corrective maneuver (e.g. post-dilatation). Therefore, in selective cases where VD-AR reveals a significant regurgitation, an ad-hoc echocardiographic confirmation of a paravalvular mechanism of regurgitation before a corrective measure is undertaken is reasonable.

It should also be noted that the increasing reliance on aortography in procedural guidance will require the use of a larger volume of contrast medium with the potential to increase the risk of acute kidney injury. This caveat calls even more for complimentary roles of VD-AR and echocardiography. The higher sensitivity of videodensitometry in detecting contrast density, as compared to visual assessment, enabled the introduction of a novel contrast-sparing synchronized (diastolic-only) aortographic injection technique. The latter has been tested in an in-vitro setting, and enabled the reduction of the contrast volume from 20 ml to 8 ml/injection without compromising diagnostic accuracy[16].

Finally, it is important to establish a VD-AR cut-point that defines device success and the need for –and the efficacy of– a corrective measure. Although a VD-AR of ≥25% corresponded to moderate-severe AR as defined by CMR in the present study, current evidence[8,9,33] suggests that even lower VD-AR values (>17%) correspond to a "clinically-relevant" PVR.

CMR-RF as a reference standard

Echocardiographic criteria of PVR severity, although advocated by the Valve Academic Research Consortium-VARC, are not adequately validated[34]. Additionally, the reproducibility of these criteria is limited[35], and can be improved through an approach that combines qualitative and semi-quantitative but not quantitative parameters[36]. Although not without limitations[4], CMR-RF is a reliable measure of PVR severity, and outperforms echocardiography in predicting clinical outcomes in patients with native[6] and prosthetic[5] AR. Moreover, like angiography, accuracy of CMR is less influenced by the number and eccentricity of the paravalvular leaks than echocardiography. Therefore, we used CMR-RF as a reference standard in the present study. It should be noted, however, that the diagnostic accuracy of CMR-RF is lower in mild AR[4]. CMR-RF was not significantly different in patients with mild AR (as defined by echocardiography) than in healthy subjects

in some studies[37,38]. The closing volume (3.3±1.2 mL per beat)[39] and the coronary flow (1.5-3 mL per beat in average)[40] are possible explanations of this phenomenon. It is also worth-mentioning that there is no consensus on the CMR-RF cut-points of AR severity[4], and that the cut-points used in this study are not well-established. In the setting of TAVR, the underlying LV is hypertrophied with a small cavity and stroke volume. Therefore, a relatively small absolute regurgitation volume might correspond to a large regurgitation fraction[18]. Accordingly, regurgitation fraction is likely more reliable in the setting of TAVR than regurgitation volume to reflect the actual severity of PVR. Additionally, the concept of the relative AUC on videodensitometry is more in-line with the fraction –than the absolute volume- of regurgitation.

Limitations

An interval of 30 days (average=11 days) between angiography and CMR was allowed and changes of blood pressure and heart rate might have influenced the assessment of AR severity between the two time points. Therefore, the correlation between both methods might have been stronger if both techniques were performed in the same day. However, this ideal scenario is impractical for a TAVR patient.

The regions of interest were drawn manually and this might have introduced some variability to the measurements. However, this effect seems to be minor as evidenced by the excellent reproducibility on repeat assessment. Efforts to make this process automated using co-registration with baseline computed tomographic images are underway.

CONCLUSION

The present study aimed at comparing a novel tool to a well-established tool of PVR quantification. The novel tool (VD-AR) provides a surrogate assessment of PVR after TAVR that correlated well with the CMR-RF. Moreover, the reproducibility of VD-AR is very much the same as that of CMR-RF.

CLINICAL PERSPECTIVES

What's known?

Aortic regurgitation quantification is required during TAVR procedures to guide timely corrective measures and improve outcomes.

What's new?

Angiographic quantification of AR using videodensitometry provides an accurate estimation of the CMR-derived regurgitation fraction.

What's next?

Online application and standardized angiographic acquisition of this novel technique will enable implementation into routine clinical practice.

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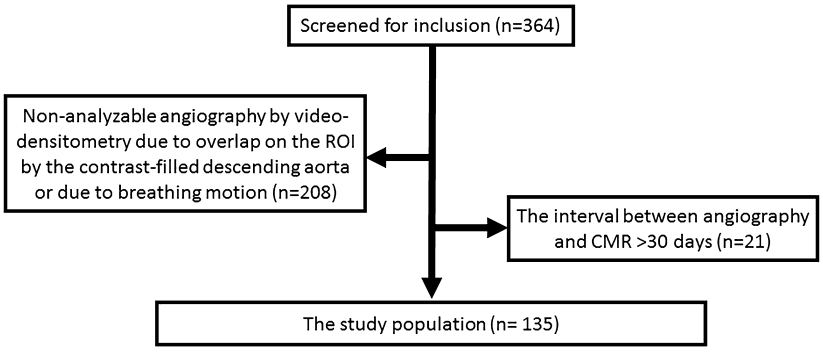
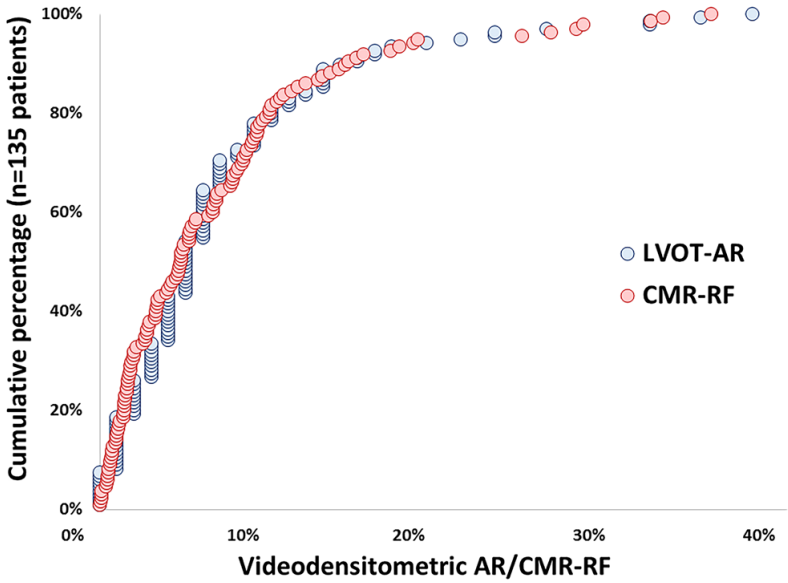
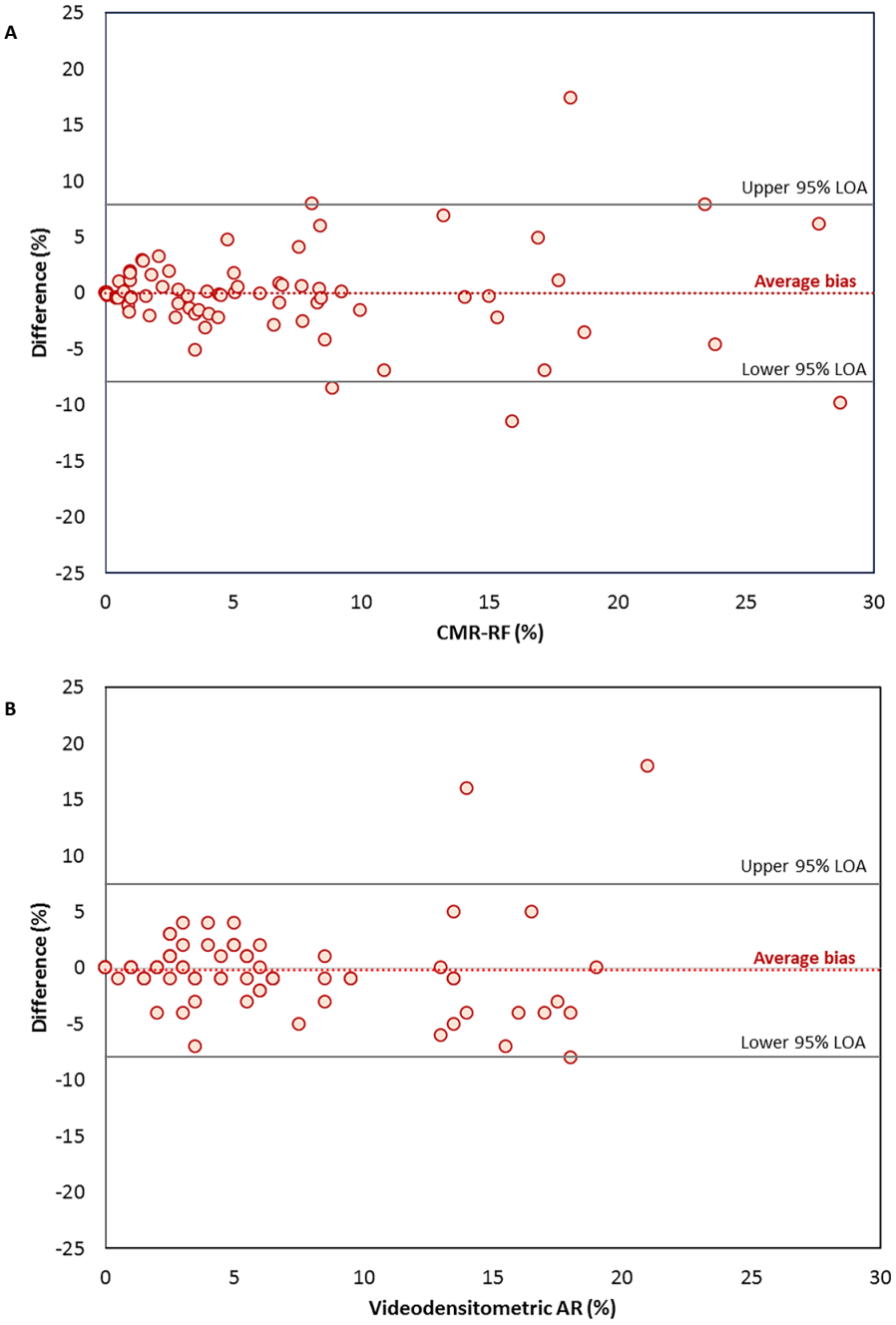
SUPPLEMENTARY FIGURES



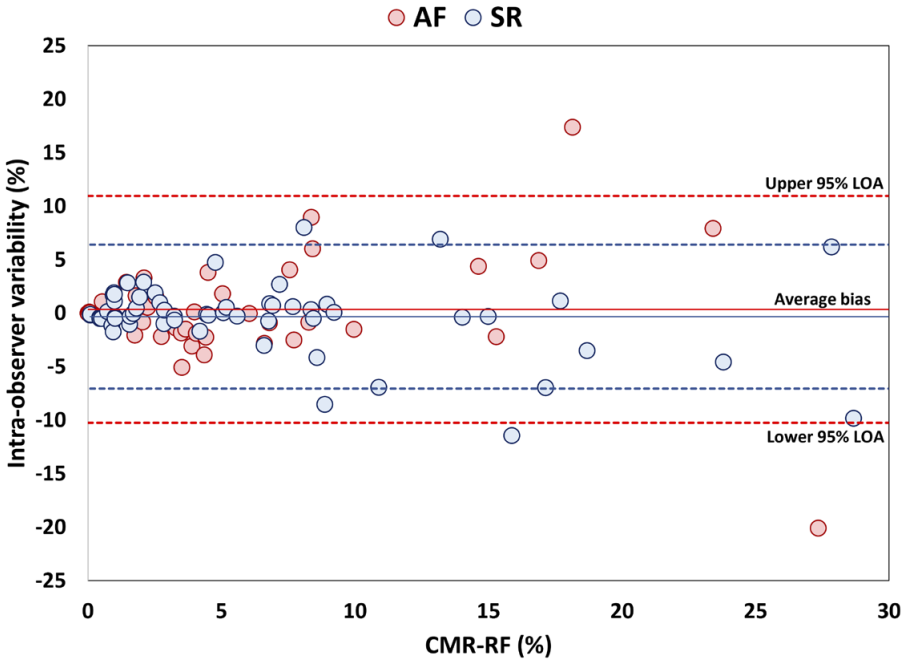
Supplementary Figure 1. The flow chart of the study.
ROI=region of interest.



Supplementary Figure 2. The cumulative curves of CMR-RF and videodensitometric AR in 135 TAVR patients.



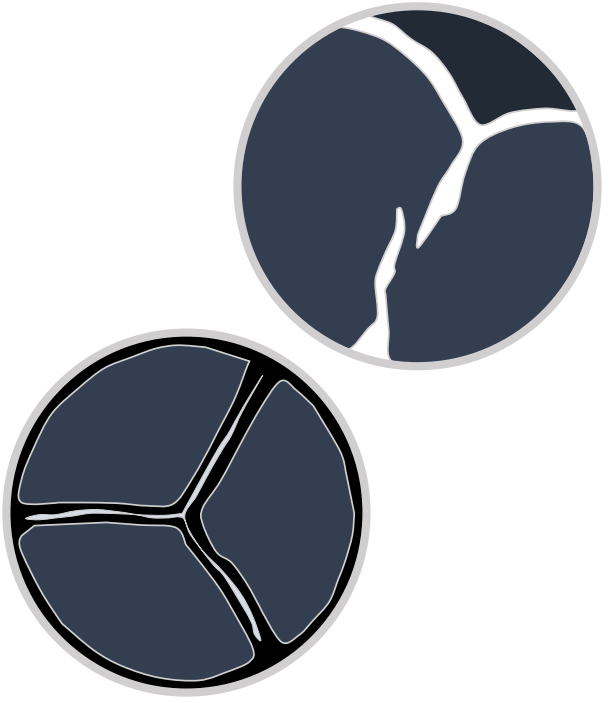
Supplementary Figure 3. Bland-Altman plots representing the intra-observer variability of CMR-RF (A) and videodensitometric AR (B) in 75 randomly-selected patients. The difference is plotted against the average of two measurements, with the average difference (red dotted line) and the 95% limits of agreement (LOA; grey continuous line) displayed.



Supplementary Figure 4. Bland-Altman plots representing the intra-observer variability of CMR-RF. Patient-dots are labeled to indicate the cardiac rhythm (atrial fibrillation-AF, red dots vs. sinus rhythm-SR, blue dots) during CMR acquisition. The difference is plotted against the average of two measurements, with the average difference and the 95% limits of agreement (LOA) displayed.

Section A.3

Long-term clinical and hemodynamic outcomes after TAVI



Chapter 8

Prevalence, predictors, and prognostic implications of residual impairment of functional capacity after transcatheter aortic valve implantation

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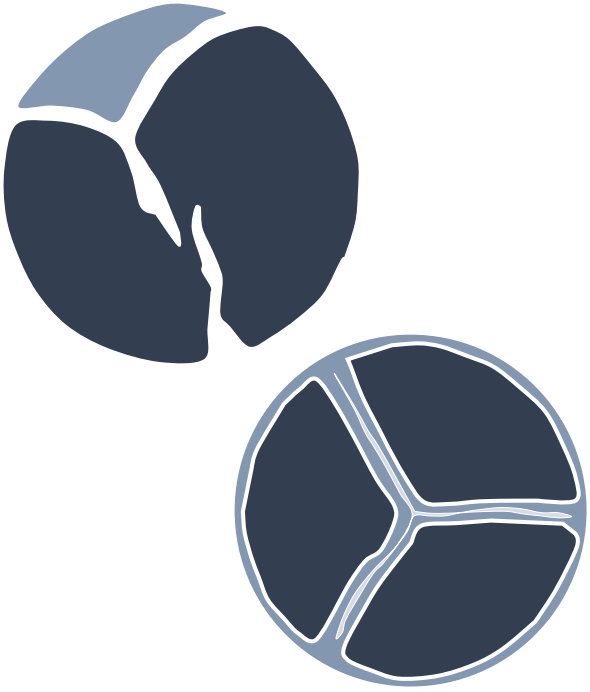
Clinical Research in Cardiology 2017;106(9):752-759.



ABSTRACT

Background:

Patients with degenerative aortic stenosis (AS) referred for transcatheter aortic valve implantation (TAVI) typically have advanced cardiac and vascular adverse remodeling and multiple comorbidities and, therefore, might not recover a normal functional capacity after valve replacement. We sought to investigate the prevalence, the predictors, and the prognostic impact of residual impairment of functional capacity after TAVI.

Methods and results:

Out of 790 patients undergoing TAVI with impaired functional capacity (NYHA II-IV) at baseline, NYHA functional class improved in 592 (86.5%) and remained unchanged/worsened in 92 (13.5%) at follow-up (median(IQR): 419(208-807) days) after TAVI. Normal functional capacity (NYHA I) was recovered in 65.5% (n=448) of patients, while the rest had variable degrees of residual impairment. On multivariable regression analysis, atrial fibrillation (odds ratio-OR, 2.08(1.21-3.58), p=0.008), low-flow low-gradient AS (OR, 1.97(1.09-3.57), p=0.026), chronic obstructive pulmonary disease (OR, 1.92 (1.19-3.12), p=0.008), and lower hemoglobin at baseline (OR, 1.11(1.01-1.21) for each g% decrement, p=0.036) were independently associated with residual impairment of functional capacity. All-cause and cardiac mortality were significantly higher in those with residual impairment of functional capacity than in those in NYHA I class (hazard ratio-HR: 2.37 (95%CI: 1.51-3.72), p<0.001 and 2.16 (95%CI: 1.08-4.35), p=0.030; respectively). Even mild residual functional impairment (NYHA II) was associated with a higher all-cause (HR: 2.02 (95%CI: 1.10-3.72), p=0.023) and cardiac (HR: 2.08 (95%CI: 1.42-3.07), p<0.001) mortality.

Conclusion:

Residual impairment of functional capacity is common after TAVI and is independently associated with increased mortality. Predictors of residual impairment of functional status are predominantly patient- rather than procedure-related.

INTRODUCTION

Patients with severe aortic stenosis (AS) typically have symptoms of heart failure and impaired quality of life and are subject to increased mortality and escalation of symptoms once they have developed[1].

Patients with degenerative AS referred for transcatheter aortic valve implantation (TAVI) typically have advanced cardiac[2] and vascular[3] adverse remodeling that may not be completely reversible after valve replacement[2,4,5]. Additionally, non-cardiovascular comorbidities are common in those patients[2]. Therefore, although TAVI can modify the dismal natural history of severe AS, restoration of a normal functional capacity may be less likely to occur. Although the major TAVI pivotal trials reported similar functional improvement after TAVI vs. surgical aortic valve replacement (SAVR)[6-8], a recent meta-analysis of randomized trials of patients at low and intermediate risk of perioperative mortality showed that transfemoral TAVI was associated with reduced mortality but increased incidence of heart failure within 2 years as compared to SAVR[9].

Consequently, TAVI might remain a futile treatment in patients who are more concerned with their functional status than with the risk of death. Given the fact that all TAVI candidates expect an improvement of their quality of life after the procedure[10] and that some patients are more concerned with their functional status than with the risk of death, it is desirable to know the likelihood, the predictors and the prognostic implications of failure to recover a normal functional capacity after the procedure. We specifically sought to identify whether residual impairment of functional capacity is linked to more advanced cardiopathy and severer symptoms at baseline, to non-cardiac comorbidities, or to procedural failure.

METHODS

The study included consecutive patients enrolled by 22 centers in the Brazilian TAVI registry from January 2008 to January 2015. Patients were considered eligible for inclusion if they had severe symptomatic AS (of the native valve or of a degenerated bioprosthetic surgical valve) and were considered by the heart team as inoperable or at high surgical risk. Operative mortality risk was estimated using the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) risk scores. List of participating centers, details of TAVI-procedure technical aspects, and adjudication of adverse events have been previously described elsewhere[11]. The study protocol complies with the Declaration of Helsinki and was approved by the ethics committee at each of the participating centers and all patients provided written informed consent. A web-based case report

form and remote electronic data monitoring were utilized with an on-site source document validation performed in a random sample (one fifth of all cases). An independent committee (including a neurologist) adjudicated all events. All end-points are reported according to the Valve Academic Research Consortium-2 (VARC-2) criteria[12]. Device failure was defined as residual trans-aortic mean pressure gradient ≥ 20 mmHg, greater than mild aortic regurgitation, and/or failure to correctly position a single device into the proper anatomical location[12].

Symptoms related to AS included: impaired functional capacity, angina, syncope, and/or pre-syncope[13]. According to the New York Heart Association (NYHA) functional classification, patients in NYHA class I have a normal functional capacity and are free from symptoms attributable to heart disease, and those in NYHA classes II, III and IV have mild, moderate and severe impairment of functional capacity due to symptoms attributable to heart disease, respectively[14].

Transfemoral vascular access was the default approach with the use of alternative approaches (transubclavian, direct transaortic and transcarotid) only when the transfemoral access was not possible. The decision to choose between sedative or general anesthesia was left to the discretion of the operators. All patients underwent transthoracic echocardiographic (TTE) study at baseline and were scheduled for TTE during the same admission for the index procedure (pre-discharge TTE) and for follow-up at 6 and 12 months and annually thereafter.

Statistical analysis: Quantitative variables are summarized as mean ± SD or median (interquartile range-IQR) and are compared by analysis of variance test while categorical variables are summarized as frequencies and proportions and are compared with the use of the chi-square test.

Uni- and multivariable logistic regression analyses were used to assess factors potentially associated with residual impairment of functional capacity. Factors with a p value < 0.10 in univariable analysis were included in a stepwise multivariable logistic model.

Cumulative survival curves for patients with and without residual impairment of functional capacity were constructed using the Kaplan-Meier method and compared with the log-rank test and Cox proportional hazards model.

All analyses were performed with SPSS 23 (IBM, Armonk, NY, USA). All probability values were two-tailed, and a p value <0.05 was considered significant.

RESULTS

A total of 819 consecutive patients with severe symptomatic AS were included (mean age 81.5±7.3 years; 49% males). Patients were at high surgical risk (EuroSCORE, 20.5±14.7; STS score, 10.3±7.8) with a high burden of comorbidities (chronic kidney disease, 77%;

coronary artery disease, 59%; and chronic obstructive pulmonary disease, 19%). TAVI was preformed predominantly under general anesthesia (91%) through a trans-femoral access (93%), and involved implanting a CoreValve (73%) or a Sapien-XT (24%) in the majority of cases.

Before TAVI, 790 patients (96%) had impaired functional capacity (NYHA II in 124 patients (15%), NYHA III in 436 patients (53%), and NYHA IV in 230 patients (28%)). Among patients with impaired functional capacity (NYHA ≥ II) at baseline, 684 were alive beyond 30 days post-procedure and available for clinical follow-up (up to 2268 days, median (IQR): 419(208-807) days). Out of those, NYHA functional class improved in 592 (86.5%) and remained unchanged/worsened in 92 (13.5%) (Supplementary Figure). Ultimately, 65.5% of patients (n=448) had recovered a normal functional capacity (NYHA I), while the rest had variable degrees of residual impairment. The latter was mild (NYHA II) in 26.5% (n=183) and moderate-severe (NYHA III or IV) in 8% (n=53).

Characteristics of patients with residual impairment of functional capacity

The baseline, periprocedural and follow-up characteristics in the patients stratified according to the functional status at follow-up are summarized in a Supplementary Table. All relevant baseline and periprocedural factors were tested for association with residual impairment of functional capacity after TAVI. Table 1 summarizes the univariable and multivariable predictors.

On multivariable logistic regression analysis, atrial fibrillation/flutter (odds ratio-OR, 2.08(1.21-3.58), p=0.008), low-flow low-gradient AS (OR, 1.97(1.09-3.57), p=0.026), chronic obstructive pulmonary disease (OR, 1.92 (1.19-3.12), p=0.008), and lower hemoglobin (OR, 1.11(1.01-1.21) for each g% decrement, p=0.036) were independently associated with residual impairment of functional capacity after TAVI. Although device failure (mainly driven by a higher trans- prosthetic valve pressure gradient) was associated with residual impairment of functional capacity in univariable analysis (OR, 1.73 (1.04-2.88), p=0.034), it was not an independent predictor in the multivariable analysis.

Cardiac remodeling in patients with recovered vs. impaired functional capacity after TAVI

Echocardiographic follow-up was available in 532 patients and was performed at a median interval of 366(161-736) days after TAVI. As shown in Figure 1, apart from left ventricular mass index (LVMi) which improved significantly in both groups with no between-group difference at follow-up, reverse cardiac remodeling was less efficient in patients with residual impairment of functional capacity.

LV diastolic diameter (LVDD), although similar at baseline, was significantly larger in those with residual impairment of functional capacity at follow-up (52.8±9.7 vs. 50.4±8.8, p=0.008). Impaired LV ejection fraction (LVEF<50%) was significantly less at follow-up as

Table 1. Univariable and multivariable predictors of residual impairment of functional capacity among survivors beyond 30 days after TAVI.

	Univariate analysis				Multivariate analysis			
	OR	Lower 95% CI for OR	Upper 95% CI for OR	*p*	OR	Lower 95% CI for OR	Upper 95% CI for OR	*p*
Body mass index (kg/m^2) at baseline	0.968	0.935	1.002	0.065	0.958	0.916	1.001	0.054
EuroSCORE at baseline	1.013	1.002	1.024	0.019	1.002	0.986	1.018	0.812
NYHA functional class at baseline	1.269	1.026	1.569	0.028	0.981	0.744	1.293	0.893
Pulmonary hypertension at baseline	1.436	0.992	2.078	0.055	0.853	0.519	1.401	0.531
Atrial fibrillation/flutter at baseline	2.019	1.280	3.186	0.003	**2.084**	**1.213**	**3.582**	**0.008**
LV posterior wall thickness (mm) at baseline	0.925	0.852	1.003	0.061	0.950	0.865	1.044	0.288
LV ejection fraction (%) at baseline	0.991	0.980	1.001	0.072	1.000	0.983	1.017	0.984
Transaortic valve mean PG (mmHg) at baseline	0.989	0.979	0.999	0.035	1.002	0.988	1.016	0.761
Low flow- low gradient AS at baseline	2.285	1.390	3.757	0.001	**1.968**	**1.086**	**3.568**	**0.026**
Hemoglobin* at baseline	1.112	1.029	1.189	0.010	**1.114**	**1.008**	**1.209**	**0.036**
Creatinine clearance (ml/min) at baseline	0.990	0.982	0.997	0.008	0.995	0.985	1.006	0.387
Chronic obstructive pulmonary disease at baseline	1.736	1.170	2.575	0.006	**1.922**	**1.186**	**3.115**	**0.008**
Device failure[§]	1.730	1.041	2.875	0.034	1.304	0.678	2.505	0.426

*Odds ratio calculated per 1 g% decrement.

[§]Defined as residual trans-aortic mean pressure gradient ≥ 20 mmHg, greater than mild aortic regurgitation, and/or failure to correctly position a single device into the proper anatomical location.

Abbreviations: AS, aortic stenosis; CI, confidence interval; LV, left ventricle; NYHA, New York Heart association; OR, odds ratio.

compared to baseline only in those with NYHA I symptoms. Accordingly, although not significantly different at baseline, the prevalence of impaired LVEF at latest follow-up was significantly higher in those with residual impairment of functional capacity (26.4% vs. 16.2%, p=0.007). Mitral regurgitation (MR) severity was similar in both groups at baseline and significantly improved at latest follow-up in those with NYHA I symptoms (moderate-severe MR, 13% at follow-up vs. 18% at baseline, p=0.005) but not in those with residual impairment of functional capacity (moderate-severe MR, 26% at follow-up vs. 23% at baseline, p=0.44). Consequently, MR severity at follow-up was significantly higher in those with residual impairment of functional capacity than in those with NYHA I symptoms (moderate-severe MR, 26% vs. 13%, p<0.001).

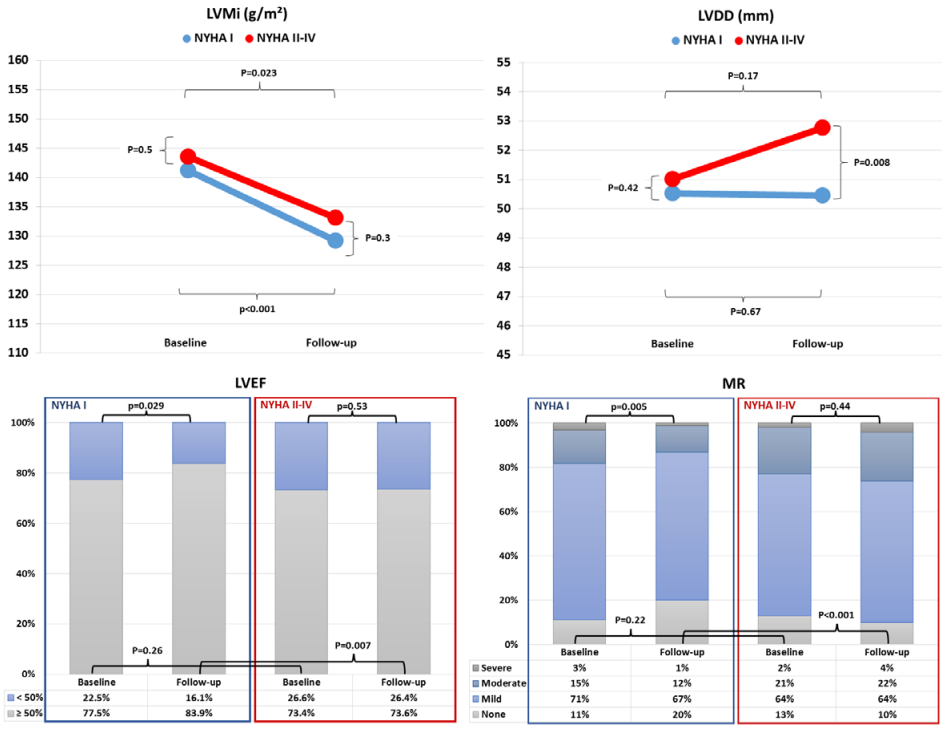


Figure 1. The change from baseline to latest follow-up in left ventricular mass index (LVMi), LV diastolic diameter (LVDD), LV ejection fraction (LVEF), and mitral regurgitation (MR) in patients with recovered vs. impaired functional capacity after TAVI

Mortality in TAVI-patients stratified according to the functional status at follow-up

During the entire follow-up period, all-cause mortality was significantly higher in those with residual impairment of functional capacity than in those who recovered a normal functional status (32.6% vs. 12.7%, log-rank p<0.001) (Figure 2.A.). Similarly, cardiac mortality was significantly higher in those with impaired functional capacity (14.4% vs. 5.4%, p<0.001) (Figure 2.B.). After adjustment for the aforementioned LV remodeling markers (LVEF, LVDD, and MR at latest follow-up), the association between residual impairment of functional capacity and all-cause mortality (hazard ratio-HR: 2.37 (95%CI: 1.51-3.72), p<0.001) and cardiac mortality (HR: 2.16 (95%CI: 1.08-4.35), p=0.030) remained significant.

To explore whether residual mild impairment of functional capacity (NYHA II) after TAVI can be detrimental, survival analysis was repeated after dividing the patients into three groups; normal (NYHA I), mildly-impaired (NYHA II), and moderate-severely impaired functional capacity (NYHA III or IV). All-cause mortality was higher in those with mild impairment (26.4%) than in those who recovered a normal functional capacity

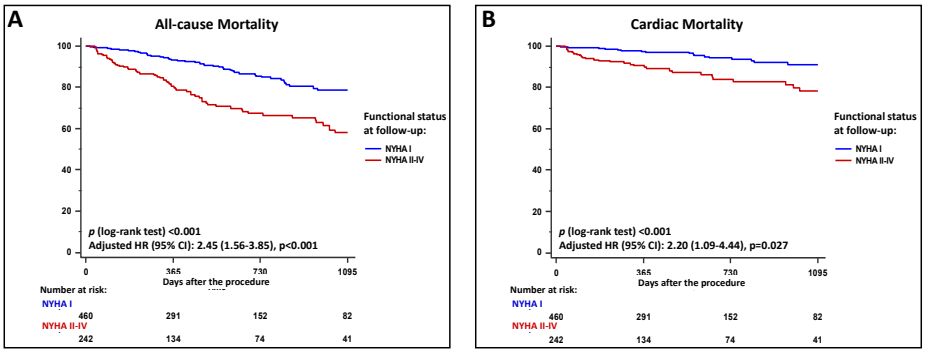


Figure 2. Kaplan-Meier survival curves for all-cause (A) and cardiac (B) death according to the functional status (normal vs. impaired) at follow-up after TAVI
CI=confidence interval, HR=hazard ratio

(12.7%, log-rank p<0.001, HR: 2.02 (95%CI: 1.10-3.72), p=0.023). Cardiac mortality was also higher in those with mild impairment (10.4%) than in those who recovered a normal functional capacity (5.2%, log-rank p=0.021, HR: 2.08 (95%CI: 1.42-3.07), p<0.001). In patients who had a residual moderate-severe functional impairment, mortality was very high (53.7%, with 27.8% being cardiac) and was significantly higher than those with mild impairment (all-cause mortality: log-rank p<0.001, HR: 2.57 (95% CI: 1.60-4.11), p<0.001; cardiac death: log-rank p<0.001, HR: 3.31 (95% CI: 1.68-6.53), p=0.001). Survival curves for the three groups are displayed in figure 3.

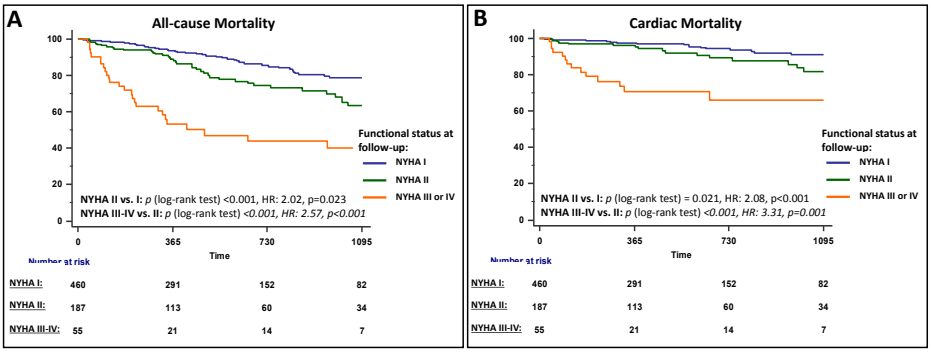


Figure 3. Kaplan-Meier survival curves for all-cause (A) and cardiac (B) death according to the functional status (normal vs. mildly-impaired vs. moderate-severely impaired) at follow-up after TAVI
CI=confidence interval, HR=hazard ratio

DISCUSSION

In the present study, we found that the majority of AS patients recover a normal functional status after TAVI despite the extensive comorbidities and the advanced cardiopathy they have at baseline. Eighty-seven percent of patients gained some improvement of their functional status (of at least one NYHA class) and moderate-severe impairment of functional capacity was reduced from 81% before to 8% after TAVI. Those who remained symptomatic (NYHA II or more), not only had their functional capacity impaired, but also had an increased risk of all-cause and cardiac death. The increased risk of mortality was not confined to those with moderate-severe residual impairment of functional capacity but also involved those with mild residual impairment, emphasizing that restoration of a normal functional capacity should be the clinical objective in TAVI patients. These results also suggest that this simple tool (NYHA functional classification) which has long been one of the main criteria for deciding the timing of intervention for AS[13,15], can also be used as a prognostic marker after valve replacement.

Although TAVI penetration and indications are expanding, there is also an increasing awareness of that some patients offered this expensive therapy fail to derive a functional, morbidity, and/or mortality benefit from it[16]. Futility of TAVI, which can be defined as the lack of survival/functional improvement in the short-term (6 months to 1 year)[16], is still an underestimated problem. The present study provides a set of baseline characteristics of patients who, in spite of TAVI, frequently fail to recover a normal functional status and to reverse the adverse cardiac remodeling and who also have an increased mortality, so that they can be identified and appropriately-counseled up-front of the procedure.

Assessment of TAVI outcome: Patients' vs. physicians' perspectives

The dismal prognosis of symptomatic severe AS if managed conservatively, drew the interest to developing prognosis-modifying strategies. TAVI emerged as a prognosis-modifying intervention with un-equivocal mortality benefit compared to conservative management in patients who cannot undergo surgery[17] and compared to surgical management in high-risk[8] and intermediate-risk[6,18] patients. However, physicians' and patients' appraisal of risks and benefits may differ[19], and symptomatic relief is, for some patients, a priority. In a study by Hussain et al, the majority of patients undergoing SAVR for severe AS were willing to accept considerably higher risk of perioperative death than what is considered by physicians/guidelines as "acceptable"[20]. Patients who had more severe symptoms and lower quality of life as well as those with pulmonary disease, impaired LVEF, or lower trans-aortic gradient were more likely to accept a high/prohibitive risk of perioperative death if a normal health is likely to be restored after valve replacement[20]. These results emphasize the importance of symptomatic improvement (vs. mere survival) among the priorities of AS patients especially those with more severe symptoms.

How much of the response to TAVI is predictable?

In the present study, two cardiac (atrial fibrillation and low-flow low-gradient AS) and two non-cardiac (COPD and anemia) baseline clinical conditions were identified as independent predictors of impaired functional status after TAVI. The benefit of identifying these markers during the decision-making process prior to TAVI is twofold: 1) to predict the functional outcome and counsel the patient in light of the lower probability of restoring a normal functional capacity; and 2) to stimulate correction of these conditions when possible knowing that failure to control these conditions will impair the functional gains from TAVI. Although not among the independent predictors, two markers of cardiac hemodynamics (transaortic valve PG and brain natriuretic peptide) seem to have an added value to the LVEF in predicting functional status after TAVI (Supplementary Table). This finding is in line with previous studies that concluded that the indices of LV mechanics other than the volumetric LVEF (e.g. longitudinal strain[21]) as well as markers of pressure overload (e.g. brain natriuretic peptide[22]) are crucial in predicting the functional status in patients with severe AS. In fact, a "low flow" status leading to a low gradient severe AS reflects the combination of a small LV cavity, a severe diastolic dysfunction, and an impaired longitudinal contractility. The combination of both low transvalvular gradient and low ejection fraction portends significantly worse outcomes [23,24]. These data together might explain why the mere reduction of LVEF at baseline was not an independent predictor of the functional outcomes after TAVI, while the combination of reduced LVEF and relatively low transaortic valve PG was.

Many attempts have been made to improve the predictability of TAVI outcomes, including the development of specific TAVI outcome-prediction scores. Although the inclusion of frailty and functional parameters into the predictive models has improved their performance as compared to surgical risk models, the accuracy of those models remain modest[16]. The complexity of the cardiovascular morbidity in patients with severe degenerative AS probably plays and important role in this suboptimal performance of predictive models.

Reduced arterial compliance is an important contributor to the increased afterload and to the adverse cardiac remodeling in AS patients[25]. This arterial component of the AS disease complex is likely even more pronounced in TAVI candidates, who are typically older with multiple risk factors for atherosclerosis, than SAVR candidates. In AS patients referred for valve replacement, a higher arterial stiffness correlate with less LV mass regression and with more adverse cardiac events after SAVR[26] and TAVI[27]. Yotti et al[4] studied arterial function before and after TAVI and reported an increase in arterial load after the procedure resulting in a residual elevation of LV pressure in 70% of patients. Moreover, myocardial response to AS involves variable degrees of myocardial fibrosis[28], the extent of which correlates with NYHA functional class at baseline[29], and predicts the improvement in NYHA class after valve replacement[29]. Arterial stiffness and myocardial fibrosis

are two examples of important contributors to the impaired cardiac performance in AS patients that might attenuate the benefit from TAVI. Therefore, the classic screening of patient's symptoms, comorbidities and valvular/myocardial function might not reflect the complete spectrum of the actual patient morbidity.

Limitations

This study has a number of limitations. Echocardiographic data were reported by the treating centers without independent core lab adjudication and follow up echocardiographic data were missing in some cases.

The list of predictors of functional recovery after TAVI that has been investigated in the present analysis included valvular and cardiac function, as well as major comorbidities. However, markers of frailty and surrogates for arterial function and myocardial fibrosis were not included in our analysis. Additionally, the socioeconomic and educational status of the patient as well as the involvement in regular exercise or rehabilitation programs might also play a role in determining the functional outcome of these patients. For future studies, we suggest to study the relation of those factors to the functional recovery after TAVI.

Clinicians assign a given patient to a NYHA class on the basis of their subjective interpretation of reported symptoms and, accordingly, interobserver variability of the functional assessment is a potential downside of this assessment. In spite of this limitation, a higher NYHA class was shown in the present study to be a marker of objective adverse cardiac remodeling and, more importantly, of a higher mortality risk. It turns out that, in spite of its limitations, this simple tool that is still used to decide the timing of intervention (as recommended by clinical practice guidelines) can still be crucial in post-TAVI clinical assessment. Other more objective, more quantitative, and purely patient-reported multidimensional assessment tools have been suggested as better indices of the quality of life. These multidimensional tools (e.g. EuroQol-5L and SF-36 questionnaires) involve dimensions that are more determined by the extra-cardiac morbidities and general frailty (e.g. pain/discomfort, anxiety/depression, and independent self-care). TAVI that effectively relieves AS and its relevant symptoms and improves survival, cannot reverse non-cardiac pathologies that profoundly impacts on the patient's overall quality of life. Previous studies revealed that the general health status visual analog scale improves after TAVI by only 2.7-7.0% (mainly driven by improvements in mobility and usual activity dimensions, while the other dimensions showed only very modest change)[30] and that the EQ-5D index also shows a modest improvement (+ 7% at 1 year)[31].

CONCLUSION

The majority of AS patients recover a normal functional status after TAVI despite the extensive comorbidities and the advanced cardiopathy they have at baseline. However, in a sub-group of patients, some degree of functional impairment persists and portends a diminished reverse cardiac remodeling and a lower survival. Chronic lung disease, anemia, atrial fibrillation, and a low-flow low-gradient AS are baseline characteristics of this group of patients.

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SUPPLEMENTARY DATA

Supplementary Table. Patient characteristics (baseline, periprocedural and follow-up) of the patients stratified according to the functional status at follow-up:

	NYHA I at latest follow-up (n=460)	NYHA II-IV at latest follow-up (n=242)	P
Baseline characteristics:			
Age at procedure	81.1±7.6	81.7±6.8	0.343
Male gender	232(50%)	120(50%)	0.874
Body mass index (kg/m^2)	26.5(4.7)	25.8(4.6)	0.064
EuroSCORE	14.5(8.9-25.5)	17.9(11.1-29.3)	0.001
STS-PROM score	7.0(4.0-14.9)	7.1(4.4-14.3)	0.694
NYHA class			0.104
II	72(16%)	34(14%)	
III	255(55%)	122(50%)	
IV	114(25%)	80(33%)	
Coronary artery disease	270(59%)	141(58%)	0.936
Carotid artery disease	65(14%)	41(17%)	0.321
Peripheral arterial disease	75(16%)	39(16%)	1.00
Chronic obstructive pulmonary disease	68(15%)	56(23%)	0.007
Diabetes mellitus	153(33%)	66(27%)	0.123
Hypertension	337(73%)	185(76%)	0.413
Chronic kidney disease	347(75%)	190(79%)	0.400
Coronary artery bypass grafting	92(20%)	43(18%)	0.546
Previous percutaneous coronary intervention	157(34%)	80(33%)	0.801
Previous aortic valvuloplasty	22(5%)	17(7%)	0.228
Previous aortic valve replacement	16(3%)	12(5%)	0.417
Ejection fraction (%)	59.4±14.6	57.3±15.5	0.072
Ejection fraction<50%	102(22.5%)	63(26.6%)	0.260
LV mass index (g/m^2)	141.2±40.9	143.6±48.7	0.542
Aortic valve area (cm^2)	0.66±0.18	0.67±0.21	0.398
Transaortic valve mean PG (mmHg)	50.3±15.6	47.6±16.6	0.034
Low flow-low gradient AS*	35(9%)	37(18%)	0.001
Pulmonary hypertension	89(19%)	62(26%)	0.066
Moderate-severe aortic regurgitation	56(13%)	37(16%)	0.242
Moderate-severe mitral regurgitation	80(18%)	53(23%)	0.154
Cardiac rhythm			0.004
Sinus rhythm	376(82%)	170(71%)	
Atrial fibrillation/flutter	46(10%)	42(18%)	
Paced rhythm	36(8%)	26(11%)	
Hemoglobin (g %)	11.9±1.8	11.6±1.8	0.009
Creatinine Clearance (ml/min)	50.4±23.1	45.7±18.8	0.004

	NYHA I at latest follow-up (n=460)	NYHA II-IV at latest follow-up (n=242)	P
Brain natriuretic peptide[¶] (pg/ml)	208(95-683)	472(135-810)	0.015
Periprocedural characteristics			
Trans-femoral access	434(94%)	225(93%)	0.509
Transcatheter heart valve type			0.052
CoreValve	329(63%)	193(37%)	
Sapien-XT	121(73%)	44(27%)	
Transcatheter heart valve diameter (mm)	27.3±2.5	27.6±2.3	0.495
Transcatheter heart valve oversizing (%)	10.7(4.0-20.8)	11.5(4.0-20.8)	0.527
Device success	424(92%)	211(87%)	0.042
Transaortic valve PG post-procedure[§]	0.0(0.0-6.0)	3.0(0.0-8.0)	0.005
Hemoglobin pre-discharge (g %)	9.8±1.7	9.5±1.5	0.022
Creatinine pre-discharge (mg/dl)	1.1(0.9-1.4)	1.2(1.0-1.6)	0.030
Ejection fraction pre-discharge (%)	61.6±12.9	59.2±14.4	0.041
Moderate-severe aortic regurgitation pre-discharge	23(5%)	19(8%)	0.132
Moderate-severe mitral regurgitation pre-discharge	62(15%)	44(20%)	0.094
Medications prescribed at discharge			
ACEI/ARB	230(50.0%)	118(48.8%)	0.812
Beta blocker	143(31.1%)	92(38.0%)	0.077
Digitalis	14 (3.0%)	15(6.2%)	0.070
Warfarin	33(7.2%)	27(11.2%)	0.088
Diuretics	189(41.1%)	124(51.2%)	0.011
Follow-up			
Days to last echocardiographic follow-up	367(163-734)	357(114-741)	0.857
Ejection fraction (%)	62.1±12.6	57.9±15.6	0.002
Ejection fraction<50%	52(16)	47(26)	0.007
LV diastolic diameter (mm)	50.5±8.9	52.8±9.7	0.010
Tran-aortic mean PG (mmHg)	9.0(6.0-12.0)	8.0(6.0-11.0)	0.604
LV mass index (g/m^2)	129.1±40.3	133.1±42.1	0.331
Moderate-severe aortic regurgitation	29(8%)	22(12%)	0.215
Moderate-severe mitral regurgitation	45(13%)	47(26%)	<0.001
All-cause death	58(13%)	79(33%)	<0.001
Cardiac death	23(5%)	35(15%)	<0.001

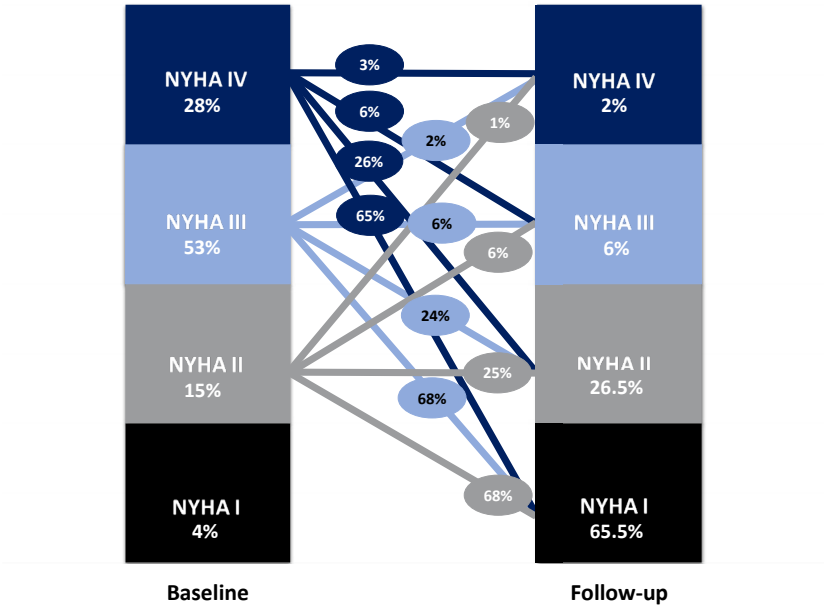
Data presented as mean±SD, median(IQR), or n(%).

*Defined as a valve area ≤1.0 cm^2 with a mean transvalvular pressure gradient ≤40 mmHg and an ejection fraction <50%.

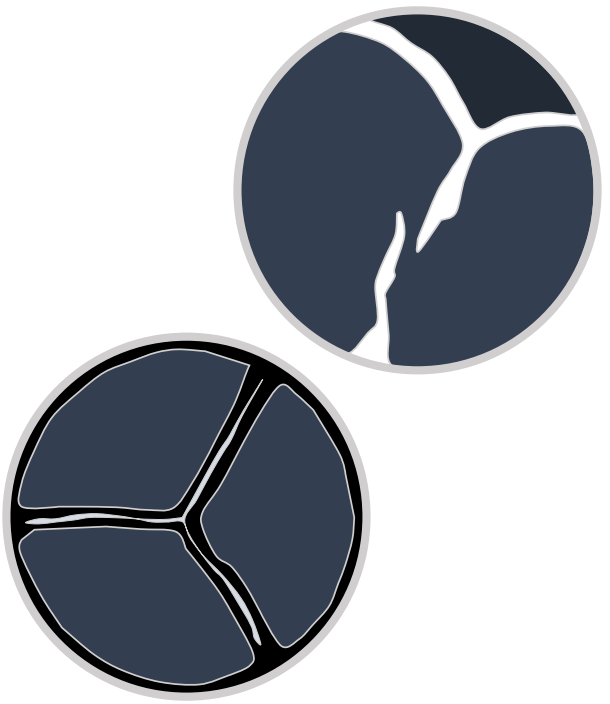
[§]Invasively-measured peak pressure gradient.

[¶]Data available in 232 patients (158 in NYHA I group and 74 in NYHA II-IV group).

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AS, aortic stenosis; LV, left ventricle; NYHA, New York Heart Association; PROM, predicted risk of mortality; PG, pressure gradient; STS, Society of Thoracic Surgeons.



Supplementary Figure. Change in functional capacity before and at follow-up after TAVI.



Chapter 9

Long-term durability and hemodynamic performance of a self-expanding transcatheter heart valve beyond 5 years after implantation: A prospective observational study applying the standardized definitions of structural deterioration and valve failure

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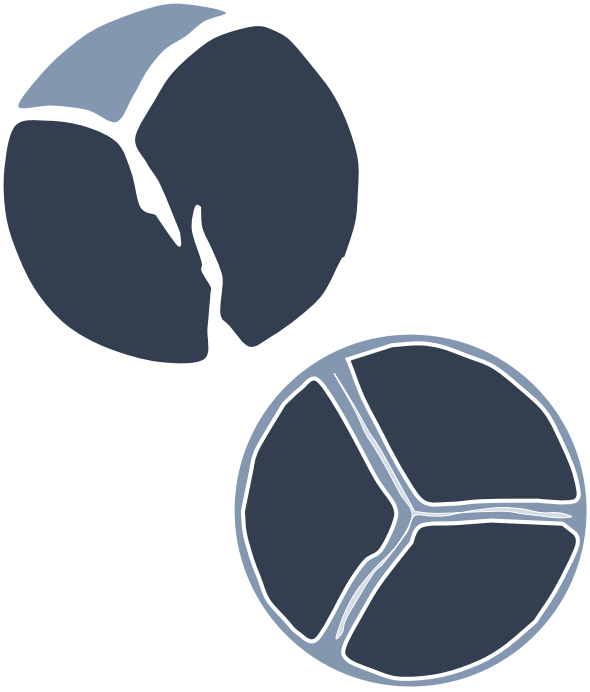

ABSTRACT

Aims:

Long-term results of transcatheter aortic valve implantation (TAVI), in particular the incidence of bioprosthetic valve failure (BVF), are uncertain.

Methods and Results:

The study prospectively included all 152 patients who had undergone TAVI with the self-expanding CoreValve™ up to December 2011 at the Heart Center, Bad Segeberg, Germany. Late BVF (>30 days) was defined as either: 1) Severe structural valve deterioration (trans-prosthetic mean pressure gradient ≥40 mmHg and/or ≥20 mmHg rise from baseline OR severe intra-prosthetic aortic regurgitation), OR 2) Bioprosthetic valve dysfunction leading to death or re-intervention. Echocardiographic follow-up at 6.3±1.0 years (range: 5.0 – 8.9 years) was 88% complete (60 out of 68 survivors beyond 5 years) and all echocardiograms were analyzed by an independent core laboratory.

All-cause mortality rate at 1, 2, 5, 6, 7 and 8 years was 14%, 20%, 50%, 60%, 65%, and 73%, respectively. Among survivors beyond 5 years, effective orifice area was 1.60±0.46 cm^2, and transvalvular mean pressure gradient was 6.7±3.1 mmHg, and no cases showed evidence of structural valve deterioration. Five patients (3.3%) had undergone redo TAVI (n=4) or surgery (n=1) 0.6 to 5.2 years after the index procedure, all due to paravalvular leakage. The estimated rate of BVF at 8 years was 7.9% for the actuarial and 4.5% for the actual analysis.

Conclusions:

Long-term follow-up up to 8.9 years after TAVI documents favorable performance of the self-expanding CoreValve™ with low rates of BVF.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is currently the standard of care for patients with severe symptomatic aortic stenosis (AS) and a high operative risk[1-3], and an established alternative to surgery in intermediate-risk patient[4]. Although the pivotal trials showed no signals of early bioprosthetic valve failure (BVF) so far, the paucity of data on transcatheter heart valve (THV) long-term durability remains of major concern. Current data on THV performance are limited to 5 years follow-up[5,6]. However, the experience with several surgical bioprostheses has shown that increasing rates of BVF may occur beyond this period[7,8]. While a durability of at least 5 years, as suggested by previous studies, is acceptable for an elderly high-risk population, an evidence of longer-term durability is mandatory before replacing surgery with TAVI in younger, lower-risk patients. In addition to the relatively short follow-up of current data on THV durability, a number of other shortcomings of current data are worth mentioning: 1) high rates of lost-to-echocardiographic follow-up among survivors, 2) lack of standardized definition of valve durability criteria, and 3) the application of inappropriate statistical analysis methods, which considers valve dysfunction as a time-dependent variable, overlooking the longitudinal nature of valve degeneration[9].

The present study presents data derived from a long-term structured follow-up program of the self-expanding CoreValve (Medtronic, Minneapolis, Minnesota), utilizing standardized definitions and core lab adjudication of valve performance[9].

METHODS

Patient population and study design

Since September 2007, all patients undergoing TAVI procedures at the Heart Center, Segeberger Kliniken, Bad Segeberg, Germany are included in a prospective registry (NCT03192774) approved by the local ethics committee and conforming to the Declaration of Helsinki.

The current analysis includes 152 consecutive patients who underwent TAVI with a self-expanding transcatheter heart valve system (CoreValve, Medtronic, Minneapolis, Minnesota) more than 5 years before the study (between September 2007 and December 2011). Technical details and implantation techniques have been described previously[1]. Clinical and echocardiographic follow-up was routinely performed at 30 days, 6 months, and 1, 2 and 5 years. Additionally, for the sake of the present analysis, all patients surviving beyond 5 years after TAVI were approached and personally interviewed (at the institution or through house visits) for clinical and echocardiographic examinations. Overall, echocardiographic data beyond 5 years (6.3±1.0 years; range: 5.0 – 8.9 years) post-TAVI

were available in 60 out of 68 patients who survived beyond 5 years post-TAVI (88.2%). The reason for incomplete echocardiographic data was death after 5 years but before a contemporary echocardiography in all 8 patients. The study flow chart is displayed in Supplementary Figure 1. Four patients who had undergone a redo valve procedure during the follow-up period were excluded from the echocardiographic analysis of long-term THV performance. The time interval from TAVI to the last echocardiographic follow-up in the remaining 56 patients was as follows: 6th post-TAVI year, n=23; 7th year, n=23; 8th year, n=6; and 9th year, n=4. An independent core laboratory (University Heart Center Zurich, Switzerland) blindly analyzed all echocardiograms prospectively acquired 5 years after TAVI. Image interpretation was based on a detailed analysis protocol according to current guidelines and standardized endpoint definitions.

Risk assessment and endpoint definitions

Predicted 30-day mortality was estimated according to the Logistic EuroSCORE and the Society of Thoracic Surgery (STS) predicted risk of mortality score. Echocardiographic and clinical endpoints are defined according to the VARC-2 criteria[10]. Primary endpoints of the study were: a) The rate of late bioprosthetic valve failure (BVF), and b) THV long-term performance (beyond 5 years). Late BVF was defined according to the recently proposed consensus definition[9], including one of the following criteria occurring >30 days after TAVI: 1) Severe hemodynamic structural valve deterioration (SVD); evidenced by a trans-prosthetic mean pressure gradient (PG) ≥40 mmHg and/or ≥20 mmHg rise from baseline OR severe transvalvular aortic regurgitation, 2) Bioprosthetic valve dysfunction leading to death or re-intervention.

Statistical Analysis

Continuous variables are summarized as mean±SD, or as median with interquartile range (IQR), as appropriate. Categorical variables are summarized as frequencies and percentages. Continuous variables were compared using the Student's t-test or the Mann-Whitney U test. Comparisons between categorical variables were performed using the Chi-square or Fisher's exact test. All tests were two tailed and a p-value of <0.05 was considered significant. The cumulative incidence of all-cause death and BVF was assessed with the Kaplan Meier method (actuarial analysis) using GraphPad Prism Version 6 (GraphPad Software, San Diego, CA, USA). Additionally, for the estimate of freedom from BVF, cumulative incidence (actual analysis) was adjusted for the competing risk of all-cause mortality using the JMP statistics software Version 13.1.0.

RESULTS

Study population, procedural details, and early outcomes

A total of 152 patients (median age, 81.0 years; STS score, 4.4) were treated with the self-expanding CoreValve THV from September 2007 to November 2011. TAVI was performed predominantly (99.3%) through a transfemoral access, and the 26 and 29 mm valve sizes were implanted in 56 (37%) and 96 (63%) patients, respectively. Initial device success was achieved in 107 patients (70.4%) with ≥ moderate residual paravalvular AR being the predominant cause of device failure. Baseline and procedural characteristics are summarized in Table 1. The rates of all-cause and cardiovascular mortality and major stroke at 30 days were 6.6%, 4.6%, and 4.5%, respectively. Other 30-day outcomes are detailed in Supplementary Table 1.

Long-term clinical outcomes

Clinical follow-up was available in 99% of the patients (n=151). A total of 94 (61.8%) patients had died during the period of observation (median time to death or latest follow-up: 5.0 [range: 0.0-8.9] years). Median time to death was 3.4 years [range: 0.0-8.2 years]). Rates of freedom from all-cause mortality at 1, 2, 5, 6, 7 and 8 years were 86%, 79%, 50%, 40%, 35%, and 27%, respectively with a 95% confidence interval for mortality at 7 years of 0.3-0.43 and at 8 years of 0.17-0.39 (Figure 1). Causes of death in the study population are summarized in Supplementary Table 2.

Bioprosthetic valve failure

During the total clinical follow-up period of up to 8.9 years, no severe SVD or death attributable to valve failure was reported. A total of 5 patients (3.3%) had undergone redo transcatheter (n=4) or surgical (n=1) valve replacement at 0.6 to 5.2 years following the index procedure, all due to moderate-severe paravalvular regurgitation.

Figure 2 displays the estimated freedom from late BVF over a follow-up period of up to 8.9 years according to both actuarial (Kaplan Meier) and actual analysis (cumulative incidence function). Estimated rate of BVF at (and beyond) 7 years was 7.9% for the actuarial and 4.5% for the actual analysis.

Long-term (≥ 5 years) prosthetic valve performance

In 56 patients with echocardiographic follow-up at 6.3±1.0 years (range: 5.0 – 8.9 years), effective orifice area (EOA) was evaluable in 50 cases, transvalvular PG in 53, and prosthetic valve regurgitation (PVR) in all cases. EOA averaged 1.60±0.46 cm^2 (range, 0.78–3.10 cm^2); transvalvular Vmax was 1.80±0.41 m/s (range, 1.10–2.96 m/s); peak PG was 13.7±6.4 mmHg (range, 4.9–35.1 mmHg); and mean PG was 6.7±3.1 mmHg (range, 2.4–18.2 mmHg).

Table 1. Baseline and procedural characteristics.

	n=152
Demographics	
Age, years (median; IQR)	81 (76.0-85.0)
Male gender, n (%)	72 (47.3)
Body mass index; kg/m^2 (median; IQR)	26.1 (24.1-29.3)
Cardiovascular risk factors, n (%)	
Diabetes mellitus	40 (26)
Dyslipidemia	98 (64.4)
Hypertension	125 (82)
Medical history, n (%)	
Previous stroke	14 (9.2)
COPD	35 (23)
Peripheral vascular disease	26 (17)
Previous myocardial infarction	34 (22)
Previous PCI	91 (60)
Previous CABG	32 (21)
Functional status	
NYHA III/IV	142 (94)
Risk scores (median; IQR)	
Logistic EuroSCORE	20.75 (14.0-30.7)
STS Score	4.3 (2.8-5.9)
Echo parameters	
Aortic valve area; cm^2 (mean±SD)	0.60±0.18
Mean pressure gradient; mmHg (median; IQR)	50.0 (40.0-65.0)
Ejection fraction; % (median; IQR)	49.8 (38.7-60.0)
Procedural characteristics	
Transfemoral access, n (%)	151 (99.3)
Valve size, n (%)	
26 mm	56 (37)
29 mm	96 (63)
Procedure time, minutes (median; IQR)	70.7 (52.5-84)
Post-delivery dilatation, n (%)	37 (24.3)
Post-interventional AR ≥ grade 2, n (%)	44 (28.9)
Early device embolization, n (%)	1 (0.7)
Device success, n (%)	107 (70.4)

AR: aortic regurgitation; IQR: interquartile range; SD: standard deviation; COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft

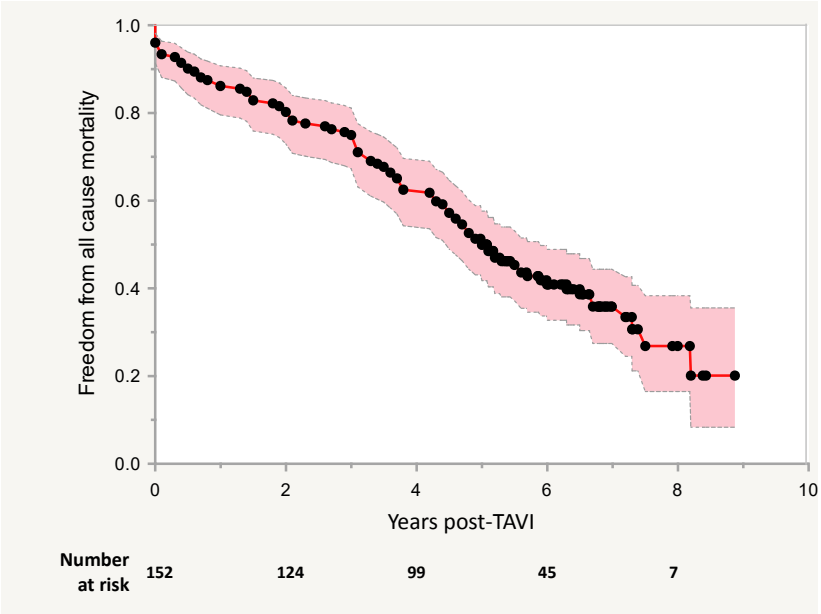

Figure 1. Kaplan Meier survival curve of the study population: Estimated freedom from all-cause mortality (red continuous line) with the 95% confidence interval (pink area). Black dots represent censored observations.

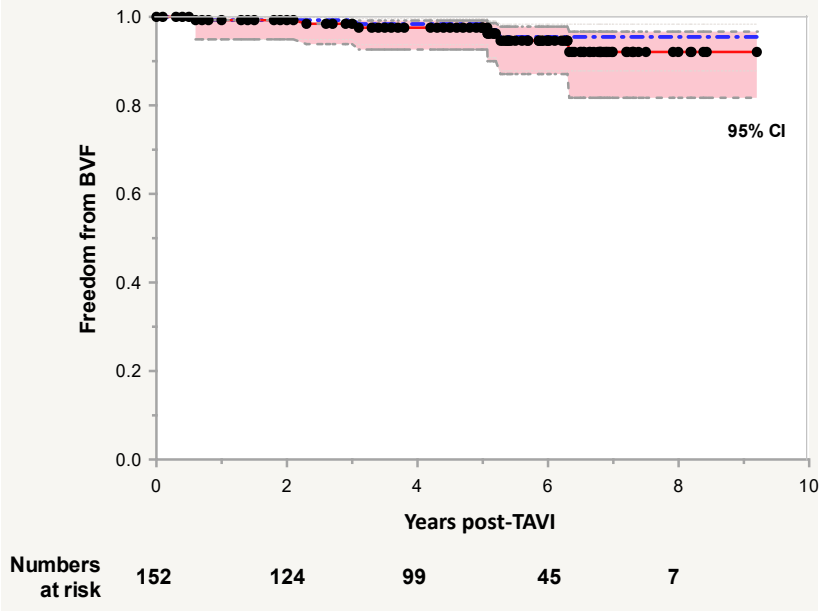

Figure 2. Freedom from BVF after CoreValve implantation: Cumulative freedom from BVF according to the Kaplan Meier estimate (red line; actuarial analysis, 92.1% at 8 years) and adjusted for the competing risk of all-cause mortality (center dotted blue line; actual analysis, 95.5% at 8 years). The pink area demarks the 95% confidence interval. Black dots represent censored observations.

Mean transvalvular PG was 6.3 ± 2.2 mmHg at the 6th-year post-TAVI (n=22), 6.8±3.5 mmHg at 7th-year post-TAVI (n=20), 7.2±4.0 mmHg at 8th-year post-TAVI (n=10), and 6.7±3.9 mmHg at ≥9th-year post-TAVI (n=4). Mean EOA in the 6th, 7th, 8th and 9th years was 1.7 cm^2, 1.6 cm^2, 1.4 cm^2 and 1.8 cm^2.

Vmax was <3 m/s and mean PG was <20 mmHg in all cases and did not increase by ≥10 mmHg from post-operative to latest follow-up echocardiography in any case. EOA was <1.1 cm^2 in four patients (range: 0.78 – 1.06 cm^2). These 4 patients were females with a relatively small body surface area (median, 1.67 m^2).

Transvalvular PVR was detected in 6 patients (all mild), paravalvular PVR in 30 (mild in 20, moderate in 9, and severe in 1 patient), and both in 4 patients (mild in 2, moderate in 1, and severe in 1). Overall, total PVR was none-trace in 13 patients (23.2%), mild in 31 (55.4%), moderate in 10 (17.9%), and severe in 2 patients (3.6%).

Moderate-severe PVR at latest follow-up (n=12) was already present at 30-day echocardiography in 2 cases, and progressed from mild in 9 and from none-trace in 1 patient. Compared to 30-day echocardiography, PVR regressed from moderate to ≤mild in 5 patients (Figure 3). Overall, PVR severity remained stable from post-operative to latest

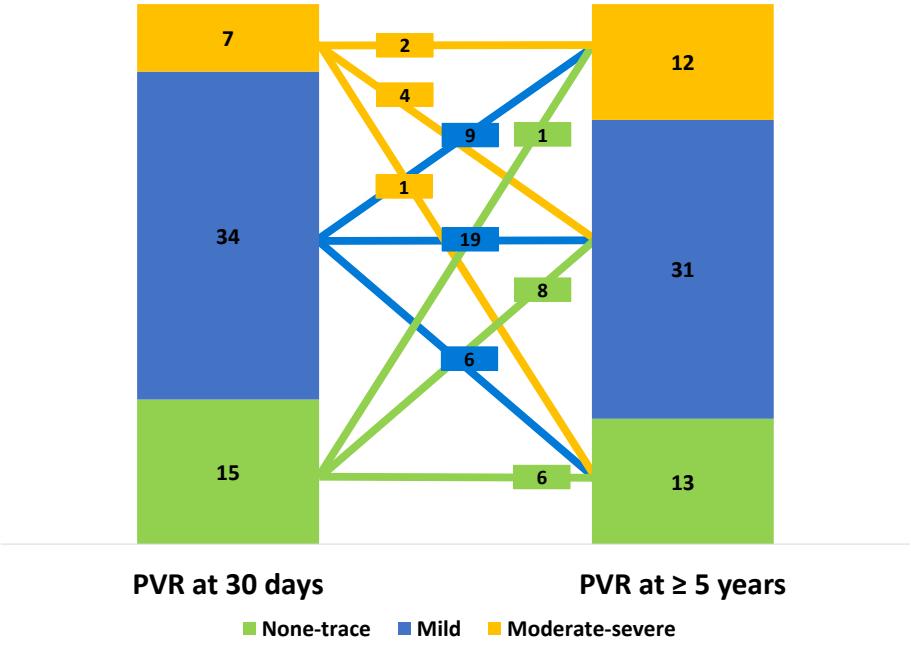

Figure 3. Temporal change in prosthetic valve regurgitation among survivors > 5 years post-TAVI: Severity of prosthetic valve regurgitation (PVR) in patients with paired transthoracic echocardiographic assessments performed at 30 days and at long-term follow-up (6.4±1.0; range: 5.0 – 8.9 years) after TAVI.

follow-up in 27 patients (48%), increased by ≥ 1 grade in 18 (32%), and improved by ≥ 1 grade in 11 (20%). Supplementary Table 3 compares echocardiographic findings at 30 days post-procedure vs. at late follow-up.

DISCUSSION

The main findings of the present study of a self-expanding THV are that: 1) the rate of BVF is <8% at long-term follow-up and is mainly due to re-intervention for paravalvular regurgitation; 2) there is no signal for early SVD up to 8 years post-TAVI; and 3) PVR severity tends to change overtime in a significant proportion of patients.

The present report is one among few long-term structured and well-documented follow-up of the performance and durability of the self-expanding CoreValve™. Despite the limited number of 5-year survivors, the particular strength of this study relies in the high rate of echocardiographic follow-up, the blinded core lab analysis of echo data, and the application of standardized definitions of valve durability and failure.

Clinical outcomes

All-cause mortality rates at 5 years in the current study are comparable to previous studies involving early TAVI patients[5,6]. Procedure-related complications and stroke were the driving causes of death in the early period up to 1 year after TAVI, while other conditions related to the patients' frailty and comorbidities such as congestive heart failure, cancer, infections, falls or unwitnessed events were more predominant causes of death at longer-term follow-up.

THV performance and BVF

Longitudinal studies with different surgical bioprosthetic valves reported a signal for BVF mostly appearing beyond 7-8 years post-implantation[7,11]. Current evidence on the durability of THV is limited to a few studies reporting short- and mid-term data up to 5 years only.

A study of a balloon-expandable THV performance (n=70 patients)[12] has confirmed a favorable mid-term (median, 3.7 years) durability with no evidence of BVF during this relatively limited follow-up period. Another group reported the absence of BVF 4 years after implantation of a balloon-expandable THV; however, after 5 years, 9.7% of living patients in that study had moderate prosthetic valve failure, which according to the investigators did not require reintervention[5]. In the PARTNER I trial, no BVF requiring redo surgical replacement was reported 5 years after balloon-expandable THV implantation[13].

With regard to the self-expanding THV, the Italian CoreValve registry reported stable echocardiographic results over 3 years, whereas a more recent multicenter analysis

described significant prosthesis failure in 1.4% and mild asymptomatic stenosis in 2.8% of the patients over a follow-up period of 5 years[6,14].

The current analysis confirms that transvalvular PG and EOA remain stable in 5-year survivors. Mild PVR was common, and ≥moderate PVR was present in 12 patients out of 56 surviving beyond 5 years and was basically paravalvular. Among the total population (n=151), 5 patients (3.3%) had a reintervention due to ≥moderate paravalvular PVR. Interestingly, re-intervention was in the form of redo-TAVI rather than surgery in 4 out of the 5 cases. Favorable, yet limited, data are available on the outcomes of redo TAVI, and suggest that TAVI can serve as the default re-intervention mode for failing THVs in the future[15,16]. Similar to our findings, two redo TAVI series identified paravalvular PVR as the most common indication for re-intervention after TAVI[15,16]. Projected rates of BVF at 8 years according to the actuarial and actual analysis were as low as 7.9% and 4.5% respectively.

The rate of ≥moderate paravalvular PVR observed beyond 5 years after CoreValve implantation is not surprising and in line with earlier, yet shorter follow-up, reports[17]. The improvement of THV design and the introduction of routine multimodality imaging prior to TAVI has led to a significant reduction in paravalvular PVR rates in contemporary practice. Future longitudinal studies may instead focus on rates of true leaflet deterioration and related clinical events. In the meantime, the present data provides a good reason to believe that SVD of self-expanding valves beyond 5 years and up to 8 years remains rare.

We found, in accordance with some previous reports, that PVR tends to change in severity over time in a large proportion of patients[18,19]. Unlike an earlier report, which suggested that paravalvular PVR after CoreValve implantation tends to regress overtime, we did not see a systematic tendency towards improvement[19]. We rather observed a variable pattern (i.e. stable course, improvement, or deterioration). The determinants of such a change should be explored by upcoming studies.

Although no significant rise of transvalvular PG was detected at long-term, 4 patients (8.0%) had a low EOA (≤ 1.1 cm^2). Transvalvular Vmax and peak and mean PG in these patients were (median [range]: 2.51 [1.8-2.7] m/s, 25.3 [13.0-30.0] mmHg, and 10.6 [5.9-15.8] mmHg. All cases with reduced EOA at follow-up were de novo (as compared to 30-day data). Whether an isolated reduction of the absolute EOA without concomitant rise of PG is clinically relevant, remains an open question. Notwithstanding, in the single case with markedly reduced EOA (0.78 cm^2), left ventricular ejection fraction was markedly reduced (30%). Although this might lead to an underestimation of the EOA, it also can account for the failure of the PG to rise in spite of reduced valvular orifice.

Study limitations

Despite a very close follow-up, the study is derived from a high-risk population with exceedingly high mortality rates and is therefore limited by the relatively low number of patients with a truly long-term follow-up. It is important to underline that assessment of long-term THV performance by echocardiography was only performed through a snapshot examination in a "surviving cohort" and therefore the competing risk of death in this particularly high-risk population may have biased the results. Finally, despite echocardiographic analysis being performed by an independent core laboratory, biases due to measurement variability in this relatively small population cannot be excluded. In line with common clinical sense as well as previous studies, we did not ascribe unwitnessed sudden death to valvular dysfunction, as the latter often manifests as a gradual or a subacute clinical deterioration.

CONCLUSIONS

In this long-term clinical and echocardiographic follow-up of patients treated with the self-expanding CoreValveTM, we found a sustained THV performance with rates of late BVF as low as 4.5% according to currently proposed definitions. The present study cannot conclude – but rather contributes to the growing evidence – upon THV durability.

IMPACT ON DAILY PRACTICE

Long-term results beyond 5 years after TAVI remain uncertain. The current follow-up (up to 8.9 years after TAVI) documents favorable performance of the self-expanding CoreValve™ with low rates of BVF. However, further large-scale studies and registries are required to confirm the non-inferiority of THV compared to surgical bioprostheses in terms of long-term durability.

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SUPPLEMENTARY DATA

Supplementary Table 1. 30-day outcomes.

	CoreValve 09/2007-12/2011 n=152
30 day outcomes	
All-cause mortality (%)	10 (6.6)
Cardiovascular mortality (%)	7 (4.6)
Myocardial infarction (%)	0 (0)
Major stroke (%)	8 (4.5)
Major bleeding (%)	23 (15.1)
Major vascular complications (%)	13 (8.5)
Akute Kidney injury	
AKIN stage 2	24 (16.1)
AKIN stage 3	3 (2)
New permanent pacemaker (%)	30 (25)*

*Expressed as percentage of patients without permanent cardiac rhythm device at baseline

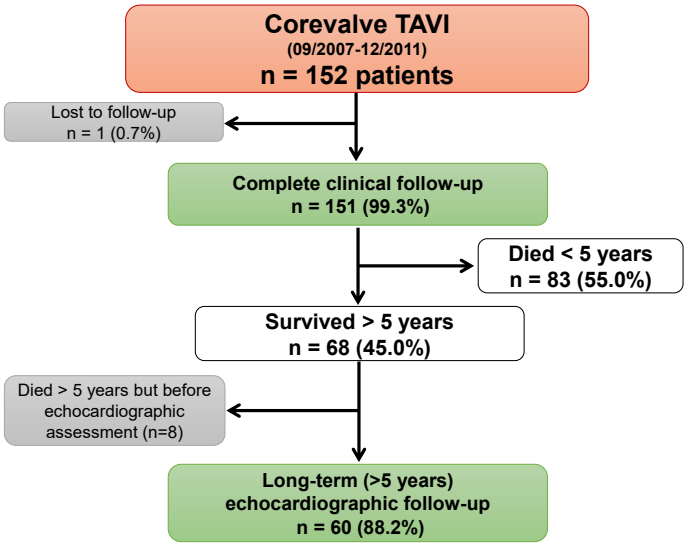
Supplementary Table 2. Causes of mortality.

	30 days n=10	1 year n=11	5 years n=55	> 5 years n=19
Cardiovascular death (%)	**7 (70)**	**9 (81.8)**	**36 (65.5)**	**14 (73.7)**
Procedure related (vascular complication, Bleeding, aortic or ventricular rupture)	6 (60)	-	-	-
Stroke (ischemic and hemorrhagic)	0	5 (45.5)	1 (2)	0
Myocardial infarction	0	0	2 (3.6)	0
Sudden cardiac death, arrhythmia	0	0	2 (3.6)	1 (5.3)
Heart failure	1 (10)	1 (9.1)	9 (16.3)	3 (15.8)
Unwitnessed, unknown	0	3 (27.2)	22 (40)	10 (52.6)
Non cardiovascular death (%)	**3 (30)**	**2 (18.2)**	**19 (34.5)**	**5 (26.3)**
Infection/sepsis	3 (30)	0	6 (11)	2 (10.5)
Cancer	0	1 (9.1)	7 (12.7)	2 (10.5)
Accident (polytrauma, femoral fracture)	0	1 (9.1)	4 (7.2)	0
Others	0	0	2 (3.6)	1 (5.3)

Supplementary Table 3. Echocardiographic measurements early after TAVI vs. at late follow up (6.3±1.0 years post-TAVI).

	30 days post-procedure	Long-term follow up
Peak pressure gradient* (mmHg)	15.3±6.9	13.8±6.4
Mean pressure gradient* (mmHg)	8.3±3.5	6.7±3.1
Aortic valve area* (cm^2)	2.22±0.59	1.59±0.48
Left ventricular ejection fraction* (%)	50.9±13.4	52.6±12.7
Moderate-severe aortic regurgitation*	7 (12.7%)	12 (21.4%)

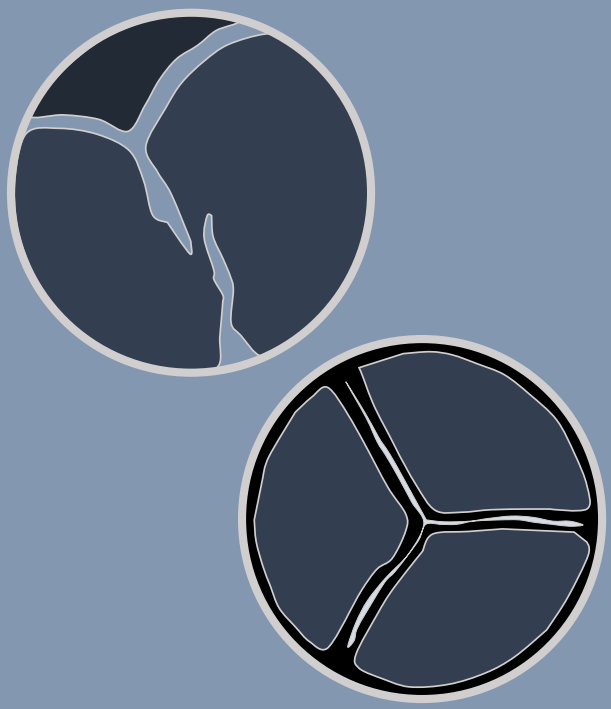
*The number of data pairs (data available both at baseline and follow up) was: 52 for pressure gradients, 40 for valve area, 53 for LV ejection fraction, and 55 for aortic regurgitation.

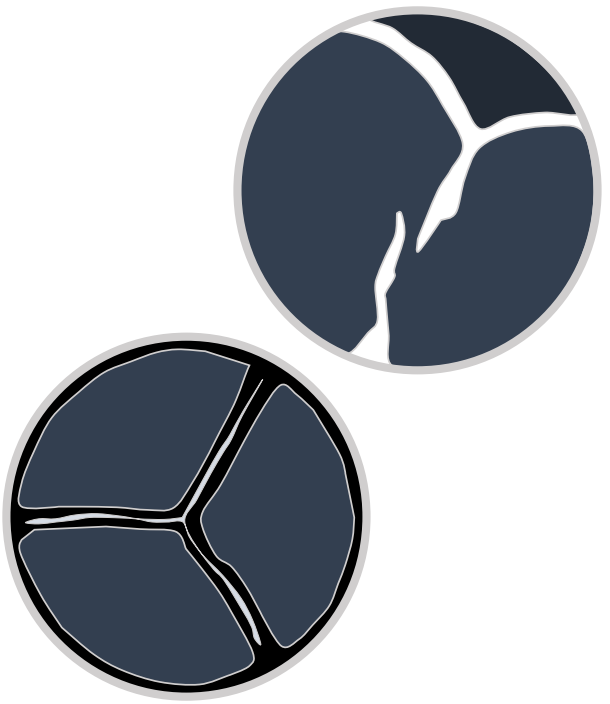


Supplementary Figure 1. Study flow chart and patient enrollment.

PART B

Transcatheter interventions for other cardiac valves



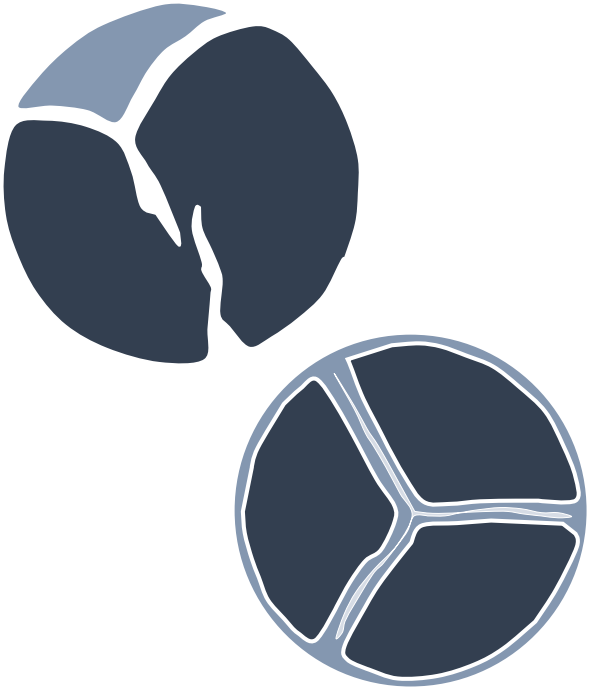


Chapter 10

A simplified and reproducible method to size the mitral annulus: implications for transcatheter mitral valve replacement

Abdelghani M, Spitzer E, Soliman OII, Beitzke D, Laggner R, Cavalcante R, Tateishi H, Campos CM, Verstraeten L, Sotomi Y, Tenekecioglu E, Onuma Y, Tijssen JG, de Winter RJ, Maisano F, Serruys PW

EHJ Cardiovascular Imaging 2017;18(6):697-706.



ABSTRACT

Aims:

Transcatheter mitral valve replacement (TMVR) provides definitive valve replacement through a minimally-invasive procedure. In the setting of TMVR, it remains unclear how relevant the differences between different mitral annular (MA) diameters are. We sought to define a simplified and reproducible method to describe the MA size.

Methods and results:

Using cardiac computed tomography angiography (CTA) studies of 47 patients, 3D MA perimeter (P_{3D}) was annotated. The aorto-mitral continuity was excluded from MA contour either by manual annotation (yielding a saddle-shape model) or by simple truncation at the medial and lateral trigones (yielding a D-shape model). The method of the least squares was used to generate the projected MA area (A_{proj}) and perimeter (P_{proj}). Intercommissural (IC) and septo-lateral (SL) diameters, Dmean= (IC diameter + SL diameter)/2, area-derived diameter ($D_{Area} = 2 \times \sqrt{(A/\pi)}$) and perimeter-derived diameter ($D_{Perimeter} = P/\pi$) were measured. MA eccentricity, height and calcification (MAC) were assessed. Thirty studies were re-read by the same and by another observer to test intra- and inter-observer reproducibility.

Patients (age, 75 ± 12 years, 66% males) had a wide range of mitral regurgitation severity (none-trace in 8%, mild in 55%, moderate-severe in 37%), MA size (area: 5-16 cm^2), eccentricity (−8 - 52%) and height (3-11 mm). MAC was seen in 11 cases, in whom MAC arc circumference occupied 26±20% of the MA circumference.

D_{Area} (36.0±4.0 mm) and $D_{Perimeter}$ (37.1±3.8 mm) correlated strongly (R^2=0.97) and were not significantly different (p=0.15). The IC (39.3±4.6 mm) and the SL (31.4±4.5 mm) diameters were significantly different from D_{Area} (p<0.001) while D_{mean} (35.4±4.0 mm) was not (p=0.5). The correlation of D_{Area} was stronger with D_{mean} (R^2= 0.96) than with IC and SL diameters (R^2=0.69 and 0.76, respectively). The average difference between D_{Area} and D_{mean} was +0.6 mm and the 95% limits of agreement were 2.1 and -0.9 mm. Similar results were found when the D-shape model was applied.

All MA diameters showed good reproducibility with high intraclass correlation coefficient (0.93-0.98), small average bias (0.37-1.1 mm), and low coefficient of variation (3-7%) for intra- and inter-observer comparisons. Reproducibility of D_{Area} was lower in patients with MAC.

Conclusion:

MA sizing by CTA is readily feasible and reproducible. Dmean is a simple index that can be used to infer the effective MA size.

INTRODUCTION

Mitral regurgitation (MR) is the most common valvular heart disease and its prevalence increases with advancing age[1]. Surgical correction is the mainstay of therapy for MR but operative mortality and morbidity rise with increasing age[2] and surgery is deferred in a large number of patients because of high surgical risk[3]. Whereas conventional replacement is associated with a lower risk of recurrence, evidence suggests that chordal-sparing therapies provide better outcomes[4]. Combining definitive valve replacement with preservation of subvalvular structures through a minimally-invasive transcatheter mitral valve replacement (TMVR) has been recently shown to be feasible[5-7] with encouraging results acutely and up to 6-months[6.]

The hemodynamic performance of a stented bioprosthetic valve is primarily determined by its orifice diameter[8]. Conformation to the native annulus is also necessary for adequate anchoring and paravalvular sealing. Therefore, accurate assessment of the native annular size and accordingly appropriate sizing of the prosthetic valve are crucial to achieve optimal hemodynamic results but can be challenging given the complex geometry of the mitral annulus (MA).

Unlike the planar aortic valve annulus, the MA is a 3-dimensional, non-planar, saddle-shaped structure[9-12]. The size of the MA, when assessed by 3D echocardiography or cardiac computed tomography angiography (CTA), is commonly reported as a projected area[9,13,14]. On the other hand, most TMVR devices are circular[15] and their sizing is, accordingly, based on a single diameter. Available data from preclinical [16-18] and small human[6] studies reveal no consensus on how to define the MA size in the setting of TMVR.

CTA imaging provides 3-dimensional volumetric data sets with sub-millimeter spatial resolution providing an accurate and complete evaluation of the MA including simple 2D diameters (e.g. the intercommissural and the septolateral diameters) and effective diameters (that account for the 3D geometry of the annulus). In the setting of TMVR, it is unclear how relevant the differences between different approaches to define the size of the MA are. We sought to define a simplified and reproducible method to describe the MA size.

METHODS

The study was approved by the institutional review board and all patients provided informed consent. The study population consisted of 47 patients who had a cardiac CTA in the diagnostic workup during consideration for coronary revascularization or transcatheter aortic valve replacement.

Prospectively-triggered cardiac CTA examinations were performed with the scan range extending from the carina to the diaphragm. Scans were performed using a 320-multi-slice scanner (Aquilion ONE, Toshiba Medical Systems, Tochigi-ken, Japan) with slice collimation of 320 x 0.5 mm, rotation time of 350 ms, tube voltage of 120 kV, and automated tube current modulation. Iodinated contrast agent (Omnipaque) was injected through an antecubital vein at a flow rate of 5 ml/sec, followed by saline solution. All datasets were stored in a remote workstation for off-line analysis.

Mid-diastolic CTA data (at a section-thickness of ≤1 mm) were analyzed using a dedicated Mitral Analysis workflow in 3mensio Structural Heart™ (Pie Medical Imaging BV, Maastricht, The Netherlands). This dedicated analysis workflow provides a double oblique multiplanar reconstruction that displays two orthogonal views; a long-axis view (the plane of which traverses the left ventricular apex and the center of the mitral annulus) and a short-axis view (Figure 1).

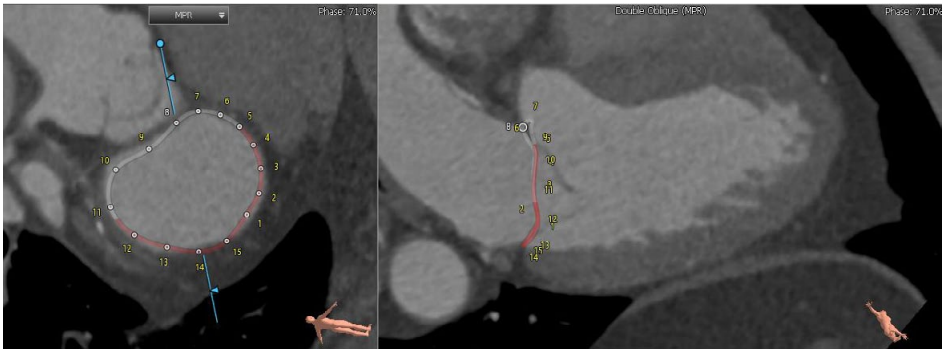


Figure 1. Fifteen seeding-points are annotated in the long-axis view (right panel) to define the mitral annulus. The en-face perspective is displayed in the short-axis view (left panel).

Assessment of the mitral annulus:

The mitral annulus was annotated on the long axis view as previously described[19,20] to trace the 3D saddle-shape annular perimeter (Figure 1). In the present study, however, we followed a more straight-forward approach for the annotation of the anterior segment of the annulus (next to the aorto-mitral continuity) to improve reproducibility of MA sizing. We defined the boundary between the anterior mitral leaflet (AML) and the intervalvular fibrosa (i.e. the aorto-mitral continuity) by first identifying the AML tip in the long axis view and then progressively scrolling cranially towards the aortic valve. The boundary is defined in the short axis view where a clear continuity is identified between the lateral and medial fibrous trigones (Figure 2).

Additionally, a D-shape model of the MA was created and analyzed by the same observer in 30 cases. In the D-shape model, the anterior border of the MA is defined by a

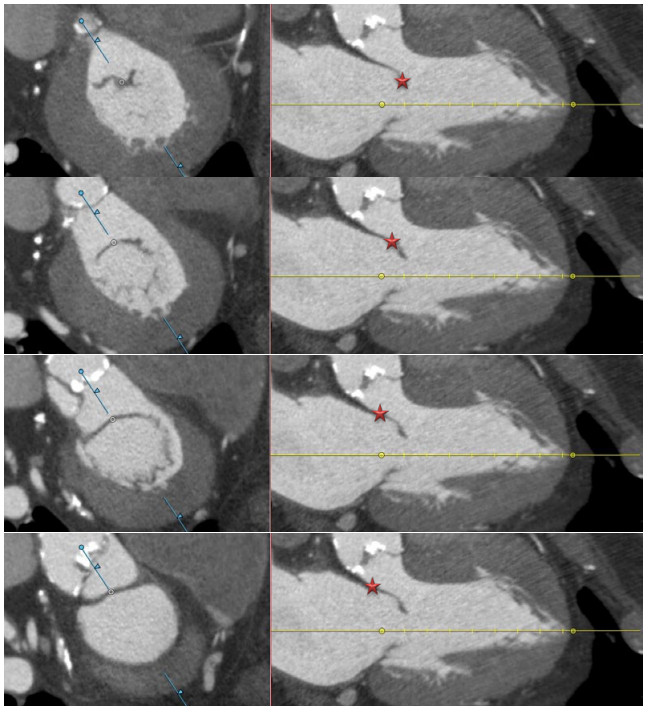


Figure 2. The methodology used for the definition of the anterior segment of the mitral annulus. We first identified the tip of the anterior mitral leaflet in the long axis view (right, upper panel) and then we scrolled cranially through the aorto-mitral curtain (displayed in succession from the upper through to the lower panels). The anterior boundary of the mitral annulus was defined where a clear continuity is identified between the lateral and medial fibrous trigones in the short axis view (left, lower panel). The star (red) indicates the mitral valve level intersected by the short axis imaging plane.

virtual (intertrigonal-IT) line connecting the lateral and medial trigones[14] truncating the anterior annular peak (Figure 3). This model has been previously proposed to afford less encroachment of the TMVR device on the left ventricular outflow tract (LVOT), maintaining its patency[14].

The method of the least squares[21] (similar to projecting the contour onto a plane) was used to derive the projected area and perimeter (Figure 4). The following MA parameters were measured: intercommissural (IC) and septo-lateral (SL) diameters, 3D perimeter (P_{3D}), projected area (A_{proj}) and perimeter (P_{proj}). The IC diameter was measured as the largest MA dimension typically transecting through the MA centroid[22]. The SL diameter was defined as the dimension perpendicular to, and bisecting, the IC diameter. All measurements were performed in mid-diastolic reconstructions to depict the largest MA size[9,13,23,24].

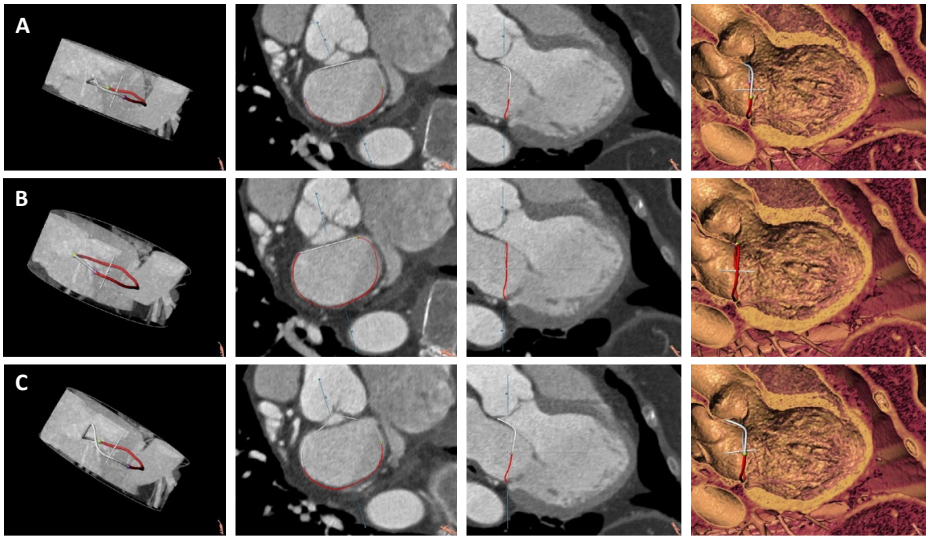


Figure 3. Three methods of mitral annular definition. In the upper and middle panels (A and B), the aorto-mitral continuity is excluded from the annular contour either by manual point-by-point annotation yielding a saddle-shape model (A) or by truncating the anterior peak of the annulus at the medial and lateral trigones yielding a D-shape model (B). In both models, the septolateral distances are not largely different (in the displayed example, 32.3 vs. 31.1 mm) as are the 3D perimeters (125 mm vs. 123 mm) and projected areas (11.5 cm^2 vs. 11.3 cm^2). In the lower panel (C), the aorto-mitral continuity is not excluded and the anterior peak is extending to the plane of the aortic annulus. The resulting model in (C) is more non-planar, extending for a longer septolateral distance (35.6 mm) and yields a larger perimeter (132 mm) and area (12 cm^2) than in (A) and (B). Left panels are free-rotatable Hockey Pucks displaying the 3D contour of the annulus.

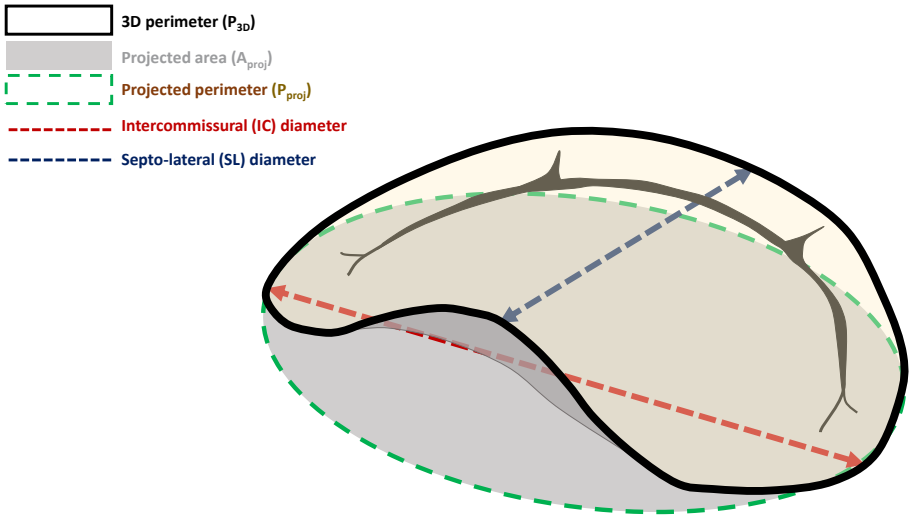


Figure 4. Different parameters of the mitral annulus size.

From these measurements, three annular diameters were then calculated; D_{mean}= (IC diameter + SL diameter)/2, area-derived diameter ($D_{Area} = 2 \times \sqrt{[A/\pi]}$) and perimeter-derived diameter ($D_{Perimeter} = P/\pi$).

MA eccentricity index (Ei) was calculated from the equation: ([IC diameter - SL diameter] / IC diameter), with an Ei of 0 representing a perfect circle while higher values indicate increasing ellipticity. MA height (the vertical distance between the highest and lowest points of the annular contour) was measured as an index of non-planarity. Mitral annular calcification (MAC) location and circumferential extent (in degrees) were assessed in a calcification view (Hockey Puck).

Assessment of the sub-mitral apparatus:

Left ventricular (LV) dimensions were measured at the papillary muscle (PM) level (at the basal edge of the PM insertion to the LV) and at the basal level (at the junction of the middle and basal thirds of the LV). Left ventricular eccentricity (defined as the ratio between the major and minor transverse diameters at the basal level) and sphericity (an estimate of PM displacement, defined as the ratio between the major LV transverse diameter at the PM level and the PM-MA distance[12,25]) were subsequently computed. LV wall thickness was measured from the 3-chamber view at the basal level (interventricular septum, IVS and posterior wall thickness, PWT).

Reproducibility analysis:

In 30 CTA studies, analysis was performed by 2 cardiologists (a CTA specialist-ES and an interventional cardiologist-MA) to investigate inter-observer reproducibility of MA parameters. Re-read by the same observer (MA) was performed at a median interval of 5 weeks to investigate intra-observer reproducibility.

Statistical analysis:

Continuous variables are summarized as mean ± SD when normally-distributed or as median and interquartile range when non-normally distributed. Categorical variables are presented as frequencies and percentages. Continuous variables were compared using the Student t test and the association between them was tested using Pearson correlation. Intraobserver and interobserver agreements for the MA measurements were expressed by the intraclass correlation coefficient (ICC). Intra- and inter-observer variability was expressed as absolute difference and as coefficient of variation (CV) calculated as the SD of inter-/intra-observer difference divided by the population mean. Bland-Altman method was used to plot the differences between MA diameters with the assessment of systematic bias and confidence limits of agreement (LOA).

Statistical analysis was performed with SPSS 23.0 (IBM, Armonk, NY, USA). All probability values were two-tailed, and a value of $P<0.05$ was considered significant.

RESULTS

Summary of the characteristics of the patients, the MA and the sub-mitral apparatus is presented in table 1. Patients (age, 75±13 years) were predominantly males (66%). Mitral regurgitation was none-trace in 8%, mild in 55%, moderate-severe in 37%. A wide range of mitral annular size (area: 5-16 cm^2), eccentricity (–8 -52%) and height (3-11 mm) was represented. The anterior peak of the MA represented the highest point of the annular contour in 40 cases while the posterior peak was higher in the remainder. The average height of the anterior peak was 5.4±1.9 mm while that of the posterior peak was 4.3±1.3 mm. The anterior peak was in average +1.1 mm higher than the posterior peak. MAC was seen in 23% of cases and its arc circumference occupied 26±20% of the MA circumference.

Mitral annular diameters:

The average MA A_{proj} was 10.3±2.3 cm^2. P_{3D} and P_{proj} were 119.8±12.6 and 116.7±11.8 mm, respectively (p=0.22). P_{3D} was larger than P_{proj} in all cases (average difference +3.1 mm). The difference correlated strongly with MA height (r=0.88, p<0.001).

As the MA is expected to conform to the TMVR bioprosthesis assuming a planar configuration, the projected area and projected perimeter-derived diameters (D_{Area} and $D_{Perimeter}$) were considered the effective MA diameters in further analysis. D_{Area} (36.0±4.0 mm) and $D_{Perimeter}$ (37.1±3.8 mm) correlated strongly (R^2=0.97) and were not significantly different (p=0.15). $D_{Perimeter}$ was larger than D_{Area} in all patients. The difference ranged from 0.04 to 3.5 mm and averaged +1.2 mm. The 95% limits of agreement were 2.5 and -0.2 mm. The difference increased with increasing annular eccentricity (r=0.78, p<0.001) (Figure 5).

The IC (39.3±4.6 mm) and the SL (31.4±4.5 mm) diameters were significantly different from D_{Area} (p <0.001) and the correlation with D_{Area} was moderate (R^2=0.69 and 0.76, respectively). On the other hand, D_{mean} (35.4±4.0 mm), was too close to D_{Area} (p=0.5) and correlated strongly with it (R^2= 0.96). Similarly, $D_{Perimeter}$ was more tightly correlated with D_{mean} (R^2=0.93) than with IC (R^2=0.78) and SL (R^2=0.63) diameters (Figure 6).

D_{Area} tended to be slightly larger than D_{mean} (Figure 7.A). The difference between D^{Area} and D_{mean} ranged from -1.9 to 2.6 mm and averaged +0.6 mm. The 95% limits of agreement were 2.1 and -0.9 mm. The difference did not correlate (p>0.05) with MA eccentricity, height or calcification severity. There has also been no correlation between the difference and LV diastolic diameters (minimum, maximum and long-axis), wall thickness, ejection fraction, eccentricity or sphericity.

$D_{Perimeter}$ was larger than D_{mean} in all cases (Figure 7.B). The difference ranged from 0.2 to 5.6 mm and averaged +1.8 mm. The 95% limits of agreement were 3.8 and -0.3 mm. The difference weakly correlated with MA eccentricity (r=0.36, p=0.013) and height (r= –0.32, p=0.03).

Table 1. Summary of the characteristics of the patients (n=47), the mitral valve and the sub-mitral apparatus:

	Range	Mean±SD
Age (years)	40.0-93.0	75 ± 13
Male gender*		66%
BMI (kg/m^2)	18.2-46.2	27.1±5.2
Mitral Valve Assessment:[§]		
MR: *		
None-trace		8%
Mild		55%
Moderate-severe		37%
IC diameter (mm)	27.0-51.0	39.3±4.6
SL diameter (mm)	19.5-42.5	31.4±4.5
D_{mean} (mm)	24.8-44.3	35.4±4.0
Area (cm^2)	5.1-16.0	10.3±2.3
3D perimeter (mm)	85.0-148.0	119.8±12.6
Projected perimeter (mm)	84.00-143.0	116.7±11.8
D_{Area} (mm)	25.5-45.1	36.0±4.0
$D_{Perimeter}$ (mm)	26.7-45.5	37.1±3.8
Ei	–0.08-0.52	0.19±0.11
MA Height (mm)	2.9-11.0	5.5±1.9
MAC*		23%
MAC arc circumference (degrees)	15-255	92±71
Sub-mitral Apparatus Assessment:		
EF (%)	30.0-77.0	56.6±14.6
PM tip-MA distance (mm)	12.1-31.0	22.2±4.1
LV diameter (2C-PM level) (mm)	34.0-72.7	53.5±9.1
LV diameter (3C-Basal level) (mm)	35.6-65.9	46.9±8.3
IVS-Thickness (mm)	6.8-20.5	14.0±3.2
PW-Thickness (mm)	7.3-13.5	10.4±1.7
LV sphericity index	0.9-2.2	1.5±0.3
LV eccentricity index	0.01-0.32	0.15±0.08

*Data presented as proportion.

[§]Mitral annulus geometry assessed using the saddle-shape model.

Abbreviations:

BMI=body mass index, D_{Area}=projected area-derived diameter, D_{mean}=average of intercommissural and septolateral diameters, $D_{Perimeter}$=projected perimeter-derived diameter, EF=ejection fraction, Ei=annulus eccentricity index, IC=intercommissural, IT=inter-trigonal, IVS=inter-ventricular septum, MA=mitral annulus, MAC=mitral annular calcification, MR=mitral regurgitation, PM=papillary muscle, PW=posterior wall, SL=septo-lateral, 2C=2-chamber view, 3C=3-chamber view, 3D=3-dimentional.

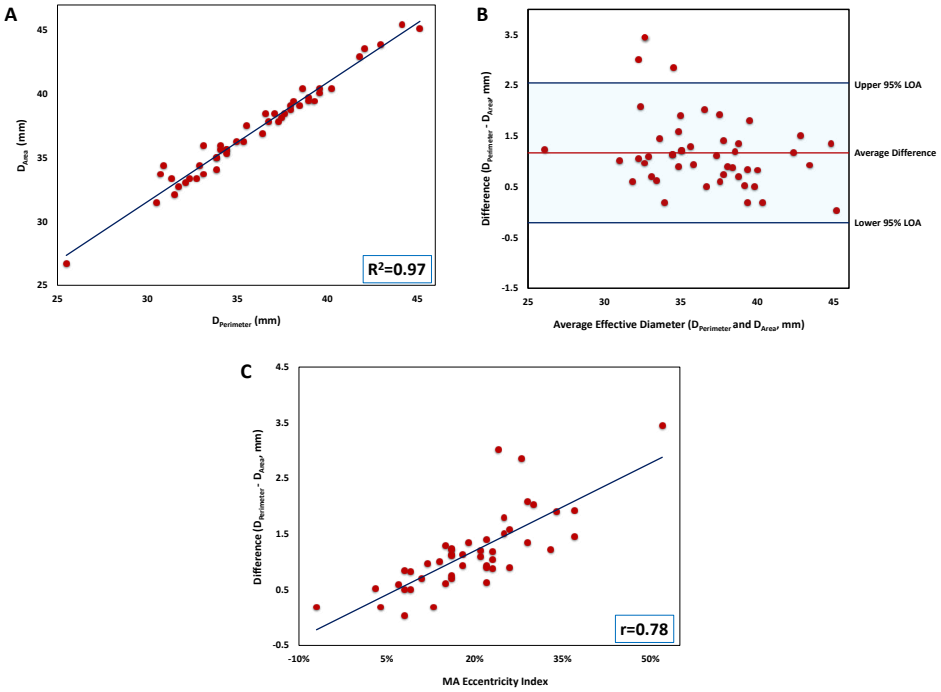


Figure 5. The correlation (A) and variability -displayed in Bland-Altman plot- (B) of the effective mitral annular diameters. The difference correlated with the degree of annular eccentricity (C).

Mitral annular diameters in the D-shape model:

Summary of the different parameters of MA size according to the D-shape model is presented in table S1. As in the saddle-shape model, D_{Area} (35.7±3.3 mm) and $D_{Perimeter}$ (37.0±3.3 mm) were strongly correlated (R^2=0.97) with a small bias (average: 1.3 mm, lower and upper 95% LOA: 0.3-2.4 mm) using the D-shape model. The correlation between D_{mean} (34.6±3.2 mm) and D_{Area} and $D_{Perimeter}$ was strong (R^2=0.95, for both). The average bias from D_{Area} was 1.0 mm and from $D_{Perimeter}$ was 2.3 mm. The lower and upper 95% LOA were - 0.4 and 2.4 mm (D_{Area} vs. D_{mean}); 0.9 and 3.8 mm ($D_{Perimeter}$ vs. D_{mean}).

Comparison of the two models of mitral annulus definition:

As expected, the SL diameter was larger in the saddle-shape (31.5±4.3 mm) than in the D-shape model (30.4±3.7 mm) and the correlation was not perfect (R^2=0.82, p<0.001). However, the difference was small (average: +1.2 mm [3.9%]) and did not reach statistical significance (p=0.25). All other parameters of the MA size (P_{3D}, P_{proj}, A_{proj}, D_{mean}, D_{Area} and $D_{Perimeter}$) were closely related in both models (Table S1).

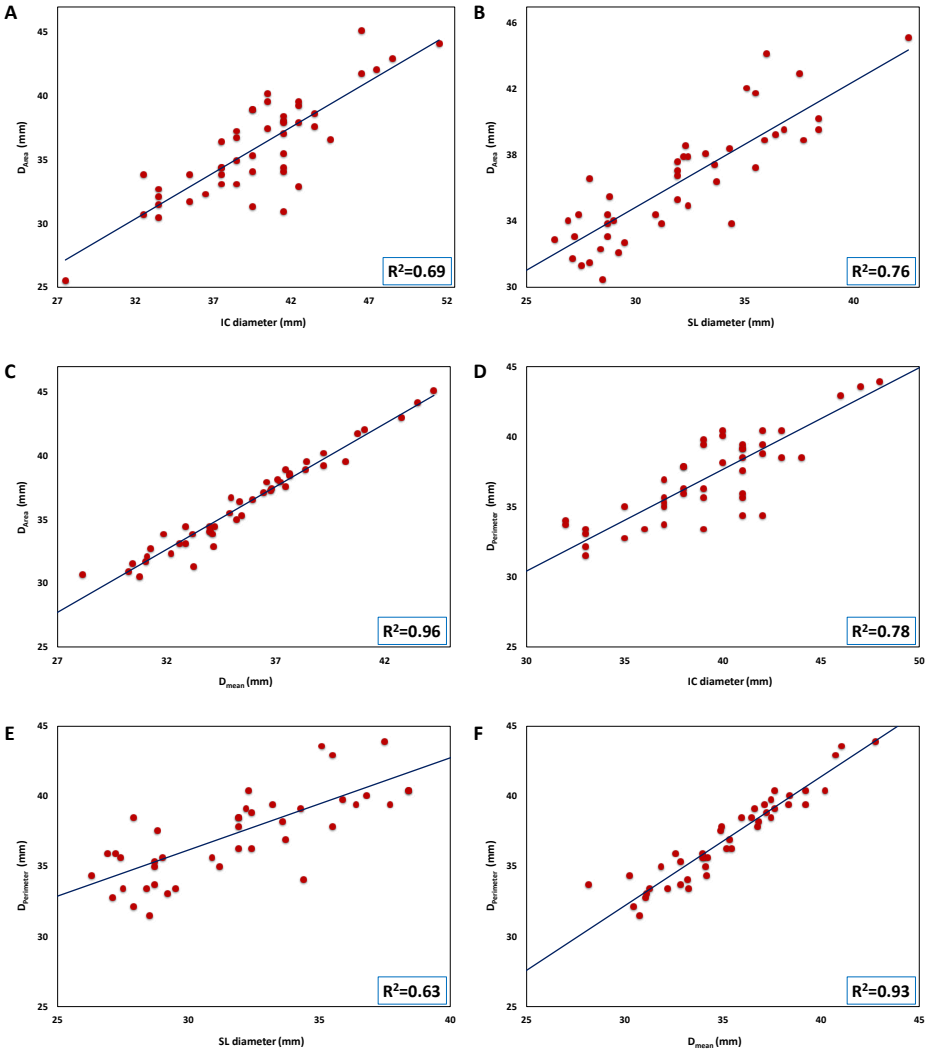


Figure 6. The correlation of intercommissural (IC) diameter, septo-lateral (SL) diameter and Dmean with area-derived diameter (DArea- A, B and C) and perimeter-derived diameter (DPerimeter- D, E and F).

Reproducibility of MA diameters:

Table 2 summarizes the indices of intra- and inter-observer reproducibility of different MA diameters. Overall, the ICC was high (0.93-0.98), the average bias was small (0.4-1.1 mm), and the CV was low (3-7%) for all diameters. Inter-observer reproducibility tended to be lower in patients with MAC, with the inter-observer bias being significantly higher in those with vs. those without MAC for D_{Area} (Table S2).

Table 2. Intra- and inter-observer reproducibility of MA diameters (n=30):

	Intra-observer Reproducibility					Inter-observer Reproducibility				
	ICC*	Average bias (mm)	95% LOA (mm)		CV	ICC*	Average bias (mm)	95% LOA (mm)		CV
			Upper	Lower				Upper	Lower	
IC diameter	0.98	-0.83	3.09	-4.76	5%	0.93	0.60	2.76	-1.56	3%
SL diameter	0.93	0.75	4.83	-3.33	7%	0.95	-1.08	2.76	-4.92	6%
D_{Area}	0.97	0.37	2.81	-2.07	4%	0.94	-1.10	2.25	-4.45	5%
$D_{Perimeter}$	0.97	0.55	2.76	-1.66	3%	0.95	-0.71	2.33	-3.75	4%
D_{mean}	0.97	0.68	3.11	-1.76	4%	0.94	-0.96	2.40	-4.31	5%

*p value <0.01 for all.
CV=coefficient of variation, ICC=intraclass correlation coefficient, LOA=limit of agreement. Other abbreviations as in table 1.

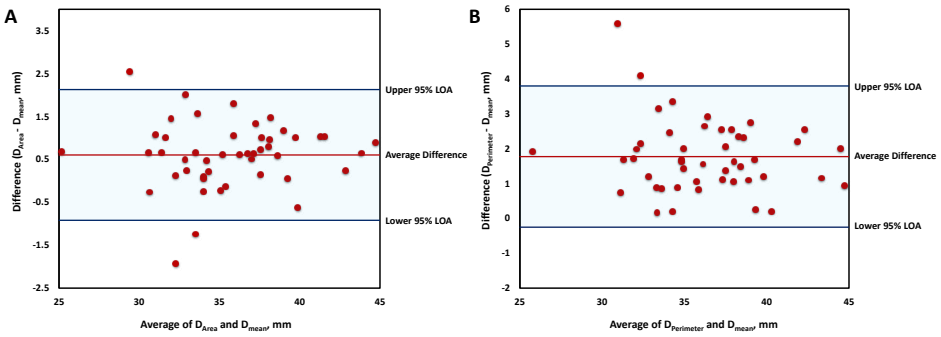


Figure 7. Bland-Altman plots of the differences between Dmean and area-derived (A) and perimeter-derived (B) diameters.

DISCUSSION

The main findings of the present study are that; 1) projected area- and perimeter-derived MA diameters are closely related with small differences, implying that either D_{Area} or $D_{Perimeter}$ could be interchangeably considered the "effective annular diameter", 2) intercommissural and septolateral diameters differed significantly from the effective annular diameters while D_{mean} was consistent with the effective diameters regardless of the annular model used for sizing (saddle-shape vs. D-shape), implying that D_{mean} could be used to infer the effective MA diameter, and 3) regardless of the parameter used to size the MA, CTA yielded an excellent reproducibility of measurements, suggesting that CTA could be reliably used to size the native MA in the setting of TMVR.

Compared with echocardiography, CTA provides 3D sets of data of cardiac morphology with excellent image quality basically owing to the higher spatial resolution, the lower signal-to-noise ratio, and the completeness of data it provides[26]. Moreover, image

quality on CTA tends to be "isotropic" throughout the data set with small variability between different structures in the scan field[26]. In the present study, adequate MA sizing was feasible by CTA in all cases and was shown to be perfectly reproducible, further confirming the usefulness of this tool in planning for interventions to treat MR. The approach used for the definition of the anterior segment of the MA (Figure 2) might have contributed to the excellent reproducibility, which was achievable even when an interventional cardiologist with no prior CTA training performed the analysis. Care should be exercised when tracing the MA contour in patients with MAC where artifacts could significantly increase inter-observer variability.

Cardiac CTA has evolved into a versatile, non-invasive imaging tool in cardiovascular medicine. However, the increasing use of CT has raised concerns about cumulative radiation dose[27]. The usage of iodinated contrast agents represents another limitation of CTA, an aspect of a special importance in elderly patients with vascular disease and renal insufficiency. Paucity of hemodynamic information and low temporal resolution are other barriers precluding the adoption of CTA as a stand-alone tool without complementation with echocardiography. A direct comparison of 3D echocardiography and CTA is awaited to define the best method for TMVR planning.

Proper sizing of the native annulus prior to valve replacement is known to be a critical determinant of prosthetic valve performance and stability as well as paravalvular sealing. Lessons learned from transcatheter aortic valve implantation imply that inaccurate sizing of the native aortic annulus leads to under/over-sizing of the transcatheter heart valve (THV) with resultant increased risk of conduction defects, paravalvular leakage (PVL), poor device fixation, annular rupture and injury of adjacent structures[28-32]. Two-dimension sizing of the aortic annulus was shown to be less accurate than area/perimeter-based sizing[29] (preferably using CTA[33,34]) and to systematically lead to THV under-sizing and the development of PVL[35]. Subsequently, it became evident that clinically-significant differences exist even between annular mean diameter, area-derived diameter and perimeter-derived diameter[36-40].

In the setting of TMVR, annular sizing is more challenging given the complex 3D non-planar and non-circular geometry[9,13]. Although the complexity of the MA geometry is well-known, the current methods used to guide TMVR device size selection lack standardization. For some of TMVR devices, sizing is based on a single annular diameter (e.g. SL diameter[6]) or considers both the IC and SL diameters[16,17]. For others[18], sizing is based on D_{mean} ([IC dimension + SL dimension]/2). The latter, was shown in the present study to be closest to the MA effective diameters. Additionally, D_{mean} determination does not need complex imputations or dedicated analysis workflow and can be derived from 2D echocardiographic measurements (e.g. from the orthogonal 2- and 3-chamber views). Intermodality (CTA and echocardiography) reproducibility of D_{mean} is, however, unknown and needs yet to be investigated.

We also found that a careful definition of the anterior segment of the annular contour yields a saddle-shape MA model that is not significantly different in size from a D-shape (truncated) model. Blanke and colleagues[14] have proposed truncating the anterior peak of the MA contour to yield a more planar and a significantly smaller MA model that encroaches less on the LVOT. In their analysis, a saddle-shape model comprised the aorto-mitral continuity extending to the plane of the aortic valve virtual annulus while in our analysis this continuity has been excluded from the MA contour (Figures 2 and 3). Accordingly, the saddle-shape model in Blanke's study had a larger height (10.6 ±1.8 mm) and SL diameter (40±5 mm) than the saddle-shape model in the present study (height: 5.5±1.9 mm, SL diameter: 31.4±4.5 mm). In Blanke's study, the MA height was significantly higher than expected for a series of patients with LV dilation (end diastolic diameter, 67±8 mm) and systolic dysfunction (EF, 29±8 %) where lower values of the MA height has been previously reported[10]. This explains the close similarity between the saddle- and the D-shape models in the present study, as both excluded the aorto-mitral continuity (by manual point-by-point annotation in the first, or by simple truncation at the IT line in the second).

One of the raised issues is the timing (in the cardiac cycle) of annulus size measurements. MA area has been shown to considerably change during the cardiac cycle being largest in mid-late diastole[9,13], when non-planarity is known to be maximum[13]. Therefore, we confined he measurements to mid-diastole. Dynamicity of the MA size, although observed in normal hearts and in different cardiac pathologies, is variable in magnitude being, for example, larger in hypertrophic cardiomyopathy than in dilated cardiomyopathy[9,13]. Non-planarity was also shown to be minimal in the latter group than in the former and to be maximal in those with no gross cardiac pathology[9]. Those influences of the LV status (e.g. dilated with impaired contractility vs. hypertrophied with small cavity and good contractility) on MA dynamicity and geometry were considered in the present study, where the geometry of the sub-mitral LV structures and its influence on MA sizing were studied. This was basically aiming at a more careful generalization of the results of the present series. The present series, albeit relatively small, represents the spectrum of sub-mitral geometry. Left ventricular ejection fraction ranged from 30 to 77%, LV antero-posterior diameter from 36 to 66 mm, IVS thickness from 7 to 21 mm, LV eccentricity index from 1.0 to 32% and LV sphericity index from 0.9 to 2.2.

Limitations

Although a wide spectrum of the geometric phenotypes of the MA and the sub-mitral apparatus was represented in the present study, patients with degenerative MR were not included in the analysis and generalization of the results to that important subgroup of patients should be cautious. Admittedly, MA area was shown to be larger and MA eccentricity was shown to be greater in patients with degenerative MR as compared

to those with functional MR[41]. Additionally, all grades of MR were represented in the present analysis while only patients with severe MR are the typical candidates for TMVR.

CONCLUSION

In the present study, mitral annulus sizing was feasible and reproducible using CTA. Regardless of the model used to define the mitral annulus, exclusion of the aorto-mitral continuity yields a consistent relation between D_{mean} and D_{Area} and $D_{Perimeter}$. D_{mean} is a simple parameter that can be used to infer the effective mitral annular size in the setting of TMVR.

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SUPPLEMENTAL DATA

Table S1. Comparison of the different parameters of mitral annular size using two models of annulus definition (n=30):

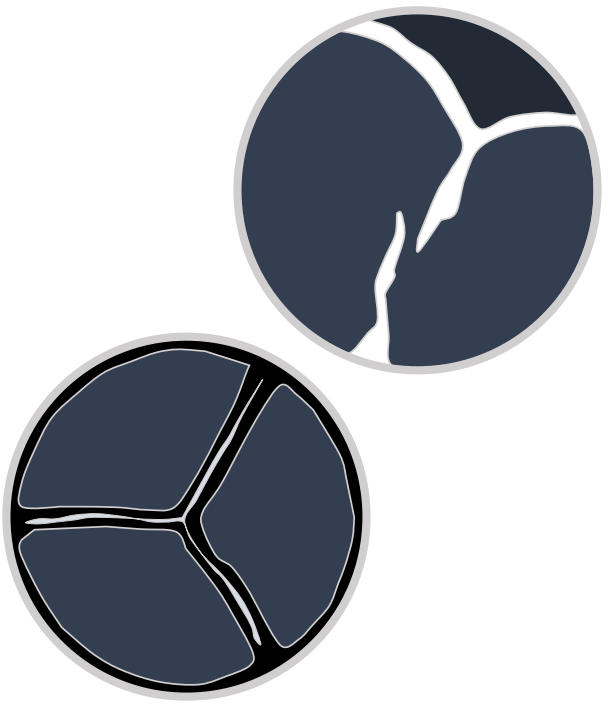
	Saddle-shape model	D-shape model	p*	R^2 §	Bias‡		
					Average	Upper LOA	Lower LOA
SL diameter (mm)	31.5±4.3	30.4±3.7	0.25	0.82	1.20 (3.9%)	4.71	-2.32
Area (cm^2)	10.3±1.9	10.1±1.9	0.66	0.97	0.22 (2.1%)	0.84	-0.41
3D perimeter (mm)	119.9±11.0	119±11.2	0.78	0.95	0.83 (0.7%)	5.66	-4.00
Projected perimeter (mm)	116.1±10.4	116.2±10.6	0.99	0.97	-0.03 (0.03%)	3.24	-3.31
D_{Area} (mm)	36.0±3.5	35.7±3.3	0.66	0.97	0.38 (1.1%)	1.49	-0.73
$D_{Perimeter}$ (mm)	36.9±3.3	37.0±3.3	0.99	0.97	-0.01 (0.03%)	1.03	-1.05
D_{mean} (mm)	35.2±3.5	34.6±3.2	0.49	0.93	0.60 (1.7%)	2.36	-1.16

*Student *t* test (unpaired); saddle-shape model vs. D-shape model.
§Pearson correlation two-tailed p<0.001 for all.
‡Saddle-shape model vs. D-shape model.

Table S2. Inter-observer reproducibility of MA diameters in patients with and without mitral annular calcification (n=30):

	ICC*		Average bias, mm (Mean ± SD)	
	MAC (n=10)	**No MAC** (n=20)	**MAC**	**No MAC**
IC diameter	0.86	0.96	-1.6 ± 2.8	-0.4 ± 1.4
SL diameter	0.87	0.95	-1.2 ± 2.1	-1.0 ± 2.0
D_{Area}	0.91	0.95	-1.9 ± 1.9§	-0.6 ± 1.5
$D_{Perimeter}$	0.95	0.94	-1.3 ± 1.6	-0.3 ± 1.4
D_{mean}	0.87	0.96	-1.4 ± 2.3	-0.7 ± 1.4

*p value <0.01 for all.
§Inter-observer bias significantly higher in patients with than in patients without MAC (Mann–Whitney U test; p value=0.03).
ICC=intra-class correlation coefficient, MAC=mitral annular calcification.



Chapter 11

Infective endocarditis after Melody valve implantation in the pulmonary position: A systematic review

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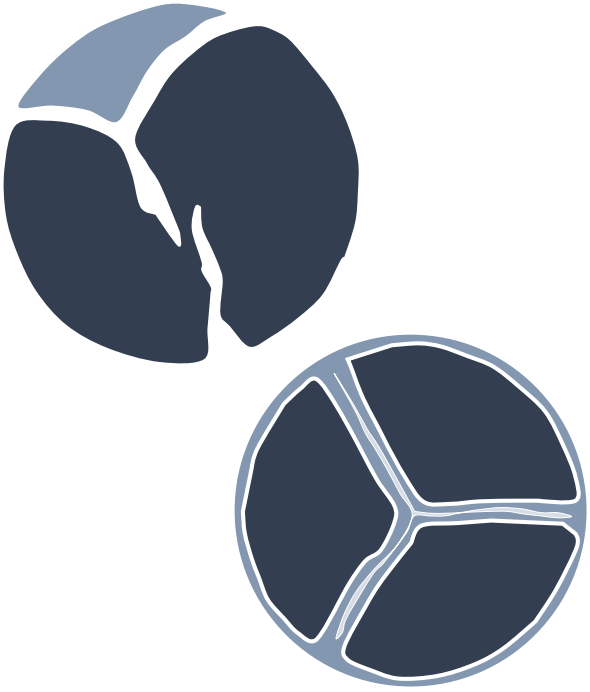

ABSTRACT

Background:

Infective endocarditis (IE) after transcatheter pulmonary valve implantation (TPVI) in dysfunctioning right ventricular outflow tract (RVOT) conduits has evoked growing concerns. We aimed to investigate the incidence and the natural history of IE after TPVI with the Melody valve through a systematic review of published data.

Methods and results:

PubMed, EMBASE, and Web of Science databases were systematically searched for articles published until March 2017 reporting on IE after TPVI with the Melody valve. Nine studies (including 851 patients and 2060 patient-years of follow-up) were included in the analysis of the incidence of IE. The cumulative incidence of IE ranged from 3.2% to 25.0%, while the annualized incidence rate ranged from 1.3 to 9.1% per patient-year. The median [IQR] time from TPVI to the onset of IE was 18.0[9.0-30.4] months (range, 1.0–72.0 months). The most common findings were positive blood culture (93%), fever (89%), and new, significant, and/or progressive RVOT obstruction (79%), while vegetations were detectable on echocardiography in only 34% of cases. Out of 69 patients with IE after TPVI, 6 patients died (8.7%) and 35 (52%) underwent surgical and/or transcatheter re-intervention. Death or re-intervention were more common in patients with new/significant RVOT obstruction (69% vs. 33%; p=0.042) and in patients with non-streptococcal IE (73% vs. 30%; p=0.001).

Conclusions:

The incidence of IE after implantation of a Melody valve is significant at least over the first three years after TPVI, and varies considerably between the studies. Although surgical/percutaneous re-intervention is a common consequence, some patients can be managed medically especially those with streptococcal infection and no RVOT obstruction.

INTRODUCTION

One decade after Bonhoeffer et al[1] demonstrated the feasibility of transcatheter pulmonary valve implantation (TPVI) in a right ventricular outflow tract (RVOT) conduit, the US food and Drug Administration approved the Melody valve (a modified version of Bonhoeffer's original device manufactured by Medtronic Inc., Minneapolis, Minnesota)[2] in 2010.

TPVI was subsequently shown to provide satisfactory hemodynamic and clinical outcomes and a low rate of primary valve dysfunction, especially with the marked reduction in the rates of stent fracture after the wide adoption of routine pre-stenting[3,4]. However, valve dysfunction secondary to infective endocarditis (IE) is increasingly recognized as a threat to valve function and patients' outcomes[3,5] after TPVI. This risk of IE should be kept in mind when considering the expansion of the indications of TPVI to patients with native RVOT, small/large pulmonary conduits[6], and as a valve-in-valve treatment[7].

The incidence rate of Melody valve IE varies considerably among the studies and is, reportedly, higher than the rate of pulmonary homograft IE[5,8]. Beyond the incidence rate, many other basic aspects of this disease entity remain obscure including microbiology, presentation and outcomes.

We aimed at investigating the incidence and natural history of IE after Melody valve implantation through a systematic review and pooled analysis of published data.

METHODS

As all results are derived from published data, the study materials will not be made available. The search methodology will be made available to other researchers for purposes of reproducing the results.

Literature search:

An electronic search in PubMed, EMBASE, and Web of Science databases for studies published until March 2017 was conducted to identify studies reporting on the incidence and/or the natural history of IE in patients treated with a Melody valve in the pulmonary/RVOT position. The details of the PubMed search items are shown in an Online Supplementary Appendix. A thorough review of the reference lists of retrieved studies as well as relevant review articles and editorials was conducted for the sake of completeness.

Eligibility criteria of studies and data extraction

The analysis consisted of two parts (The search strategy is shown as PRISMA flowchart[9] in Supplementary Figure 1):

1. The study-level non-pooled analysis of the incidence rate of IE: For inclusion in this analysis, the studies were required to (1) include ≥20 consecutive patients; (2) involve an average follow-up time of at least 12 months after TPVI; and (3) be published in peer-reviewed literature (conference abstracts were excluded conforming to Cochrane guidelines). As shown in Supplementary Figure 1, 329 studies were initially identified, out of which 248 were excluded after title/abstract review. Out of the remaining 56 studies, 33 did not meet the inclusion criteria (non-consecutive series, n=13; short follow-up, n=11; mixed cohort with other devices/non-pulmonary position, n=2; and congress abstracts without published details, n=7). Inclusion criteria were fulfilled by 23 studies, out of which 14 were excluded due to overlapping population. Nine studies (including 851 patients) were eventually included in this analysis.

2. The patient-level pooled analysis: The individual-patient characteristics were extracted from studies reporting detailed individual patients' data (individual case reports/case series). Extracted data included baseline patient characteristics, TPVI peri-procedural data, and details of IE including time of onset, presentation, microbiologic studies, management, and outcome. Twenty two studies (comprising 69 case reports) were included in this analysis. Special attention was exercised to avoid inclusion of duplicate cases (the same case reported in more than one publication).

Definitions

Overall, IE was defined as any documented blood-born infection treated with intravenous antimicrobial therapy for at least 2 weeks presumed to be related to Melody valve in the absence of an alternative focus of infection. Endocarditis was reported according to the authors' judgment or using the modified Duke criteria[10,11]. Definite TPV-related IE was confirmed by the presence of vegetation(s) seen on the Melody valve leaflets or stent or on adjacent RVOT conduit wall as documented by transthoracic/transesophageal/intracardiac echocardiography, positron emission tomography (PET), surgical explant examination, or on autopsy. IE episodes occurring within one year after TPVI were defined as "early IE"[12].

New/progressive RVOT obstruction was defined as a ≥15 mmHg increase in RVOT pressure gradient and/ or worsening of stenosis severity to moderate-severe on the first Echo-Doppler study after IE onset as compared to the latest study before IE. New/worsening pulmonary regurgitation (PR) was defined as PR that progressed from ≤mild to moderate-severe PR on the first Echo-Doppler study after IE onset as compared to the latest study before IE. Death attributable to IE was defined as cardiac death during the same hospital admission for IE.

Statistical methods:

The systematic review was performed according to the MOOSE (Research-Checklist) guidelines[13]. Continuous variables are expressed as mean± standard deviation (SD) or as median and interquartile ranges (IQR), as appropriate. Categorical variables are presented as frequencies and percentages. Linear correlation between the rate of IE in the individual studies and the sample size/length of follow up/years of enrollment was assessed using the non-parametric Spearman's correlation coefficient. Binary logistic regression analysis was used to study the predictors of IE-related death/re-intervention, and the odds ratio and its 95% confidence interval (CI) were presented. Independent variables were included in the final multivariable model if associated with death/re-intervention in univariable analysis (p value <0.10).

Statistical analysis was performed with SPSS 23 (IBM, Armonk, NY, USA). All probability values were two-tailed, and a p value <0.05 was considered significant.

RESULTS

The incidence of Melody valve IE:

A total of 9 studies[14-22] were included in the analysis of the incidence of IE after TPVI using the Melody valve. The characteristics of the studies are summarized in Table 1. The publication year was 2008 to 2017, and the reported cases received TPVI from 2000 to 2015. A total of 851 patients received Melody valve in the pulmonary/RVOT position, mostly (89%) after pre-stenting. The median follow-up period was 31 [range, 20-59] months and a total of 2060 patient-years of follow-up were included.

The cumulative incidence of IE varied between the studies (range, 3.2 – 25.0%) as was the annualized incidence rate (range, 1.3 – 9.1% per patient-year). In studies applying the modified Duke criteria (n=4 studies[16,19,21,22]), the cumulative incidence of IE ranged from 7.5% to 25.0%, and the annualized incidence rate from 3.7% to 6.3%. Both cumulative and annualized incidence of IE were higher in studies with lower number of patients (Figure 1A and 1B[14-22]). On the other hand, the incidence was not influenced by the follow up duration (Figure 2A and 2B[14-22]). Figure 3 shows a summary of the time period of patient enrollment in each study and the respective cumulative (Figure 3A[14-22]) and annualized incidence rate of IE (Figure 3B[14-22]), both trending to be higher in later than in earlier studies.

Individual-patient characteristics of Melody valve endocarditis cases:

In total, 69 detailed case reports of patients who developed Melody valve IE were identified[17-38]. The characteristics of these patients are summarized in Table 2.

Table 1. The characteristics of 9 studies[14-22] included for the estimation of the rate of IE after TPVI:

Study, year of publication	Country	Period of patient enrollment	No of patients	Follow up (months)	Patient-years of follow-up	Age, years*	Male	TOF	TA	AS (S/P Ross procedure)	RVOT conduit, homograft	Prestenting	IE absolute incidence	IE incidence rate/ patient year
Biernacka et al, 2015	**Poland**	2008-2012	26	20.4	44	NA	NA	NA	NA	NA	NA	100.0%	15.4%	9.1%
O'Donnell et al, 2016	**New Zeeland**	2009–2015	25	35	73	18 (11-51)	60.0%	64.0%	24.0%	12.0%	92.0%	96.0%	16.0%	5.5%
Cheung et al, 2013	**Denmark**	2006-2012	42	27	95	25 (6-67)	NA	NA	NA	NA	NA	NA	14.3%	6.3%
Hascoet et al, 2017	**France**	2008-2014	31	58.8	151.9	19 [15.8-28.9] [§]	53.0%	81.0%		9.0%	25.0%	91.0%	25.0%	5.3%
Butera et al, 2013	**Italy**	2007-2010	61	30	153	24 (11-65)	52.0%	44.0%	8.0%	15.0%	54.0%	87.0%	3.2%	1.3%
Malekzadeh-Milani et al, 2014	**France**	2009-2013	93	23.8	184	20.1 (18.2-21.8)	56.0%	26.0%	12.0%	14.0%	20.0%	NA	8.6%	4.4%
Van Dijck et al, 2015	**Belgium**	2006-2013	107	24	214	14.3 (4.5-80.5)	66.0%	52.0%	7.0%	19.0%	57.0%	NA	7.5%	3.7%
Lurz et al, 2008	**UK-France**	2000-2007	155	28.4	367	21.2 (7-71)	58.0%	61.0%	11.0%	8.0%	81.0%	NA	3.2%	1.4%
McElhinney et al, 2013	**USA, Canada, and Europe**	2007-2012	311	30	778	18.2 (5-59)	NA	44.0%		18.0%	70.0%	73.0%	5.1%	2.1%
Total		**2000-2015**	**851**	**30.8**	**2059.9**	**20.0**	**57.5%**	**48.5%**	**12.4%**	**13.6%**	**57.0%**	**89.4%**	**10.92%**	**4.33%**

*Average (range).

[§]Median [interquartile range].

Abbreviations: AS, aortic stenosis; RVOT, right ventricular outflow tract; TA, truncus arteriosus; TOF, tetralogy of Fallot.

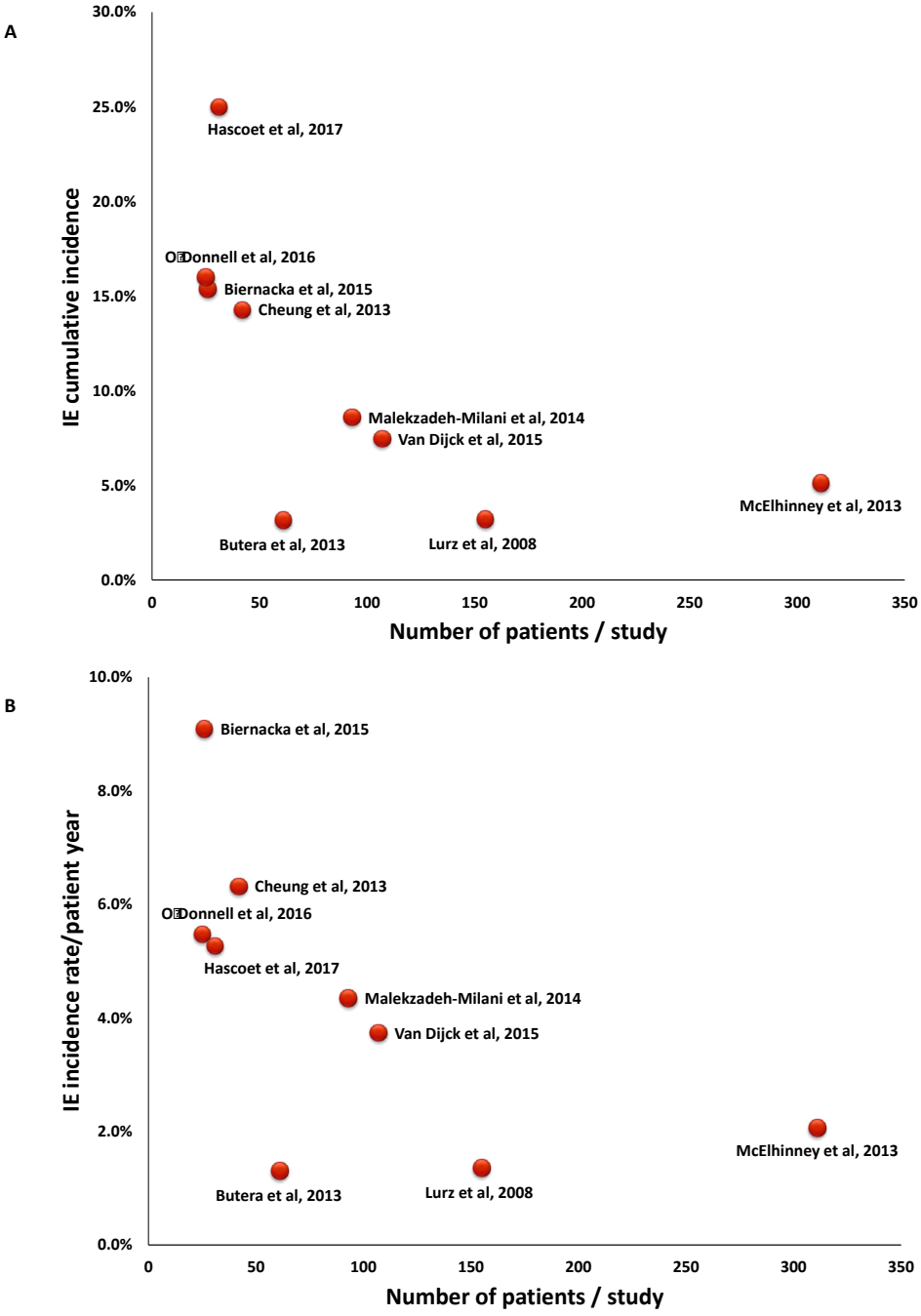

Figure 1. Scatter plots of the cumulative (**A**) and annualized (**B**) incidence rate of IE plotted against the sample size (number of patients) of the individual studies (Spearman correlation coefficient = -0.80 and -0.73, p=0.010 and 0.025; respectively).

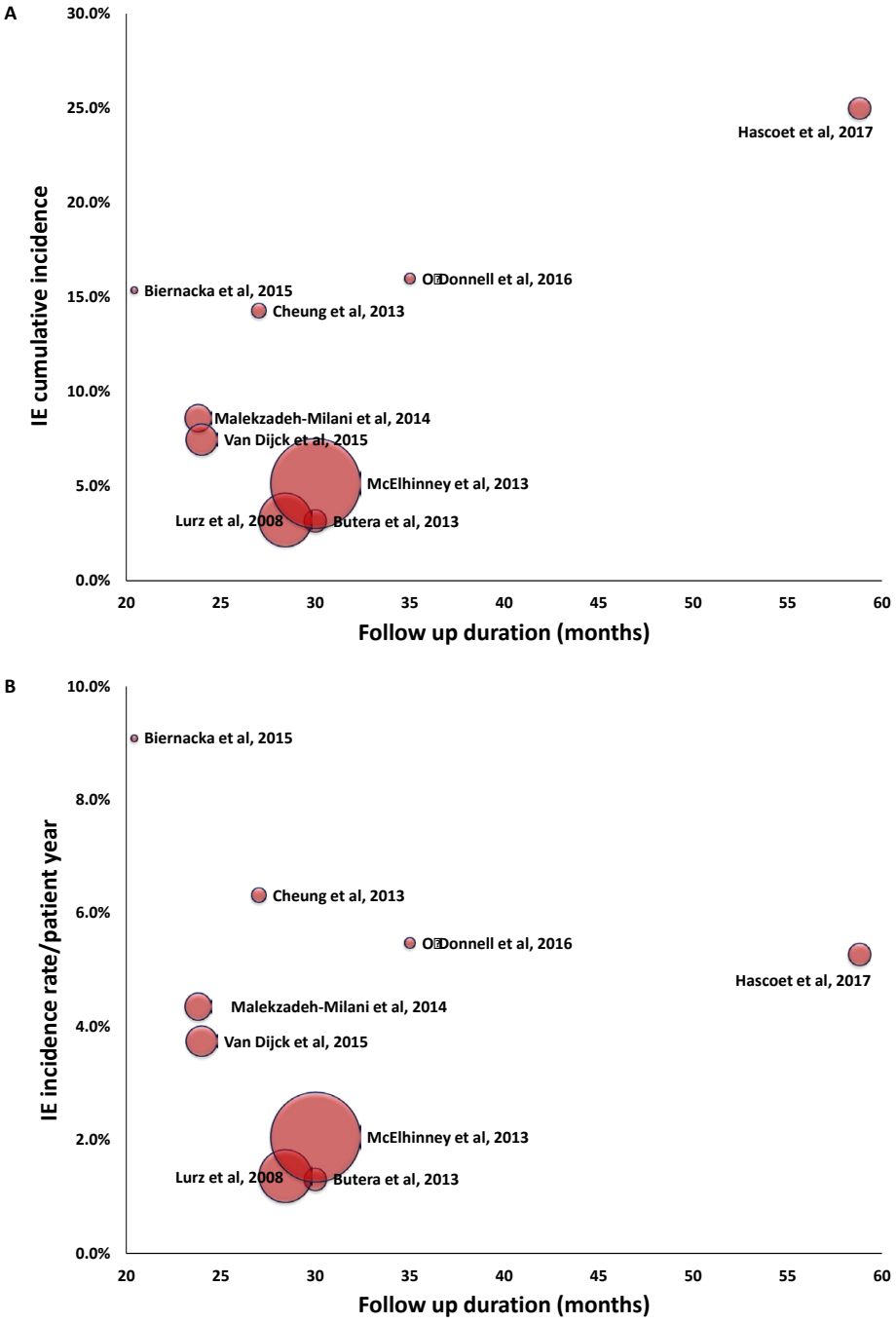

Figure 2. Scatter plots of the cumulative (**A**) and annualized (**B**) incidence rate of IE plotted against the follow up duration (in months) of the individual studies (Spearman correlation coefficient = 0.16 and -0.27, p>0.05 for both). Dot size is proportionate to the sample size (number of patients) of each study.

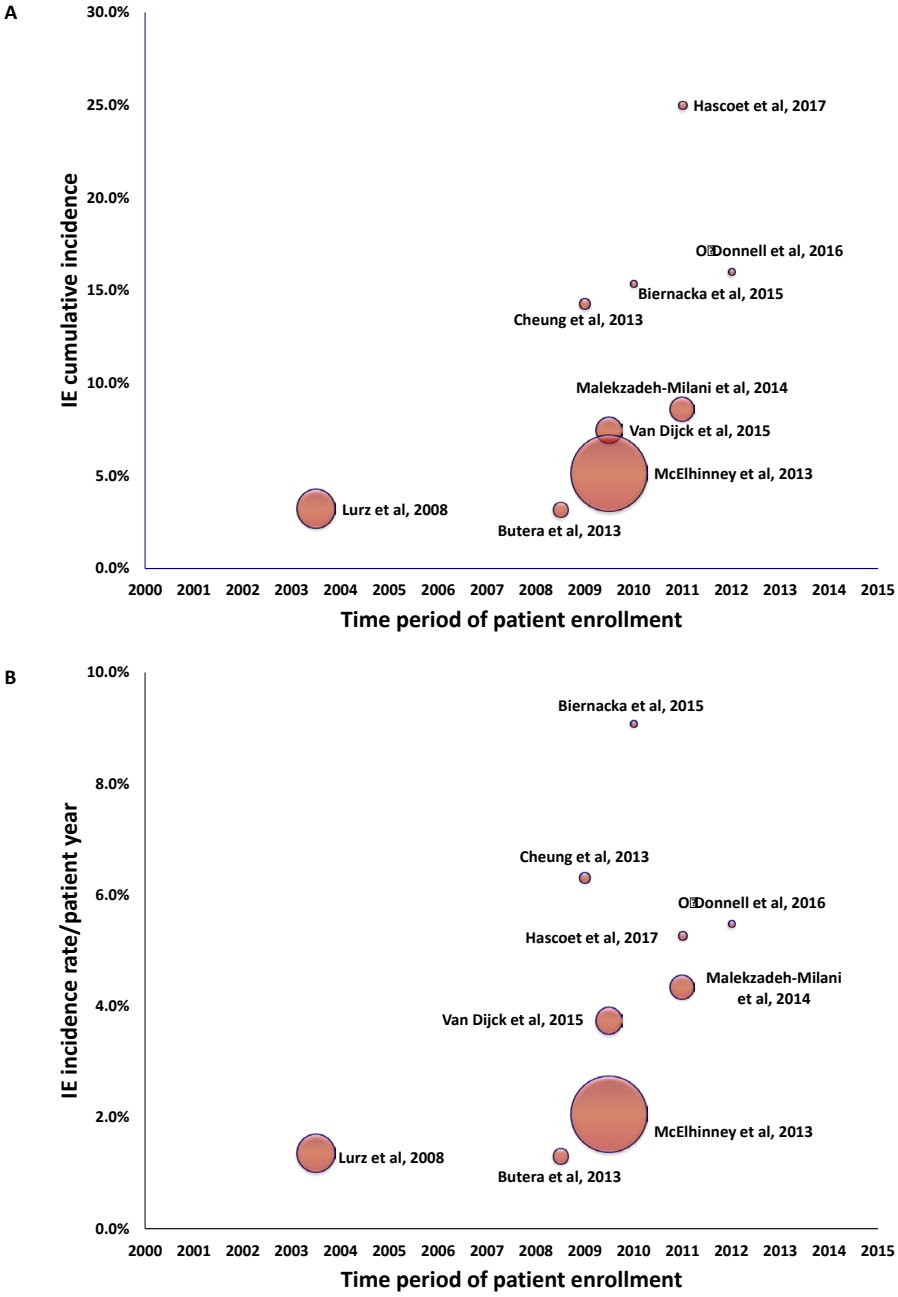

Figure 3. Scatter plots of the cumulative (**A**) and annualized (**B**) incidence rate of IE plotted against the time period of patient enrollment of the individual studies (Spearman correlation coefficient =0.81 and 0.57, p=0.008 and 0.11; respectively). Dots correspond to the middle of the enrollment time interval for each study and dot size is proportionate to the sample size (number of patients) of each study. The characteristics of the 9 studies are summarized in Table 1.

Patients had a mean age of 22±11 (range: 4–56) years and were predominantly males (84%). The majority had a pulmonary homograft (55%) or a bioprosthetic valve/valved conduit (38%) implanted in the setting of correction of tetralogy of Fallot (50%), aortic stenosis treated by a Ross procedure (18%), truncus arteriosus (15%), or transposition of the great arteries (10%).

Interval post-TPVI:

The median time from TPVI to onset of IE was 18.0 months (IQR, 9.0-30.4; range, 1.0–72.0 months). As shown in Figure 4, 32% of cases occurred within 1 year after TPVI, 27% in the second year, 18% in the third year, and 23% beyond 3 years after the procedure.

Precipitating factors:

An identifiable portal for IE was reported in 25 cases. An unprotected dental procedure/orthodontic/oral trauma was reported in 9 of 25 (36%). Other portals included: an infected wound (n=3), cat scratches and bites/veterinary medical practice (n=2), paranasal sinusitis (2), cardiac catheterization (n=2), gastroenteritis (n=1), pneumonia

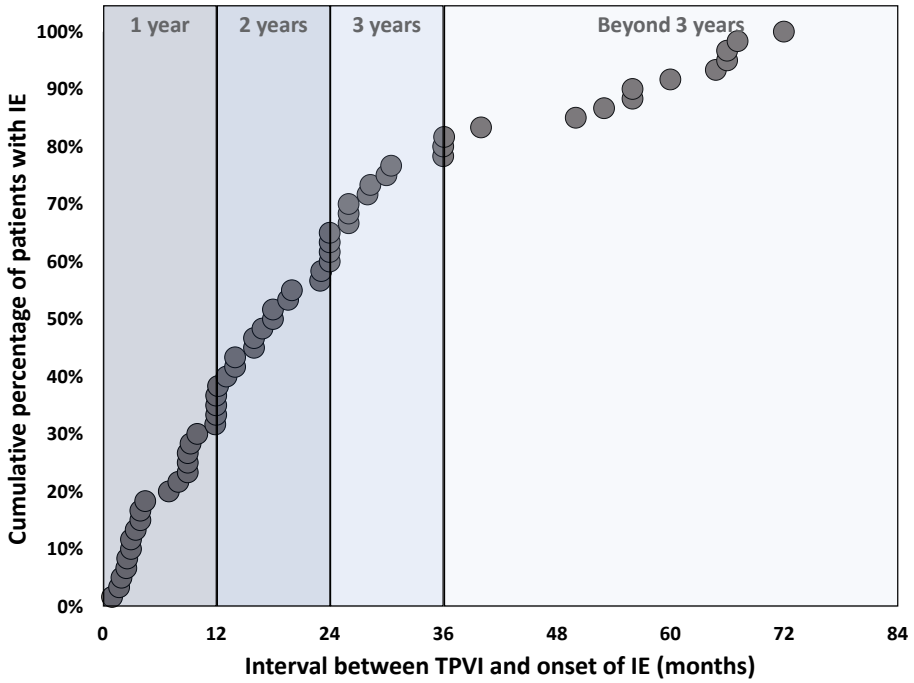

Figure 4. A cumulative curve of the individual patients with Melody valve endocarditis displaying (on the horizontal axis) the time interval between transcatheter pulmonary valve implantation (TPVI) and the onset of IE. The figure represents data from 59 (out of 69) patients in whom the exact time interval from TPVI to IE was reported.

(n=1), cystitis (n=1), dermatophytosis complex (n=1), nail biting and bad hygiene (n=1), hemodialysis (n=1), and tattooing (n=1).

Clinical presentation:
Fever was the most common presenting symptom (89%), while vegetations were visualized by echocardiography in only 34%. New, significant, and/or progressive RVOT obstruction occurred in 79% of cases and the pressure gradient rise averaged 17±8 mmHg. New significant PR was documented in two cases (Table 2). Other presentations of IE included right ventricular failure (n=5), severe sepsis (n=5), septic pulmonary embolism (n=5), gastrointestinal symptoms (n=4), glomerulonephritis (n=1), and macrophage activation syndrome (n=1).

Microbiologic features:
As shown in Table 2, the majority of cases involved Gram positive cocci (42% staphylococci and 30% streptococci). This microbiologic profile was similar between early (47% staphylococci and 32% streptococci) and late IE (46% staphylococci and 27% streptococci, p>0.05). Bacterial culture was negative in 5 cases, of which serology and/or polymerase chain reaction of excised valve revealed Bartonella henselae in 3 cases.

Treatment and outcome:
Six patients died (8.7%) in the course of IE, and 11 patients required urgent intervention (percutaneous and/or surgical) to relieve critical RVOT obstruction or to remove the infected valve to control septicemia. Further 24 patients required intervention (mostly to relieve RVOT obstruction); either during the same hospital admission (n=10) or electively thereafter at a median of 4 months after IE onset (n=14). Overall, 39 re-interventions (31 surgical replacement, 3 percutaneous stenting, 3 balloon dilatation, and 2 Melody-in-Melody implantation) were performed, while antibiotic therapy (for 6.2±1.3 weeks) was sufficient for clinical stabilization without the need for any intervention in 23 patients (34%). Clinical outcome was not reported in one patient and the mode of treatment was not specified in five.

In total, 59.7% of the patients either died (n=6) or required re-intervention (n=35). In one of these patients, re-intervention was followed by death. Death or re-intervention were more common in patients with new, significant, and/or progressive RVOT obstruction (69% vs. 33%; p=0.042) and was lower (p=0.015) in streptococcal IE (30%) than in staphylococcal (72%) and Gram negative bacterial IE (73%). On multivariate regression analysis, non-streptococcal IE was an independent predictor of death/re-intervention (odds ratio, 4.28 [95% CI: 1.16 to 15.78]; p=0.029).

Table 2. The characteristics of patients with IE after TPVI (n=69)*:

Parameter	Proportion OR mean±SD
Baseline characteristics:	
Male Gender	84%
Age, years	21.7±11.2
Underlying initial pathology	
TOF	50%
AS (S/P Ross procedure)	18%
TA	15%
TGA	10%
Other	7%
RVOT conduit	
Homograft	55%
Bioprosthetic valve/valved conduit	38%
Bare stent/ Melody valve	7%
Manifestations of IE:	
Onset post-TPVI, months	23.6±19.7
Fever	89%
Vegetation	34%
New/worsening >mild RVOT obstruction	79%
PG rise in the setting of TPVI (mmHg)	16.9±8.4
New/worsening >mild PR	6%
Blood culture:	
Staphylococci	42.0%
Streptococci	30.4%
Corynebacterium group*	5.8%
HACEK group	4.3%
Haemophilus group§	2.9%
Rothia dentocariosa	1.4%
Aerococcus viridans	1.4%
Escherichia Coli	1.4%
Enterococcus Foecalis	1.4%
Aspergillus Fumigatus	1.4%
Negative culture¶	7.2%

*From 22 reports published between 2011-2017[17-38]

*C. pseudodiphtheriticum in 3 cases and C. striatum in one case.

§H. influenzae in one case and H. parainfluenzae in another case.

¶In 3 cases, serology and polymerase chain reaction of excised valves revealed Bartonella Henselae.

Abbreviations: AS, aortic stenosis; PG, pressure gradient; PR, pulmonary regurgitation; RVOT, right ventricular outflow tract; S/P, status post; TA, truncus arteriosus; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TPVI, transcatheter pulmonary valve implantation.

DISCUSSION

Clinical trials have shown the safety and efficacy of TPVI with excellent short term outcomes[2], and freedom from reintervention in the majority of patients up to five years[3]. However, the risk of IE of the Melody valve is increasingly recognized as a significant threat to the long-term valve function.

Although IE is associated with high mortality and severe complications[12], its management is mostly based on expert opinion rather than on evidence[12]. Shortage of evidence is basically due to the low incidence of the disease and the scarcity of randomized trials and meta-analyses[12]. Original studies are, definitely, more robust than inferences from reviews/meta-analyses but only when original studies are adequately powered. Given the fact that IE is a relatively uncommon disease, frequently occurring long after the index procedure, and is challenging to diagnose in many instances, data from individual registries are often inadequate to derive evidence on the natural history and the management of IE. Because more and more reports from small single center registries are reporting an extraordinarily-high IE risk with the Melody valve, we conducted this systematic review. Although desirable in the field of congenital heart diseases where studies are usually small-scale, meta-analysis of observational studies with differences in baseline characteristics and anatomic substrates, procedural characteristics, and follow-up durations might introduce imprecision into the results, even when proper statistical methods are applied. Therefore, we opted to pool patient-level data, while study-level data were systematically-reviewed without pooling.

The risk of IE after Melody valve implantation:

The data provided in the present review highlight that only large, well-designed prospective studies will be able to assess the actual rate and the potential risk factors for IE after TPVI.

The phenomenon of reporting higher rates of IE in the later than the earlier studies (Figure 3) can be in part due to the increasing awareness of the risk of IE that led to a more careful surveillance and is in line with a global trend toward an increased incidence of IE[39]. We found that early post-implantation Melody valve endocarditis is uncommon, that only one third (32%) of cases occur within the first year after TPVI, and that the risk persists thereafter with 23% of cases developing beyond 3 years after the procedure. This comes in agreement with the findings of a large contemporary study of patients with adult congenital heart disease (n= 14 224 patients)[40], where the presence of valve-containing prosthetics was independently associated with greater risk of IE that persists in the long term (hazard ratio of IE beyond 12 months after prosthesis implantation: 5.3 [3.5–7.9]). The authors suggested that this reflects the fact that the risk is likely not

attributable only to surgical factors associated with implantation, but also to the mere long-term presence of those prostheses[40].

Patient- vs. device-related vulnerability to IE:

We found that in many patients with Melody valve IE, an identifiable portal of bacteria was present and most frequently involved an unprotected dental procedure/orthodontic/oral trauma. This highlights the importance of pre-TPVI counseling (including a meticulous dental review) and continuous education of patients and families to lower the exposure to portals of infection, as well as the necessity of routine antibiotic prophylaxis before any invasive maneuver. Notwithstanding, patients with Melody valve implantation combine two conditions predisposing to a higher rate of IE and a higher risk of adverse outcome from endocarditis; the use of a prosthetic cardiac valve in the setting of a repaired complex congenital heart disease and an unfavorable hemodynamic environment in the vicinity of that prosthesis (which could interfere with complete prosthesis endothelialization)[41]. The most recent American and European guidelines on the management of valvular heart diseases recommend antibiotic prophylaxis before dental procedures in patients with prosthetic cardiac valves, including transcatheter implanted prostheses[42,43]. Although some clinical guidelines –on the other hand- advise against routine antibiotic prophylaxis against IE even in patients with a high risk of acquiring IE and of having a worse outcome of IE, there have been some signals indicting this conservative antibiotic prophylaxis approach for a trend of IE rates to rise[39,44]. Our data give an example of a condition and a patient population with an exceptionally significant rate of IE, with many of the episodes being linked to dental procedures.

In addition to patient-related risk factors (e.g. older age[26], male gender[26], history of IE[17], discontinuation of antiplatelets[29], and exposure to unprotected medical procedure29) and procedure-related risk factors (e.g. longer procedure[26], higher number of stents[26], and higher residual RVOT gradient[14]), some inherent device characteristics have been indicted by histopathologic studies as risk factors predisposing to IE. A selective propensity of bovine jugular tissue (the precursor of the Melody valve leaflets) to histological lesions during procedural steps[45] and to bacterial adherence[46] was shown in in-vitro studies, especially after procedural manipulation-induced leaflet damage[46]. These findings are in line with the observed higher propensity of valves with bovine jugular vein leaflets (Melody valve and Contegra graft) to IE than pulmonary homografts[18,19,47]. The risk of IE after TPVI with the Sapien valve (Edwards Lifesciences, Irvine, California) which has bovine pericardial tissue leaflets, albeit still present[48], seems to be lower than with the Melody valve[20,22,49]. It should be noted, however, that the number of implanted Sapien valves in the pulmonary position and the duration of follow-up are far lower than the Melody valve, and this might lead to underestimating the incidence of IE in Sapien valves.

In another in-vitro study of explanted infected Melody valves[50], pathologic examination revealed the presence of granulocytes in the preexisting surgical conduit in all cases, denoting that the space between the Melody valve stent and the underlying conduit with little neovascularization might represent a blind-spot that cannot be reached by antibiotics. This blind-spot seems to harbor the micro-organism leading to failure of antibiotics to eradicate the infection. This is further supported by the association between a higher number of stents in the RVOT and the risk of Melody valve IE reported in one study[25].

In the same in-vitro study[50], a thrombotic material was found at the basis of the leaflets or at the graft wall in the majority of cases. Turbulent blood flow in the RVOT might lead to endothelial damage predisposing to nonbacterial thrombotic endocarditis that can turn infective after any transient bacteremia[5]. These findings further support the association between discontinuation of anti-platelets and the development of endocarditis reported in one study[28]. Data from transcatheter aortic valve replacement studies refer to a significant risk of clinical/subclinical leaflet thrombosis, that can be prevented and effectively treated by oral anticoagulation[51,52]. It is, however, unknown whether the same phenomenon is relevant to TPVI. Notwithstanding, more rigorous use of multislice computed tomography (MSCT) in post-TPVI surveillance (especially in cases with rising RVOT pressure) might provide more insights into the actual incidence of hypo-attenuated leaflet thickening after TPVI and its clinical significance.

The risk of IE after transcatheter vs. surgical pulmonary valve replacement:

In a large series (n=586 patients) reported by Mery et al, including a total of 792 valved pulmonary conduits, 23 conduits (2.9%) developed endocarditis at a median of 5 years (range, 19 days to 11 years) after surgery. Bovine jugular grafts were associated with a significantly greater risk of late endocarditis (hazard ratio, 9.05; 95% CI, 2.6–31.8 compared to homografts)[47]. None of the patients with endocarditis died of related causes and 16 (70%) of infected conduits were surgically replaced. In another study by van Dijck et al[19], Melody valves, homografts, and Contegra grafts were compared for the incidence of IE. The annualized rate of IE was more than three-fold higher after Melody valve implantation (3.0% [95% CI: 1.3-5.8%] per patient-year) than after homograft implantation (0.8% [95% CI: 0.4-1.3%] per patient-year), while it was 2.4% [95% CI: 1.0-3.8%] per patient-year in the Contegra group. In a recent meta-analysis of 50 studies involving 7,063 patients, bovine jugular vein valves, independent of implantation technique, were associated with a higher cumulative risk of IE compared with other types of right ventricle-to-pulmonary artery conduits (median cumulative incidence; 5.4% vs. 1.2%; $p < 0.0001$), with no difference in the incidence of endocarditis between catheter-based vs. surgically implanted bovine valves, suggesting that the substrate for infection is related to the tissue precursor of the valve[8]. However, this meta-analysis is limited by

reporting the incidence of endocarditis, which is a time-dependent event, in terms of a crude cumulative incidence[53].

The risk of IE after transcatheter pulmonary vs. aortic valve replacement (TAVR):
In a large study by Regueiro et al[54] that included 20 006 TAVR patients, 250 had definite IE (incidence, 1.1% per patient-year; [95% CI, 1.1%-1.4%]) at a median interval of 5.3 months (IQR, 1.5-13.4 months) after the procedure, and IE was early in 178 patients (71.2%). In-hospital mortality and surgical conversion rates were 36% and 15%, respectively. In a pooled analysis of multiple studies, IE developed at 241±287 days after TAVR, 28% of patients required a surgical intervention, and 30-day mortality was 22%[55]. These studies, and others[56-58], highlight that IE seems to be remarkably less common and to occur earlier after TAVR than after TPVR.

Microbiology and outcomes of Melody valve IE:

We found that post-TPVI endocarditis involves staphylococci (42%) or streptococci (30%) in the majority of cases. This comes in line with the overall microbiologic profile of IE in adults (staphylococci 42% and streptococci in 29%)[59] and in pediatrics (staphylococci 43% and streptococci in 40%)[60]. Similar patterns were also reported in prosthetic valve endocarditis (PVE: staphylococci 40% and streptococci in 22%)[59] and in pulmonary surgical conduit IE (staphylococci in 53% and streptococci in 43%)[47]. Accordingly, it can be suggested that initial empirical antibiotic therapy in cases with suspected Melody valve IE should follow a similar protocol to that of PVE which specifically targets the virulent staphylococcus aureus[12]. This microorganism was shown in the present study to be the single most common organism involved in Melody valve IE, and to be associated with a worse outcome than streptococcal infection.

We found that Melody valve IE leads to re-intervention in 52% of cases and with death in 8.7%; compared to a 65-70% rate of surgical re-intervention[35,47] and a mortality rate of ~13%[16,35] in the setting of pulmonary surgical conduit IE. This comparison emphasizes that although the rate of IE is generally lower in pulmonary surgical conduits than after TPVI, IE-related morbidity and mortality risks might be higher.

We found that streptococcal infection and the lack of RVOT obstruction are associated with a significantly better outcome. A similar association between streptococcal involvement and the freedom from in-hospital death was previously reported in adults with IE[59]. It turns out that these two criteria (the type of the organism and the presence/absence of RVOT obstruction) can be used for risk stratification of patients presenting with Melody valve IE.

Diagnostic criteria:

In the initial phase of TPVI experience, re-obstruction of the RVOT with subsequent re-intervention was relatively common, and was mostly due to stent fracture[3]. In the more contemporary TPVI experience, with the adoption of routine pre-stenting, re-intervention due to recurrent valve obstruction became uncommon[4,24,61,62]. In the present review, a strong association between IE and Melody valve obstructive dysfunction was obviated. The direction of causality of this relationship (IE leading to valve obstruction vs. valve dysfunction predisposing to IE) is not easy to conclude upon. Notwithstanding, in some reports[22,30,31,36], in-hospital serial Doppler studies have documented a progressive pressure gradient rise during the course of IE. RVOT obstruction was the reason for most re-interventions, and whether pressure rise can be –in part- due to leaflet thrombosis and can be resolved by anticoagulation treatment without re-intervention, is still an open question.

Although considered by Duke criteria as a sign of valve involvement in IE, new valve regurgitation was reported in only 2 out of 69 cases. Histopathologic studies have confirmed the same finding[50] as have other reports[14,19]concluding that insufficiency is a rare manifestation of Melody valve IE.

It is well-acknowledged that echocardiography, especially transthoracic echocardiography (TTE), affords only modest sensitivity (50%) for the detection of vegetations in PVE[12]. In the setting of IE after Melody valve implantation, echocardiographic detection of vegetations is limited to only one third of published case reports, likely due to the anterior position of the RVOT and artefacts from the prosthetic valve stent and the underlying –mostly degenerated calcified- conduit. Some relevant points of clinical importance are worth-mentioning: First, failure to visualize vegetations using cardiac imaging does not exclude their presence, as they can still be visualized intra-operatively[18,22] or on autopsy[27] in cases with initially negative imaging studies. Secondly, unlike classical left-side PVE where TEE is superior to TTE in detecting vegetations, TEE does not always have an added value to TTE results in transcatheter and surgical prosthetic pulmonary valve endocarditis[21,23,33,35,38]. Diagnostic accuracy of TEE can be improved using biplane imaging[63] and by utilizing dedicated acquisition views[64] (e.g. high esophageal interrogation of the distal valve stent). A systematic combination of TTE and TEE[35] was suggested to improve diagnostic accuracy, as compared to either modality used alone. In some studies[21,23,38], intra-cardiac echocardiography was successful in detecting vegetations missed by TTE/TEE. Thirdly, other imaging tools (e.g. MSCT[29] and PET scan[28]) can detect vegetations missed by echocardiography.

The combination of MSCT with PET has been shown to have an added value over TTE/TEE in confirming PVE[65,66] especially in patients with negative or doubtful echocardiographic results[67]. Based on these data, the latest guidelines on the management of IE[12] considered an abnormal activity around the site of the prosthetic valve detected on

PET/MSCT as a "major criterion" of IE. There are few, but rather encouraging, reports on the success of PET/MSCT to provide a good alternative to echocardiography in IE after Melody valve implantation[28,29].

It turns out that the classic approach recommended by the practice guidelines[12] to confirm valvular involvement in the setting of PVE (i.e. detection of vegetation(s) and/or (para-) prosthetic regurgitation by TTE/TEE) is inefficient in a large proportion of patients with Melody valve IE. This observation calls for a modified diagnostic approach in these cases, possibly including progressive RVOT obstruction and abnormal activity on MSCT/PET as important additional diagnostic criteria.

Finally, given the aforementioned diagnostic challenges, pathological examination of tissue samples that are excised during surgery should be routinely applied. This histological examination of resected valvular tissue is considered by the guidelines[12] as "the gold standard" for the diagnosis of IE.

Limitations

This review, although intended to be comprehensive, still bears the limitations inherent to a retrospective review of published data e.g. selection bias of patients with a relatively better outcome. In general, comparisons between patients with vs. without IE were either missing or, when present, significantly heterogeneous and seriously limited by the small number in either/both groups; precluding appropriateness for pooled analysis.

CONCLUSIONS AND CLINICAL IMPLICATIONS

The risk of IE after implantation of a Melody valve is significant at least over the first three years after TPVI, with few cases occurring in the early post-procedural period. However, the reported incidence varies considerably between the studies. Diagnosis is challenging especially in terms of the documentation of valvular involvement in the infective process. The classic modified Duke criteria, which heavily rely on echocardiographic signs, show a modest diagnostic yield in post-TPVI endocarditis. Approximately 52% of patients require re-intervention, either surgically or percutaneously, with the infection being controllable with antibiotics in some cases, especially when streptococci are involved and the RVOT is not obstructed.

CLINICAL PERSPECTIVE

1) What is new?

- The risk of IE after implantation of the Melody valve is significant, extending at least over the first three years after the procedure.
- The diagnosis is challenging, and the modified Duke criteria have a modest diagnostic yield in this setting.
- Approximately 52% of patients require re-intervention, either surgically or percutaneously.
- The outcome is favorable when streptococci are the causative organism and the right ventricular outflow tract is not obstructed.

2) What are the clinical implications?

- More attention should be paid to prevent and early detect IE in patients who receive Melody valve implantation.
- Documentation of valvular involvement on echocardiography is challenging, and failure to visualize vegetations should not exclude the diagnosis of IE when the clinical suspicion is high.
- The causative organism and the pressure gradient across the valve can be used for risk stratification of the patients.

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SUPPLEMENTARY DATA

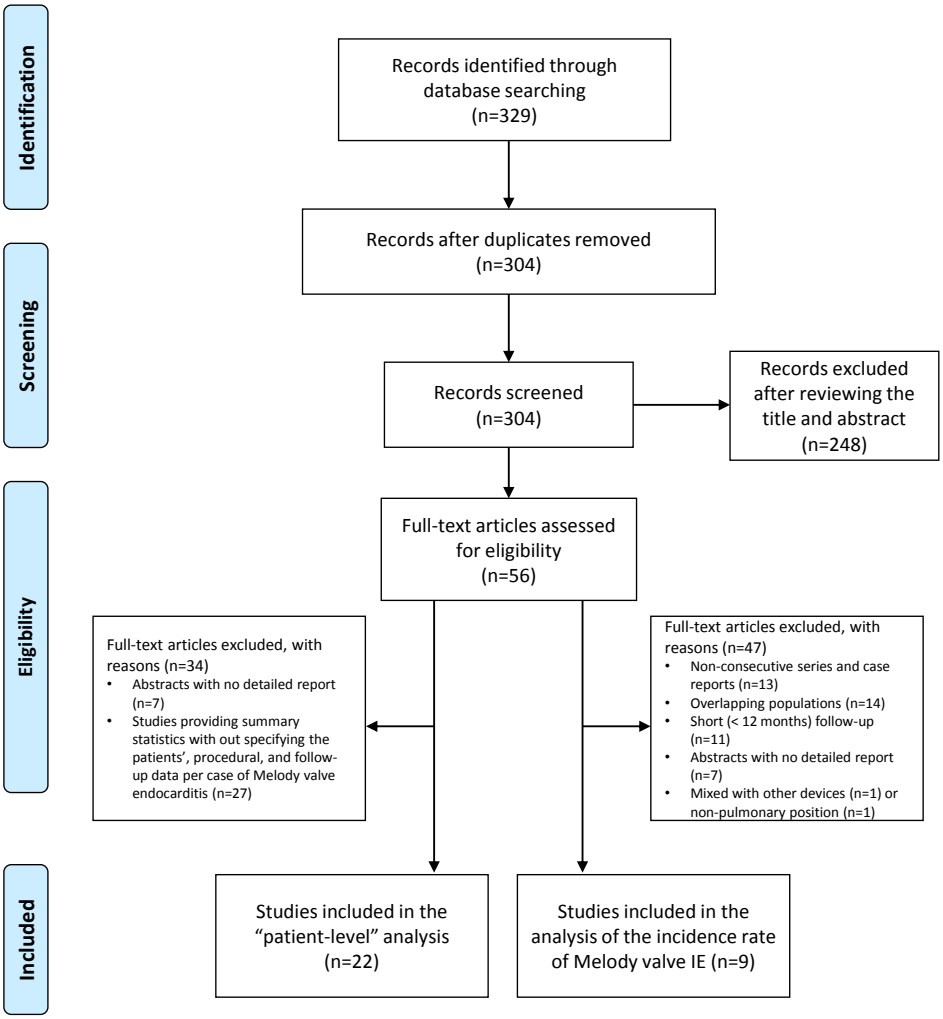
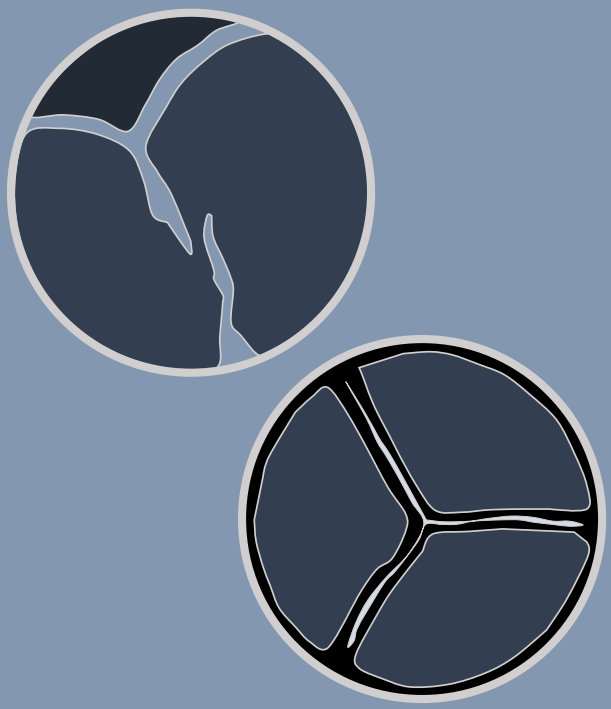
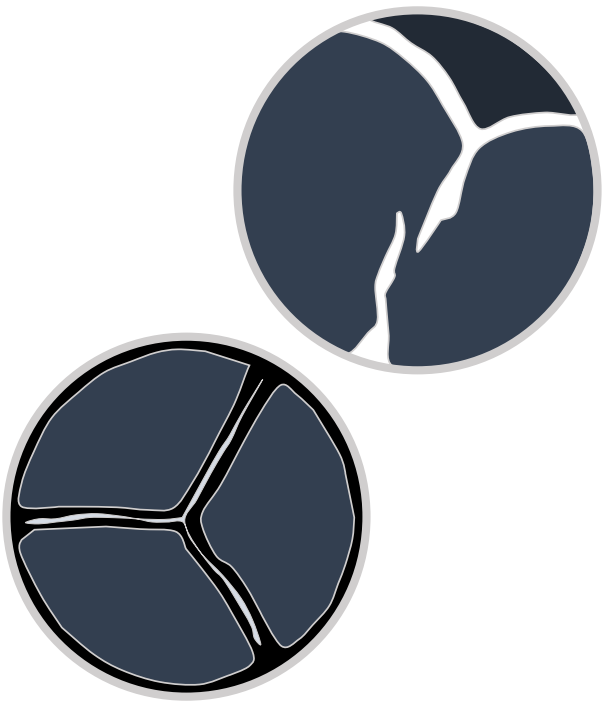


Figure S1. The PRISMA flow chart of the literature search.

PART C

Transcatheter closure of inter-atrial communications; foreseeing device-host interactions





Chapter 12

Residual tricuspid regurgitation after percutaneous atrial septal defect closure

Nassif M, van der Kley F, Abdelghani M, Kalkman DN, de Bruin-Bon RHACM, Bouma BJ, Schalij MJ, Koolbergen DR, Tijssen JG, Mulder BJM, de Winter RJ

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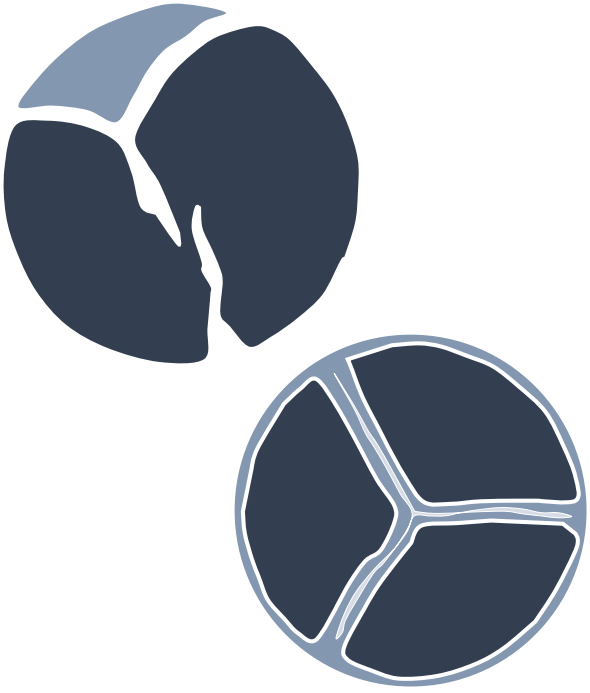


ABSTRACT

Aims:

Functional tricuspid regurgitation (TR) associated with atrial septal defects (ASDs) is frequently present due to right-sided volume-overload. Tricuspid valve (TV) repair is often considered in candidates for surgical ASD closure, and percutaneous TV repair is currently under clinical investigation. In this study we develop a prediction model to identify patients with residual moderate/severe TR after percutaneous ASD closure.

Methods and results:

In this observational study, 172 adult patients (26% male, age 49±17years) with successful percutaneous ASD closure had pre-and post-procedural echocardiography. Right heart dimensions/function were measured. TR was assessed semi-quantitatively. A prediction model for six-month post-procedural moderate/severe TR was derived from uni-and multivariable logistic regression. Clinical follow-up was updated and adverse events were defined as cardiovascular death or hospitalization for heart failure. Pre-procedural TR was present in 130(76%) patients (moderate/severe: n=64) of which 72(55%) had ≥1grade reduction post-closure. Independent predictors of post-procedural moderate/severe TR (n=36) were age ≥60y (OR=2.57;P=0.095), right atrial end-diastolic area ≥10cm^2/m^2 (OR=3.36;P=0.032), right ventricular systolic pressure ≥44mmHg (OR=6.44;P=0.001) and TAPSE ≤2.3cm (OR=3.29;P=0.037), producing a model with optimism-corrected C-index=0.82 (P<0.001). Sensitivity analysis excluding baseline ≤mild TR yielded similar results. Patients with moderate/severe TR at six-month follow-up had higher adverse event rates (hazard ratio=6.2[95%CI 1.5-26]; log-rank P=0.004) across a median of 45[30-76]months clinical follow-up.

Conclusion:

This study shows that, parallel to reduction of volume-overload and reverse remodeling after percutaneous ASD closure, TR improved substantially despite significant TR at baseline. Our proposed risk model helps identify ASD patients in whom TR regression is unlikely after successful percutaneous closure.

INTRODUCTION

Secundum atrial septal defects (ASDs) are one of the most common adult congenital heart defects.[1]Functional tricuspid regurgitation (TR) can occur secondary to ASD-based volume-overload due to right heart- and tricuspid annular dilatation. Percutaneous ASD closure may improve functional TR by reverse remodeling and prevent further right heart deterioration from volume- and eventual pressure-overload.

Functional TR is the most prevalent tricuspid valve (TV) disease in the West and independently predicts cardiovascular morbidity and mortality,[1] especially if moderate/severe.[2-4] Following the recognition of the clinical relevance of functional TR, an active therapeutic strategy is currently advocated.[5-7] TV repair is considered in candidates for surgical ASD closure with annular diameter ≥40mm. However, current European[8] and American[9] guidelines recommend repair of functional TR as part of left-sided heart disease only, therefore management of ASD-based TR remains undetermined and simultaneous surgical ASD and TV repair is often performed.

Apart from a few studies reporting the frequency and risk factors of significant TR after ASD closure,[10,11] no risk stratification of moderate/severe TR at post-procedural follow-up exists for adult candidates of ASD closure. Our aim was to develop a clinical prediction model for the risk of persistent TR after percutaneous ASD closure to help identify patients in whom TR improvement may not occur.

METHODS

Study design

In this retrospective cohort study, all adult ASD patients from two university hospitals who underwent percutaneous closure were evaluated. The study cohort comprised consecutive patients who underwent successful percutaneous ASD closure (i.e. without device embolization/thrombosis or significant residual shunting) and who had transthoracic echocardiography (TTE) at baseline and at approximately six months follow-up (inclusion range of 3-18 months). Patient characteristics and echocardiographic studies were gathered from medical records, and clinical outcomes were updated from patient contact by telephone or alternatively gathered from the last medical follow-up. This study complies with the declaration of Helsinki and is in compliance with national legislation; each center's local medical ethical committee approved this study with a waiver and all patients provided informed consent.

ASD closure

The Grown-Up Congenital Heart disease (GUCH) heart team determined the indication for ASD closure according to recommendations of the current European guidelines, based on either hemodynamically significant left-to-right shunting with pulmonary vascular resistance <5 Woods units (Class I, level B) or suspicion of paradoxical embolism (Class IIa, level C).[12] Percutaneous ASD closure was performed under either general or local anesthesia and an Amplatzer Septal Occluder (St. Jude Medical, Minneapolis, MN, USA) of appropriate size was implanted. Post-procedural therapy included a six-month regimen of either dual antiplatelet therapy with aspirin 100mg and clopidogrel 75mg daily after a 600mg loading dose, or only aspirin 300mg daily, depending on the treating center's protocol.

Echocardiography

Two-dimensional transthoracic echocardiography was performed both at baseline and post-procedural follow-up as part of routine clinical outpatient visits. Echocardiographic views were acquired on a Vivid 7-9.5 (GE Healthcare, Horten, Norway) based on guideline recommendations,[13]and analyses were performed offline on EchoPAC PC v.201 (GE Healthcare, Horten, Norway). Right atrial (RA) and ventricular (RV) dimensions and maximal tricuspid annular diameter were obtained from the apical four-chamber view, and RV systolic function was assessed by fractional area change, tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular systolic motion velocity. Tricuspid regurgitation was semi-quantitatively scored based on valve morphology, visual assessment of color-flow TR jet, vena contracta width, shape and intensity of the continuous wave Doppler TR jet signal, and hepatic venous flow pattern.[14] In the absence of inferior vena cava measurements (n=64 baseline, n=54 follow-up), right atrial pressure was estimated at 8mmHg when RA area>18cm^2 and 3mmHg if smaller.[15] Peak TR jet velocity was obtained from multiple Doppler views, and right ventricular systolic pressure was calculated using the modified Bernoulli equation.[16]

Definition of outcomes

The main outcome measure of this study was moderate/severe TR on echocardiography at six-month post-procedural follow-up. Secondly, to assess the predictive value of the tricuspid valve severity on clinical outcome, all patients were contacted by telephone to update clinical information and assess symptomatology between June-November 2017. An adverse clinical event was defined as the composite of cardiovascular death or hospitalization for heart failure. All deaths were marked cardiovascular unless an unequivocal non-cardiac cause could be established. Heart failure hospitalization was defined as hospital admission of ≥12 hours for worsening heart failure symptoms that required parenteral therapy. Time-to-event was time to first event, whichever came first.

In addition, symptoms of dyspnea, peripheral edema, chest pain, palpitations, dizziness, syncope and fatigue were assessed at latest clinical follow-up.

Statistical analysis

Analyses were performed on R v.3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS v.23 (IBM Corp., Armonk, NY, USA). Baseline characteristics, hemodynamics and pulmonary function parameters are presented as mean ± standard deviation, median [25th-75th percentile], or frequency (percentage) according to variable type and distribution. The two-tailed paired- and independent t-tests were used for paired resp. between-group testing in continuous variables. Categorical variables were compared using the Chi-square test and the McNemar test in independent resp. paired testing. Correlations were linearly tested unless mentioned otherwise. A $P<0.05$ was considered statistically significant.

Two investigators (MN and MA), blinded to patient information and clinical outcome, assessed TR severity in 60 randomly selected cases. Inter-observer agreement was then analyzed using Cohen's kappa for TR grading.

Univariable logistic regression analyses were used to identify determinants of moderate/severe TR at post-procedural follow-up. Candidate risk factors were clinically relevant patient and ASD characteristics, and baseline echocardiographic parameters that statistically differed between the outcome and the non-outcome group. Continuous variables were dichotomized using the Youden index to facilitate potential use of this prediction model in clinical practice.

Variables with $P\leq0.10$ in univariable analysis were initially incorporated in three multivariable analyses; one with only clinical variables, another with additional echocardiographic parameters, and the third from a backward selection in which variables with $P<0.10$ by the Wald statistic were identified. The discriminative value of these models was compared using the C-index, Akaike Information Criterion, Net Reclassification Improvement and Integrated Discrimination Improvement.[17] The final model was defined as the simplest and highest discriminative model of these. Sensitivity analysis excluding patients with ≤mild TR was performed to validate the model specifically in patients with moderate/severe TR at baseline. Proportional to their odds ratio (OR), independent predictors in the final model were assigned scores in which a higher cumulative score indicated higher estimated risk of moderate/severe TR at six-month follow-up.

Adverse event rates were based on Kaplan-Meier estimates in time-to-event analyses with a landmark at six months post-closure. Follow-up of patients was censored at the time of last telephone contact or, if not available, at the last medical contact. For time-to-event analyses between patients with and without moderate/severe TR at follow-up, the hazard ratio was determined by Cox regression analysis and Kaplan-Meier curves were compared using the log-rank test.

RESULTS

Study population

The total cohort consisted of 202 adult patients (Figure S1), of which 172 patients (74% female, mean age 49±17 years, range 18-84 years) were included in this study for having complete baseline (median 4.0[2.0-7.0] months before closure) and follow-up echocardiograms (median 6.0[5.0-7.0] months after closure). The indication for ASD closure was hemodynamically significant left-to-right shunting in 83%- and paradoxical embolism

Table 1. Baseline patient characteristics.

	n=172
Demographics	
Age, y	49 ±17
Female	128 (74)
BSA, m^2	1.8 ±0.2
Medical history	
Hypertension	58 (34)
Dyslipidemia	34 (20)
Diabetes mellitus	13 (8)
Coronary intervention	4 (2)
Cerebrovascular accident	29 (17)
Atrial arrhythmia	40 (23)
Paroxysmal atrial fibrillation	27 (16)
Persistent atrial fibrillation	10 (6)
Atrial flutter	3 (2)
Pulmonary hypertension*	14 (8)
Right ventricular systolic pressure, mmHg	37 ±12
Symptoms	
Palpitations	50 (29)
NYHA class I	87 (52)
NYHA class II	59 (34)
NYHA class III	22 (13)
NYHA class unknown	4 (2)
ASD-related characteristics	
TEE max. defect size, mm (n=161)	19 ±7.5
Device size, mm	21 ±7.3
Qp:Qs ratio†	1.9 ±0.6

Data are presented as mean ± SD or frequencies (%). BSA=Body surface area; NYHA= New York Heart Association; TEE= transesophageal echocardiography; Qp:Qs= pulmonary to systemic flow ratio.

* Right ventricular systolic pressure ≥50mmHg by TTE[15].

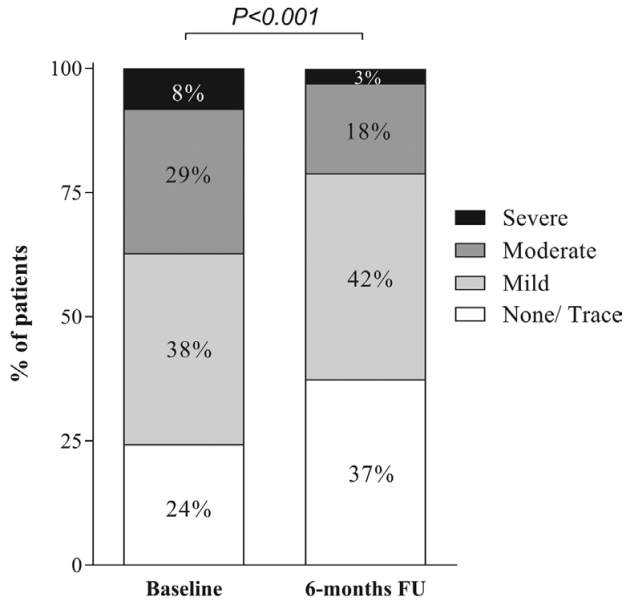
† By echocardiography or CMR (n=74).

in 17% of patients. Patient characteristics and ASD-related measurements are shown in Table 1, and baseline cardiac medication is listed in Table S1.

TR and reverse remodeling

At baseline, 130(76%) patients had ≥mild TR (Figure 1A) and of these, 72(55%) patients experienced ≥1 TR grade reduction at post-procedural follow-up. Of the 64 patients who had moderate/severe TR at baseline, 34(53%) patients improved to none/mild at follow-up (Figure 1B). Six patients were classified from baseline mild TR to post-procedural moderate TR, thus 36 patients eventually had moderate/severe TR at six-month post-procedural follow-up. Mild residual shunting was present in three patients (n=2 with none/mild TR), one of which had a small second ASD not intended for closure. The inter-observer variability in TR severity assessment yielded a very good agreement (n=56 out of n=60) with Cohen's kappa= 0.830 (95%CI 0.669-0.991), P<0.001.

A



B

		TR grade at 6-month FU				
N		None/trace	Mild	Moderate	Severe	Total
Baseline TR grade	None/trace	27	14	1	0	42
	Mild	33	28	5	0	66
	Moderate	3	24	20	3	50
	Severe	2	5	5	2	14
Total		65	71	31	5	172

Figure 1. Pre-and post-closure tricuspid regurgitation.
Pre- and post-procedural tricuspid regurgitation grades in percentages (**A**) and number of patients (**B**). Percentages may not sum to 100% due to rounding. FU= follow-up; TR= tricuspid regurgitation.

The echocardiographic parameters of reverse remodeling are given in Table 2. Overall, RA and RV dimensions and RV systolic pressure regressed, even more significantly in patients with baseline moderate/severe TR, possibly explained by larger right-sided dimensions and a higher RV systolic pressure at baseline. Right ventricular systolic function parameters RV fractional area change and TAPSE significantly reduced after closure, which reflect the volume-load dependency of these variables together with the volume reduction that results from the shunt closure. Left ventricular ejection fraction was ≥50% in all patients and remained unchanged after closure.

Tricuspid annular diameter showed modest association with TR grade, both at baseline and at follow-up (r=0.32 resp. r=0.37; P<0.001), see Figure S2. Tricuspid annular diameter reduction was more significant in patients who had ≥1 TR grade improvement (Δ-13±13% vs. Δ-8±16%; P=0.018).

Table 2. Baseline and post-procedural change in hemodynamic parameters stratified to TR severity at baseline.

	None/ mild TR				Moderate/ severe TR				*P-value**
	n	baseline	Δ (%)	P-value (paired)	n	baseline	Δ (%)	P-value (paired)	
Chamber dimensions									
RA end-systolic area, cm^2/m^2	106	12 ±3.6	-16 ±27	<0.001	61	16 ±6.1†	-26 ±17	<0.001	0.006
RA end-diastolic area, cm^2/m^2	106	7.5 ±3.0	-14±35	<0.001	61	11 ±5.9†	-24 ±19	<0.001	0.04
RV end-systolic basal diameter, cm	107	3.8 ±0.8	-3 ±38	0.05	62	4.0 ±0.7	-2 ±50	0.46	0.92
RV end-systolic length, cm	107	6.3 ±1.0	0.5 ±19	0.54	62	6.2 ±0.7	-1 ±17	0.36	0.60
RV end-systolic area, cm^2	107	19 ±6.2	-10 ±29	<0.001	62	20 ±5.0	-16 ±27	<0.001	0.24
RV end-diastolic basal diameter, cm	107	4.3 ±1.0	-14 ±16	<0.001	62	4.4 ±0.9	-12 ±12	<0.001	0.54
RV end-diastolic length, cm	107	8.1 ±1.1	-3 ±18	0.02	62	7.8 ±0.9	-5 ±16	0.004	0.54
RV end-diastolic area, cm^2	107	31 ±9.2	-18 ±23	<0.001	62	32 ±6.3	-26 ±16	<0.001	0.009
Tricuspid valve									
TV annular diameter, cm	108	3.7 ±0.7	-8 ±17	<0.001	64	3.9 ±0.6	-11 ±13	<0.001	0.28
Vena contracta, mm	108	2.1 ±1.5	-12 ±84	0.21	64	5.1 ±0.02†	-21 ±61	<0.001	0.003
RV systolic pressure, mmHg	81	32 ±8.5	-2 ±42	0.01	62	44 ±13†	-15 ±21	<0.001	0.03
Right ventricular systolic function									
RV fractional area change, %	107	38 ±14	-13 ±47	0.005	62	38 ±15	-16 ±62	0.01	0.73
TAPSE, cm	93	2.8 ±0.5	-6 ±21	<0.001	50	2.6 ±0.06‡	-6 ±23	0.01	1.00
RV S′, cm/s	36	14 ±3.0	-5 ±15	0.08	21	17 ±0.2	-14 ±27	0.26	0.24

Data are presented as mean±SD of both absolute values (baseline) and percentages (delta of post-versus pre-procedural values). RA= right atrial; ES= end-systolic; ED= end-diastolic; RV= right ventricular; TV= tricuspid valve; TR=tricuspid regurgitation; TAPSE= Tricuspid annular plane systolic excursion; RV S′=Tricuspid annular systolic motion velocity.

* Comparison of percentage change stratified by baseline TR severity.

† P<0.001; ‡ P<0.05; for all comparisons of baseline value stratified by TR severity.

Predictors of post-procedural TR

Univariable predictors of moderate/severe TR at post-procedural follow-up are shown in Table 3. After comparing three multivariable models (Table S2), the final model included age ≥60 years (OR 2.57; P=0.10), RA end-diastolic area index ≥10cm^2/m^2 (OR 3.36; P=0.03), RV systolic pressure ≥44mmHg (OR 6.44; P=0.001) and TAPSE ≤2.3cm (OR 3.29; P=0.04) as independent predictors. This model was statistically significant (χ^2[4]=35.57; P<0.001), and correctly classified 82% of cases by internal validation (C-index=0.85 [95%CI 0.76-0.93]; P<0.001). In a sensitivity analysis including only patients with baseline moderate/severe TR (n=64), this model remained significantly predictive of residual moderate/severe TR (C-index=0.72 [95%CI 0.58-0.86]; P=0.008). Figure 2 shows a simplified risk stratification using OR-based risk score, along with corresponding predicted and observed rate of moderate/severe TR at six-month follow-up. A risk score of ≥4

Table 3. Uni- and multivariable logistic regression for moderate/severe tricuspid regurgitation at follow-up.

	Variable present	Variable absent	Univariable			Multivariable		
			OR	95%CI	P-value	OR	95%CI	P-value
Patient characteristics								
Age at closure ≥60 years	**38%** (19/50)	**14%** (17/122)	3.8	1.8-8.2	0.001	2.6	0.9-7.6	0.10
Female gender	**23%** (30/128)	**14%** (6/44)	1.9	0.8-5.0	0.17			
Hypertension	**29%** (17/58)	**17%** (19/114)	2.1	1.0-4.4	0.06			
Atrial arrhythmia	**38%** (15/40)	**16%** (21/132)	3.2	1.4-7.0	0.004			
NYHA class ≥III	**45%** (10/22)	**17%** (26/150)	4.0	1.6-10.2	0.004			
ASD characteristics								
TEE max. defect size ≥24 mm	**29%** (12/41)	**19%** (23/120)	1.8	0.8-3.9	0.18			
Device size ≥26 mm	**29%** (13/45)	**18%** (23/127)	1.8	0.8-4.0	0.14			
Qp:Qs ratio ≥2.3	**26%** (5/19)	**16%** (9/55)	1.8	0.5-6.3	0.34			
Baseline echocardiography								
RA ES area ≥15 cm^2/m^2	**35%** (18/51)	**15%** (17/116)	3.2	1.5-6.9	<0.001			
RA ED area ≥10 cm^2/m^2	**45%** (19/42)	**13%** (16/125)	5.7	2.5-12.6	<0.001	3.4	1.1-10.1	0.03
RV ES basal diameter ≥4 cm	**31%** (23/75)	**13%** (12/94)	3.0	1.4-6.6	0.005			
RV ED basal diameter ≥5 cm	**30%** (10/33)	**18%** (25/136)	1.9	0.8-4.6	0.13			
TV annular diameter ≥4 cm	**36%** (20/55)	**14%** (16/117)	3.6	1.7-7.7	0.001			
Vena contracta ≥5 mm	**50%** (20/40)	**12%** (16/132)	7.7	3.4-17.6	<0.001			
RV systolic pressure ≥44 mmHg	**54%** (20/37)	**14%** (15/106)	7.1	3.1-16.6	<0.001	6.4	2.1-19.7	0.001
RV fractional area change ≤30%	**25%** (8/32)	**20%** (27/137)	1.4	0.6-3.4	0.51			
TAPSE ≤2.3 cm	**35%** (13/37)	**15%** (16/106)	3.1	1.3-7.2	0.01	3.3	1.1-10.1	0.04

Data are presented as frequencies (%). Cut-off values correspond to the 75th percentile. Abbreviations as in Table 1.

	Risk model score
Age ≥60 years	1
RA end-diastolic area ≥10cm^2/m^2	1
RV systolic pressure ≥44mmHg	2
TAPSE ≤2.3cm	1

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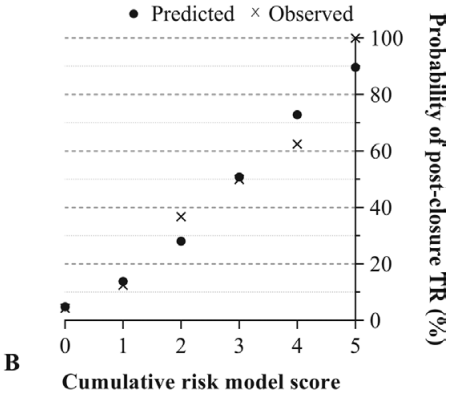

B

Figure 2. Prediction model for moderate/severe TR after percutaneous ASD closure in adults.
(**A**) Risk model scores per independent predictor, weighted according to respective odds ratios. (**B**) Plotted cumulative risk score against predicted and observed probability of moderate/severe TR six months after ASD closure. A higher cumulative risk score (range 0-5) indicated a higher predicted probability (5%, 14%, 29%, 52%, 75% resp. 90%) and showed a higher observed rate (4%, 13%, 37%, 50%, 63% resp. 100%) of post-closure moderate/severe TR; C-index=0.85 (95%CI 0.76-0.93), P<0.001. Abbreviations as in Table 1.

yielded a predicted probability of ≥75% for moderate/severe TR at FU, see Figure 2B. In patients with a risk score of ≥4 (n=12), 9 patients (75%) actually had moderate/severe TR at post-procedural FU.

Clinical outcomes

The median clinical post-procedural follow-up duration was 45[30-76] months (range 9-146 months). Six patients died during follow-up; three in each outcome group, i.e. with and without moderate/severe TR at six-months follow-up, and in each two cardiovascular deaths occurred. One patient died of ovarian carcinoma (outcome group) and another of bladder cancer (non-outcome group).

Between June-November 2017, 155(93%) of the surviving patients could be contacted by telephone to update clinical follow-up. The unavailable patients had a median follow-up of 33[24-54] months. Patients with moderate/severe TR at follow-up had significantly higher adverse event rates (Figure 3) with a hazard ratio of 6.2 (95%CI 1.5-26) and log-rank P=0.004. This was mainly driven by a higher rate of heart failure hospitalizations (n=3 in outcome group, n=1 in non-outcome group).

Symptoms at latest clinical follow-up are shown in Table 4. Patients with persistent moderate/severe TR had more symptoms of dyspnea and peripheral edema than patients in whom TR had reduced to none/mild (30% vs. 16% resp. 41% vs. 16%). The latter were comparable to patients who maintained none/mild TR (15% resp. 20%). Regardless of TR severity at follow-up, palpitations and fatigue were the most frequently reported symptoms post-closure.

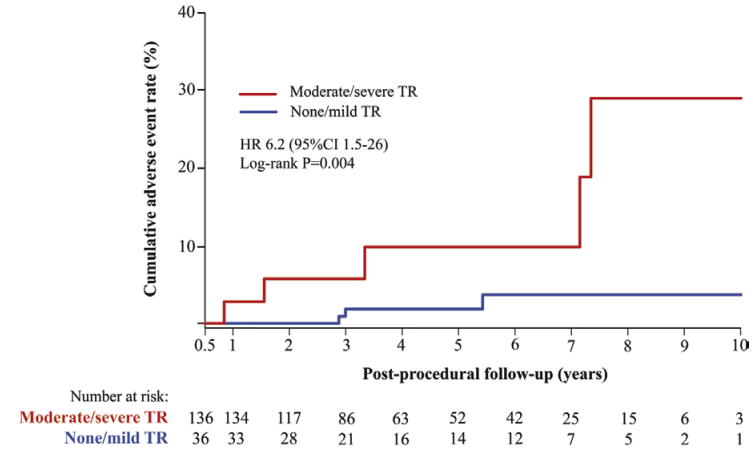

Figure 3. Adverse event rate during post-procedural follow-up.
Event rates of cardiovascular mortality or hospitalization for heart failure in patients with none/mild and moderate/severe TR, with a landmark at six-month post-procedural follow-up.

Table 4. Patient symptoms at latest clinical follow-up.

	Moderate/severe TR before and after closure	Moderate/severe TR reduced to none/mild TR	None/mild TR before and after closure
	n=27	n=32	n=101
Dyspnea	8 (30)	5 (16)	15 (15)
Peripheral edema	11 (41)	5 (16)*	20 (20)
Chest pain	2 (7)	0 (0)	6 (6)
Palpitations	12 (44)	16 (50)	42 (42)
Dizziness	9 (33)	7 (22)	32 (32)
Syncope	3 (11)	2 (6)	5 (5)
Fatigue	9 (33)	10 (31)	31 (31)

Data are presented as frequencies (%) of surviving patients' reported symptoms at median 45[30-76] months post-procedural follow-up.
* P<0.05 for moderate/severe TR that persisted vs. reduced to none/mild TR.

DISCUSSION

This study is the first to propose a clinical prediction model for residual TR after successful percutaneous ASD closure in adults. Age ≥60 years, RA end-diastolic area index ≥10cm^2/m^2, RV systolic pressure ≥44mmHg and TAPSE ≤2.3cm each independently predicted moderate/severe TR at six-month post-procedural follow-up, and together yielded a highly predictive model. Patients with persistent significant TR at six-month post-closure had a higher adverse event rate during long-term follow-up.

TR and reverse remodeling

Functional TR in patients with ASD and left-to-right shunting is mainly the result of RV dilatation and free wall stretch causing both tricuspid annular dilatation as well as leaflet malcoaptation and tethering.[6,18] Atrial tachyarrhythmia and/or increased pulmonary artery pressures contribute to this pathophysiology. In turn, functional TR can further contribute to RA and RV dilatation irrespective of pulmonary artery pressure.[19]

In line with previous studies,[10,11,20] our study reports significant TR reduction at six-month follow-up post ASD closure despite significant TR at baseline. Successful closure unloads the right heart and initiates a reduction of right heart dimensions, occurring mostly within one-month post-closure[21] followed by slow additional improvement up to six to 24 months.[4,22] Our observed improvement of functional TR was parallel to significant reduction of the tricuspid annulus diameter and RV reverse remodeling. In line with previous studies,[20,23] post-procedural decrease in RV systolic pressure (RVSP) also contributed to TR improvement and took place even in patients with mildly elevated pulmonary pressures. Six patients had increase from baseline none/trace to post-procedural moderate TR. Fang et al.[10] reported similar observations and suggested a mechanical influence of the ASD occluder.

Predictors of post-procedural TR

Despite general TR improvement after ASD closure, persistent moderate/severe TR was observed in 30/64(47%) patients, consistent with previous reports.[10,11] The predicted probability of post-closure moderate/severe TR was translated into a more practical 6-point cumulative risk score which performed satisfactorily in all risk strata (see Figure 2). For example, patients with the highest cumulative score (≥4) had a predicted and observed probability of 75% for post-closure moderate/severe TR.

In line with our findings, most studies investigating ASD-based TR agree that in a subgroup of patients with significantly elevated RVSP, post-closure TR regression is less likely.[11,20,24] Toyono et al.[11] even recommend TV repair to be considered in all ASD patients with concomitant pulmonary hypertension. Rather than maintaining TR intrinsically, elevated RVSP provokes RV dysfunction by pressure-overload[22,24-26] causing leaflet tethering and further annular dilatation.[6,18,27] Leaflet tethering is therefore expected to be a stronger predictor than RVSP, which Fang et al.[10] demonstrated indeed. Although TV geometry assessment is an appealing approach to predict post-closure TR, this is difficult to measure from 2D echocardiographic images,[18] and high-quality 3D echocardiographic techniques were yet unavailable when most of this patient cohort underwent ASD closure.

Older age increases the risk of atrial fibrillation among others, and RA dilatation cannot be seen separately from atrial arrhythmia; it induces atrial arrhythmia and vice versa.[18,28] Therefore, we found a strong collinearity between the presence of atrial arrhythmia and

both age and end-diastolic RA size, which explains its exclusion from our model. Older age is also associated with higher pulmonary artery pressure,[20] yet although the latter is the strongest predictor in our model, age does independently contribute to significant TR since it remained significant in the multivariable model.

Atrial fibrillation and NYHA class, which are previously reported predictors of moderate/severe TR,[4] were eliminated in the final multivariable model because of strong associations with RA size and TAPSE respectively. Exclusion of these clinical variables provided a higher discrimination in our final model based on the optimism-corrected C-index and Akaike Information Criterion (see Table S2). Although it can be argued that a model comprising only clinical variables would facilitate its use in daily practice, such a model also lowers its discriminative properties (Table S2) compared to the combination of age with echocardiographic parameters that are still routinely collected in candidates for ASD closure.

Clinical implications

ASD patients are at high risk of functional TR, therefore it is essential not to overlook the improvement of TR as an important target of ASD closure. TR regression is however not guaranteed in all patients, which prevents it from being an indication for ASD closure itself. Our predictive model may help in identifying patients in whom TR may remain after successful percutaneous ASD closure. Among other factors such as anatomical suitability, the likelihood of moderate/severe TR to persist after ASD closure should be considered by the interventional heart-team when deciding between surgical and percutaneous ASD closure. The debate as to whether a high likelihood of moderate/severe TR post ASD closure justifies that surgical closure be favored over percutaneous closure merely to facilitate simultaneous TV repair, is far from being settled.[29]The optimal strategy has yet to be explored in future studies, particularly in light of the rapidly evolving less-invasive percutaneous TV repair techniques which currently show promising results.[30,31]

Limitations

This study has a retrospective design, therefore we cannot account for all potential confounders in our prediction model despite multivariable analysis. Given the relatively low frequency of moderate/severe TR even with our multicenter data, predictors' regression coefficients may be overestimated even after optimism-correction. The limited number of adverse clinical events did not allow for additional multivariable analysis. Our study did not validate our prediction model in a second patient cohort so future studies are needed to externally validate our model. Finally, echocardiographic follow-up duration was limited to six months, however as shown in previous studies,[4,21] the largest reverse remodeling and consequent TR change occurs within six months post-closure.

CONCLUSIONS

This study is the first to provide a practical prediction model for the risk of residual TR after percutaneous ASD closure. TR significantly improved in some patients despite significant TR at baseline, and moderate/severe TR post-closure is best predicted by the combination of age, RA size, RV systolic pressure and the extent of RV dysfunction. This model may help identify a subgroup of patients in whom TR regression after ASD closure is unlikely.

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SUPPLEMENTAL DATA

Table S1. Cardiac medication at baseline.

	n=172
Diuretics	
Hydrochloorthiazide	6 (3)
Furosemide	12 (7)
Spironolacton	6 (3)
Bumetanide	6 (3)
β-blocking agents	
Metoprolol	18 (10)
Bisoprolol	6 (3)
Propranolol	1 (1)
Nebivolol	2 (1)
Atenolol	2 (1)
Calcium channel blockers	
Verapamil	3 (2)
Amlodipine	4 (2)
Nifedipine	2 (1)
Barnidipine	1 (1)
Renin-angiotensin system agents	
Perindopril	6 (3)
Lisinopril	6 (3)
Enalapril	3 (2)
Fosinopril	1 (1)
Irbesartan	3 (2)
Candesartan	2 (1)
Losartan	1 (1)
Antiarrhythmics	
Sotalol	5 (3)
Amiodaron	2 (1)
Digoxin	6 (3)
Flecainide	2 (1)
Anticoagulation	
Acenocoumarol	15 (9)
Fenprocoumon	5 (3)
Rivaroxaban	1 (1)
Dabigatran	2 (1)

Data are presented as frequencies (%). Medication remained unchanged at six-month post-closure follow-up.

Table S2. Comparison of three prediction models for moderate/severe TR at six-month follow-up.

	Model containing only clinical variables			Model of both clinical and echocardiographic variables			Final simplified model of clinical and echocardiographic variables		
	n=172			n=119			n=119		
Model predictors	**B**	**SE**	**P-value**	**B**	**SE**	**P-value**	**B**	**SE**	**P-value**
Age ≥60 years	0.871	0.439	0.048	0.888	0.583	0.128	0.942	0.564	0.095
Atrial arrhythmia	0.796	0.451	0.078	0.229	0.702	0.744			
NYHA class ≥III	1.096	.515	0.033	0.216	0.756	0.775			
RAEDA≥10cm^2/m^2				1.096	0.646	0.090	1.212	0.564	0.032
RVSP ≥44 mmHg				1.779	0.620	0.004	1.863	0.572	0.001
TAPSE ≤2.3 cm				1.164	0.578	0.044	1.192	0.572	0.037
Model properties									
C- index	0.707			0.846			0.845		
Optimism-corrected C-index*	0.690			0.803			0.820		
Nagelkerke's R^2	0.160			0.395			0.393		
Hosmer-Lemeshow	0.999			0.980			0.991		
Model comparison									
Akaike Information Criterion	166			106			102		
Net Reclassification Improvement†	Reference			0.310; P<0.001			0.310; P<0.001		
Integrated Discrimination Improvement‡	Reference			0.167; P<0.001			0.165; P<0.001		

B= Regression coefficient; SE= Standard error; NYHA= New York Heart Association; RAEDA= Right atrial end-diastolic area in cm^2/m^2; RVSP= Right ventricular systolic pressure; TAPSE= Tricuspid annular plane systolic excursion.

* By n=1000 bootstrapping of the model.

† Defined as (Pimproved_prediction_among_outcome + Pimproved_prediction_among_no_outcome) – (Pworse_prediction_among_outcome + Pworse_prediction_among_no_outcome) for continuous predicted probabilities with P= proportion of patients.

‡ Defined as (Σ^ioutcome(Pnew(i) – Pold(i)) / n(outcome)) – (Σ^jno_outcome(Pnew(j) – Pold(j)) / n(no_outcome)) with P= predicted probability for the outcome.

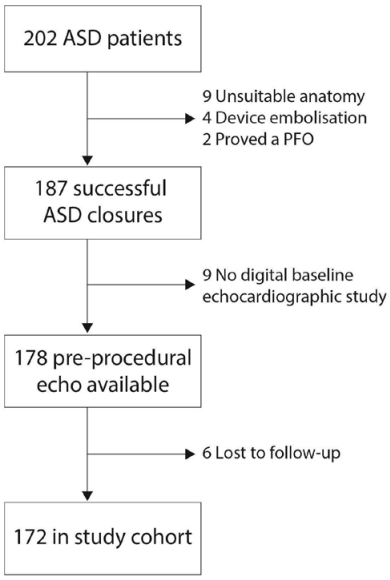


Figure S1. Study flow chart.

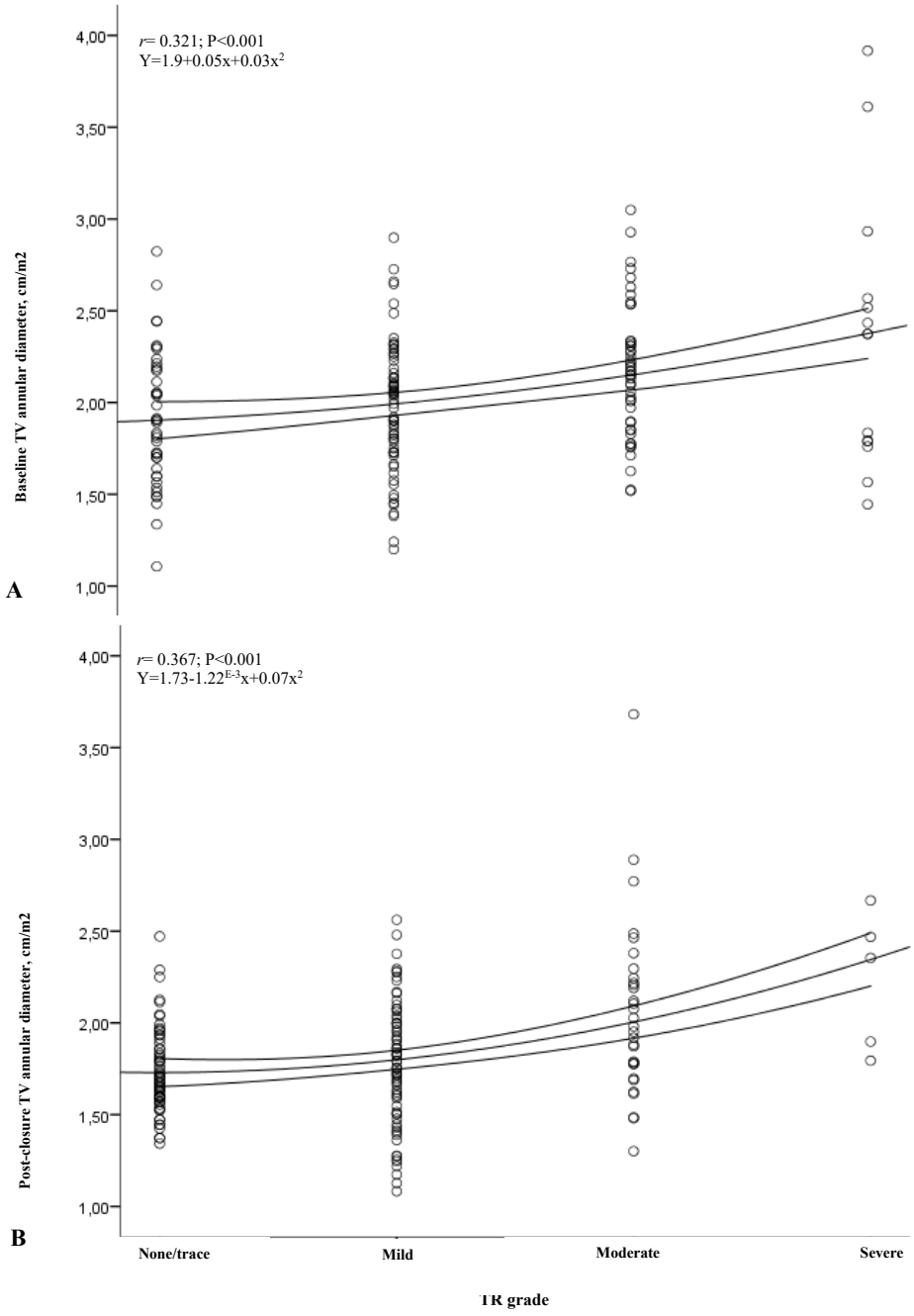
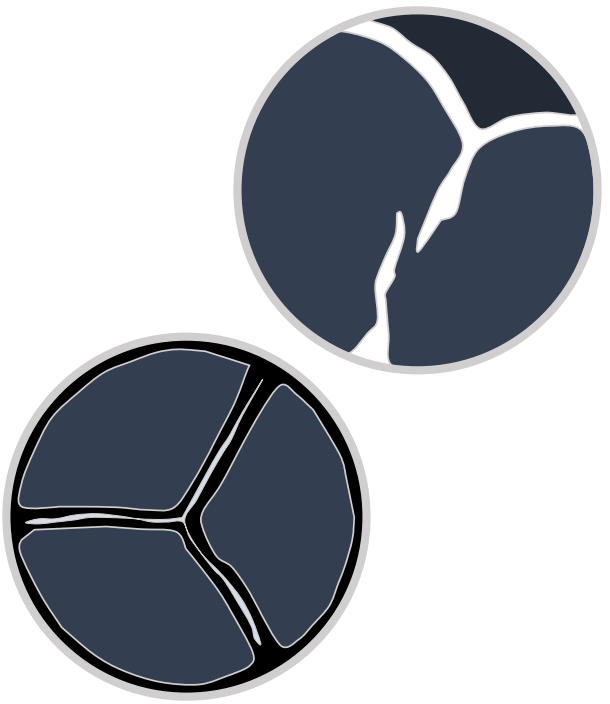


Figure S2. BSA-indexed tricuspid annular diameter shows a moderate association with increasing TR grade at baseline (A) and six-month follow-up (B).



Chapter 13

Aortic root geometric and dynamic changes after device closure of interatrial shunts

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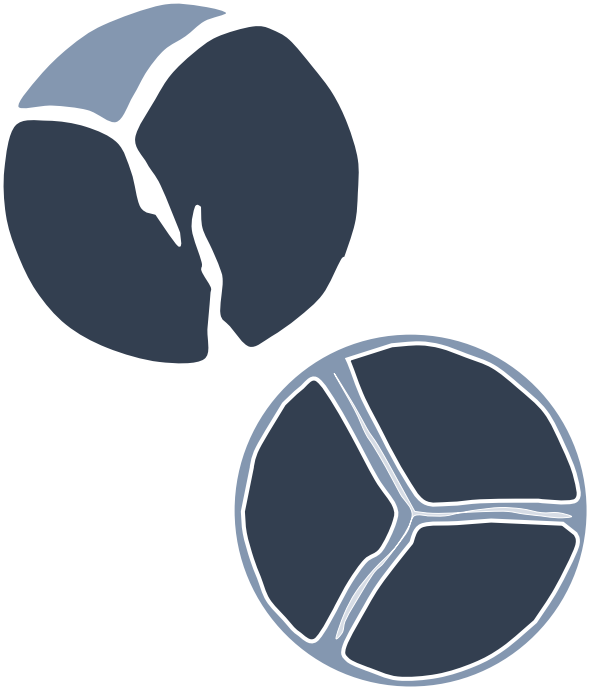
*Both authors contributed equally



ABSTRACT

Objective:

The spatial relationship between atrial septal occluders and the aorta and subsequent impact on the geometry and mechanics of the aortic root are under-investigated. We sought to evaluate the occluder-aorta interaction after device closure of atrial septal defect (ASD) or patent foramen ovale (PFO) using 3D- transesophageal echocardiography (TEE) and 2D-speckle tracking echocardiography.

Methods:

In 65 adult patients (47±14 years; 71% females) who underwent ASD (n=35) or PFO (n=30) closure with the Amplatzer ASD/PFO Occluder, the occluder-aorta contact was evaluated on 3D-TEE and defined as continuous, intermittent or absent. Sinus of Valsalva diameter, height, eccentricity, and strain were measured before and immediately after occluder implantation.

Results:

The occluder-total septal length and occluder-body surface area (BSA) ratios were significantly larger after PFO than after ASD closure. The occluder was in contact with the aorta in 93.8% of cases (ASD, 91.4%; PFO, 96.7%). After ASD closure, occluder-aorta contact was very common both in those with an aortic rim <5 mm (100%) and those with an aortic rim ≥5 mm (79%). However, a continuous occluder-aorta contact was more frequent in those with aortic rim <5 mm (95% vs. 50%). Factors influencing aortic root strain after occluder implantation included: the pattern of occluder-aorta relationship and the occluder-BSA ratio.

Conclusions:

Most inter-atrial septal occluders are in contact with the aortic root, even in ASD patients with a sufficient aortic rim and in PFO patients. However, a continuous occluder-aorta contact is more likely in ASD patients with a deficient aortic rim. The pattern of occluder-aorta relationship and the occluder-BSA ratio affect aortic root strain.

INTRODUCTION

Device closure is the treatment of choice for secundum atrial septal defects (ASD)[1] and reduces the risk of recurrent cerebrovascular events in patients with patent foramen ovale (PFO)[2-4]. Device closure of ASD and PFO is associated with a low rate of serious complications[5,6].

The Amplatzer Septal/PFO Occluders (Abbott Vascular Inc., Santa Clara, CA, USA) are the most commonly used devices to close inter-atrial communications, and have demonstrated favorable safety and efficacy profiles[7,8]. The nitinol wire frame of Amplatzer occluders makes them relatively rigid devices facilitating positioning and stabilization, on the one hand; and carrying the potential for compressing, damaging, or eroding adjacent cardiac structures, on the other hand[9]. Damage to adjacent cardiac structures may manifest as device erosion into aorta/pericardial space[10], aortic valve incompetence[11], coronary artery compression[12], or atrial arrhythmia[2]. In order to establish an evidence-based approach for prediction of these grave complications, understanding the spatial relationship between the occluder and adjacent structures is required[9].

Among the above-mentioned complications, device erosion into aorta is the most feared complication of ASD/PFO device closure. Impingement/protrusion of the device into the aorta has been suggested as a potential risk marker of device erosion, and is speculated to occur more frequently in patients with a deficient aortic rim[10,13-15]. So far, no standardized method exists to assess the presence and extent of device impingement on the aortic wall and subsequent aortic root deformation. Should this be established, it can potentially help identify patients at a higher risk of device erosion. We hypothesized that ASD/PFO occluder implantation is associated with a measurable change in aortic root strain, and that this change is influenced by the pattern of occluder-aorta interaction and the occluder size. We sought to evaluate occluder-aorta interaction and changes in aortic root geometry and mechanics by 3D transesophageal echocardiography (3D-TEE) and 2D speckle tracking echocardiography (2D-ST) performed before and immediately after occluder implantation.

MATERIAL AND METHODS

Study design

The study included 65 adult patients who underwent percutaneous ASD (n=35) or PFO (n=30) closure between March 2015 and January 2018 at the Academic Medical Center, University of Amsterdam, The Netherlands, in whom 3D-TEE was acquired directly before and after occluder implantation according to the study protocol. This study complies to the declaration of Helsinki, was approved by the local Medical Ethics Committee, and all patients provided a written informed consent.

ASD/PFO closure

The heart team determined the indication for ASD/PFO closure according to the European guidelines[1]. Percutaneous ASD/PFO closure was performed under general anesthesia and TEE guidance and an Amplatzer Septal or PFO Occluder (Abbott Vascular Inc., Santa Clara, CA, USA) of appropriate size was implanted.

Echocardiographic data:

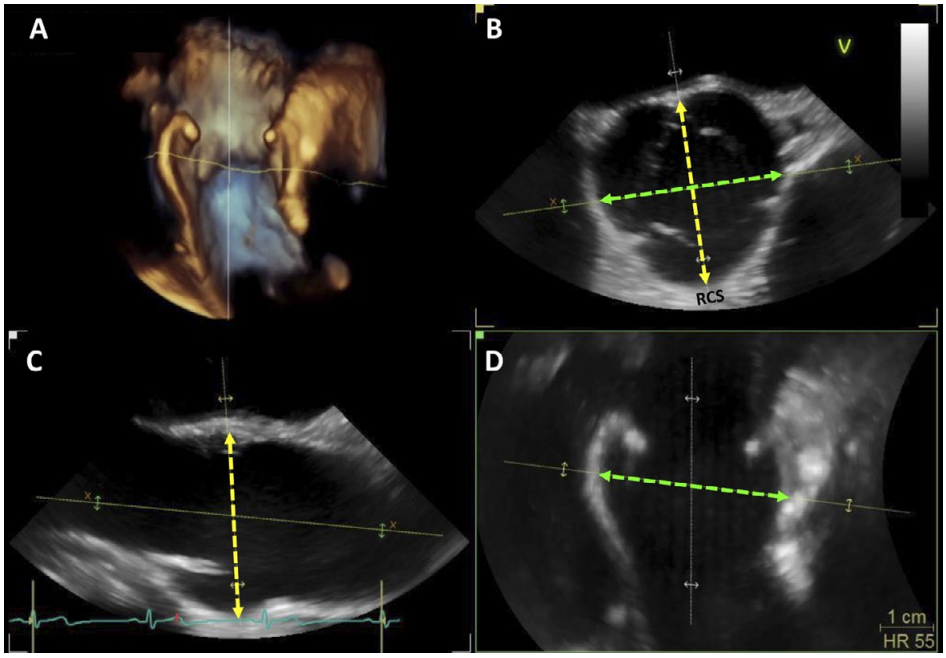
Image acquisition:

Standard preprocedural transthoracic and transesophageal echocardiography were performed to assess: 1) ASD dimensions and sufficiency of septal rims (aortic, superior vena cava, posterior, inferior vena cava, and atrio-ventricular), 2) PFO features, including tunnel length, and 3) interatrial septum features, including total septal length (TSL) and the presence of atrial septal aneurysm (ASA). Intraprocedural transesophageal echocardiographic images were acquired using Vivid E95 machine (GE Healthcare, Horten, Norway) by an experienced imaging cardiologist (BJB). A predefined 3D image acquisition protocol was applied and entailed a detailed visualization of the aortic valve and root before closure, and the Amplatzer occluder and the aortic valve and root after closure. 3D images were acquired in the long-axis view, including the left ventricular outflow tract up to the highest visible part of the ascending aorta, with frame rate of >10 frames/second (19±8.5 pre-closure, 19±8.6 post-closure). Directly after occluder implantation, paired views of the same angle and aortic position were obtained. Analyses were performed offline on EchoPAC PC v.201 (GE Healthcare) by two investigators (MN and MA) who were blinded to patient characteristics and device properties.

2D short-axis views of the ascending aorta were obtained at the mid-sinus of Valsalva (SOV) level. The frame rate was kept >50 frames/second (91±30 pre-closure, 98±28 post-closure). 2D-ST analysis was retrospectively performed on the 2D short-axis images of the mid- SOV if the entire aortic wall contour was captured and the frame rate was adequate. These criteria were fulfilled in 40/65 patients included in the study, and 2D-ST analysis was therefore confined to this subgroup of patients.

3D-TEE data processing and analysis:

Assessment of aortic root dimensions: Aortic root dimensions were assessed both in systole (in a mid-systolic frame showing the maximal aortic valve excursion) and in late diastole; before as well as after occluder implantation. Two orthogonal long-axis (LAX) planes of the aortic root (antero-posterior and medio-lateral) and a third short-axis (SAX) plane perpendicular to the LAX planes were extracted from the zoomed 3D datasets using the multiplanar reconstruction mode. The LAX planes were manipulated to be parallel to the LAX of the left ventricular outflow tract and the proximal ascending aorta.



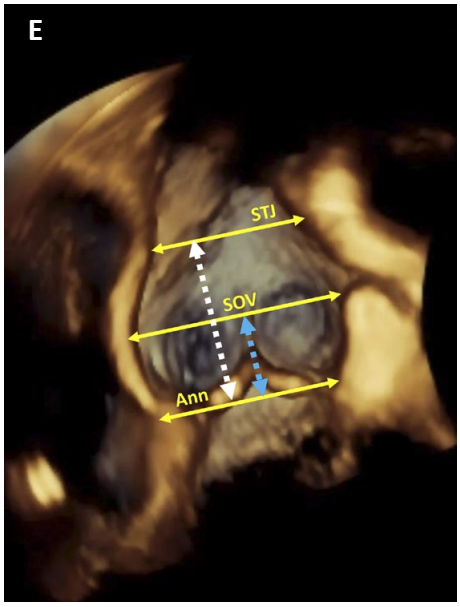


Figure 1. 3D-TEE analysis of aortic root dimensions. From the 3D-zoom datasets, 3 planes are derived: 2 long-axis views (antero-posterior displayed in **panel C** and medio-lateral displayed in **panel D**) and a short-axis view orthogonal to these long-axis views (**panel B**). The short-axis view was adjusted to cut through the maximum dimension of the sinus of Valsalva (SOV). The antero-posterior long axis plane was then further adjusted to cut through the middle of the right coronary sinus (RCS) and the medio-lateral plane was adjusted to be exactly perpendicular to it. The SOV maximum antero-posterior and medio-lateral diameters are represented by the interrupted yellow and green double-arrows, respectively. Measurement of these two dimensions was performed in the short-axis view and confirmed in the corresponding long-axis view. **Panel E**: From a long axis view, the aortic valve annulus plane (Ann), the plane of sinus of Valsalva Dmax (SOV), and the sino-tubular junction plane (STJ) were identified. The vertical distance from Ann to STJ represents the SOV height (white interrupted double-arrow) while the distance from the Ann to the SOV represents the "Annulus-to-Dmax distance" (blue interrupted double-arrow). Please note that the actual measurements were measured from the 2D slices of the 3D image.

The SAX plane was manipulated to cut through the plane of the SOV maximal dimension (Dmax). The antero-posterior LAX plane was then re-adjusted to bisect the right coronary sinus. The medio-lateral LAX plane was manipulated to be exactly perpendicular to the antero-posterior LAX plane (Figure 1). The SOV antero-posterior and medio-lateral Dmax were measured in the SAX plane and confirmed in the respective perpendicular LAX plane (Figure 1), and their average (Dmean) and ratio (SOV eccentricity) were calculated. From the antero-posterior LAX plane, the SOV height was measured as the distance between the plane of aortic valve annulus and the sinotubular junction. The annulus-to-Dmax distance was also measured in the same plane (Figure 1.E).

Assessment of the occluder-aorta interaction: In the final post-occluder implantation 3D dataset, the cropping mode was used to let the two LAX planes cut through the two discs of the occluder (Figure 2). The SAX plane was then re-adjusted to cut through the aortic root at the level of the occluder-aorta interface (the point of maximum approximation, contact, or impingement). The distance between the aortic annulus and that level (annulus to occluder-aorta interface) was measured in LAX view(s). Using live mode, the dynamic relationship between the occluder and the aortic root was assessed in the LAX and SAX planes in at least five cardiac cycles, and classified into: no contact

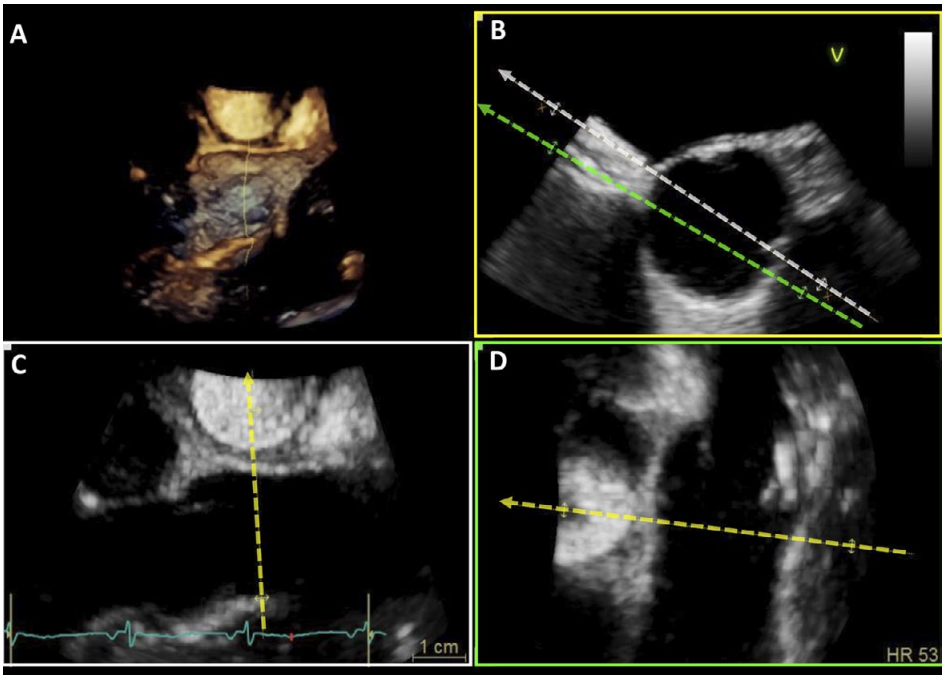


Figure 2. 3D-TEE analysis of the interaction between the occluder and the aortic root. From the 3D-zoom dataset (**panel A**), the SAX plane was used to adjust the LAX planes to cut through the atrial discs of the occluder device (**panel B**). The 2 LAX planes were then used to re-adjust the SAX plane to cut through the plane of the occluder-aortic root interface (maximum contact) (**panels C and D**).

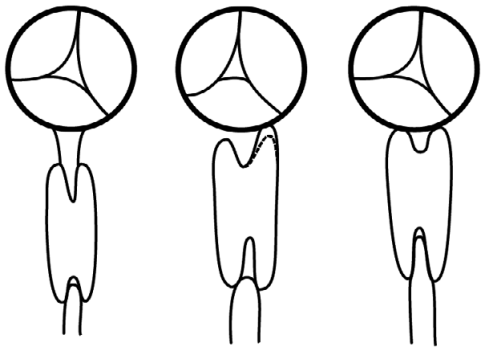


Figure 3. Patterns of interaction between the occluder and the aortic root. Three patterns of occluder-aorta interaction were identified on 3D-TEE: no contact (left panel), intermittent contact (middle panel), and continuous contact (right panel).

(no direct apposition between the occluder and the aortic root), intermittent contact (at systole and/or diastole), and continuous contact (throughout the cardiac cycle) (Figure 3 and Videos 1 and 2).

2D speckle tracking (2D-ST) data processing and analysis:
Regional and global ascending aortic wall deformation was analyzed off-line using high frame rate SAX images of the mid-SOV. A line was manually drawn along the inner side of the aortic wall and the software then automatically generated an additional outer line near the outer side of the vessel wall (Figure S1). Given the small thickness of the aortic wall in comparison with myocardial thickness, the width of the region of interest was reduced to a minimum[16,17]. A cine loop was previewed to confirm that the region of interest follows the aortic wall motion throughout the cardiac cycle, otherwise manual adjustment was applied. The aortic wall was divided into six equal segments[17,18], the first being the septal segment extending from 9 to 11 o'clock (Figure S1). Analysis began after the time point of aortic valve closure as manually marked after inspection of the echocardiographic cine loop. Radial and circumferential strains were calculated and their values were color-coded and also represented as quantitative curves plotted against time (Figure 4). Numeric values for strain in each of the 6 segments of the aortic wall represented the mean values derived from all points in the segment. Additionally, global circumferential strain (GCS) was calculated as the average of all segments. Minimal and maximal strain were measured both in systole and diastole.

Statistical analysis

Analyses were performed on SPSS v.24 (IBM Corp., Armonk, NY, USA). Data are summarized as mean ± standard deviation, median [25th-75th percentile], or frequency (percentage) according to variable type and distribution. The two-tailed paired- and

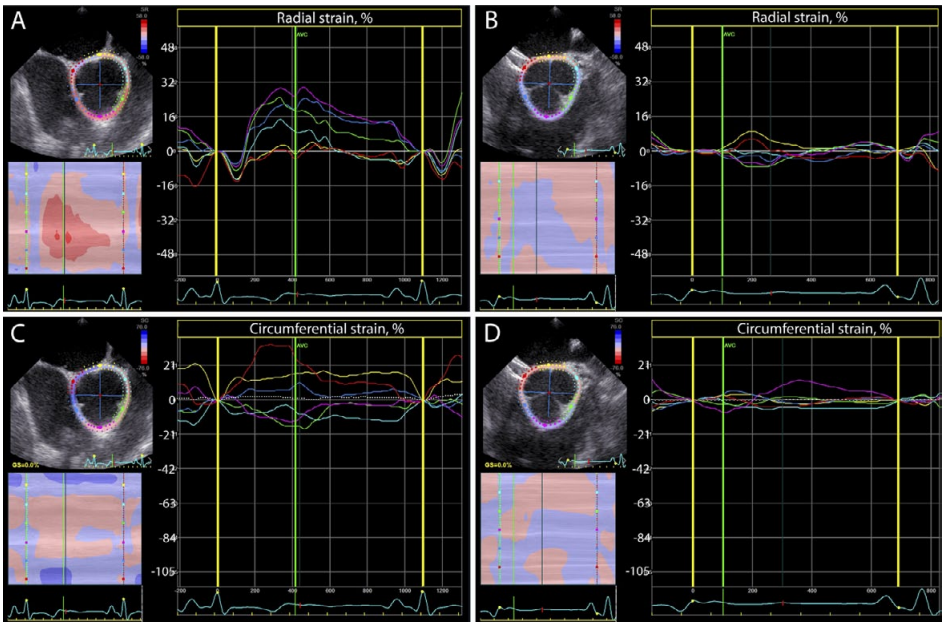


Figure 4. 2D-ST analysis. Radial and circumferential strain of a 47-year-old male PFO patient just before (**panels A** and **C**) and directly after device implantation (**panels B** and **D**), showing reduction of radial and circumferential strain. Each curve corresponds to one of the six segments of the aortic wall (see Figure S1), the red representing the right-posterior segment, etc. The green vertical line corresponds to the manually determined time point of aortic valve closure (AVC). For corresponding 3D analysis, please see Figure S2.

independent t-tests and the Mann-Whitney U test were used for paired- and between-group comparisons of continuous variables, as appropriate. Categorical variables were compared using the Chi-square test. Correlations were tested using the Spearman's rank-order correlation. A p value <0.05 was considered statistically significant.

RESULTS

The characteristics of the study population (age, 47±14 years; 71% females) are summarized in Table 1.

In patients with ASD, the indication for closure was right heart volume overload in 32 patients (91%) and paradoxical embolism in three. The widest defect diameter on echocardiography was 17.5±6.5 mm, aortic rim was deficient in 21 patients (60%), and deficiency of any of the non-aortic rims was present in 8 patients (25%; atrio-ventricular rim in 6, posterior rim in 5, and superior vena cava rim in 1). The Amplatzer Septal Occluder diameter was 20.4±6.5 mm, and the most commonly used occluder size was the 18 mm (n=7). The occluder-defect diameter ratio was 1.39±1.33, occluder-body surface area (BSA) ratio was 11.1±3.8 cm/m^2, and the occluder-TSL ratio was 0.41±0.19.

Table 1. Baseline characteristics of the study population.

	ASD (n=35)	PFO (n=30)	*p* value
Demographics			
Age, y	48.4 ±16.6	44.6 ±10.1	0.256
Female	30 (86%)	16 (53%)	0.006
Body surface area (BSA), m^2	1.85±0.20	1.91±0.18	0.259
Cardiac comorbidities			
Hypertension	12 (34.3%)	1 (3.3%)	0.002
Atrial fibrillation	14 (40.0%)	0	<0.001
Aortic root dimensions			
Systolic			
SOV height	19.5±3.2	21.2±4.6	0.110
SOV antero-posterior Dmax	29.8±2.9	31.5±4.4	0.088
SOV medio-lateral Dmax	30.3±2.9	31.2±3.9	0.319
SOV Dmean	30.0±2.7	31.4±4.0	0.143
SOV eccentricity	1.33±1.45	0.71±2.11	0.196
Annulus-to-Dmax distance	11.2±2.0	10.8±2.5	0.452
Diastolic			
SOV height	19.6±3.4	21.0±4.8	0.204
SOV antero-posterior Dmax	29.1±2.6	30.5±4.0	0.113
SOV medio-lateral Dmax	29.3±2.9	30.6±3.6	0.120
SOV Dmean	29.2±2.6	30.6±3.7	0.089
SOV eccentricity	1.02±1.17	1.06±2.0	0.936
Annulus-to-Dmax distance	10.6±2.3	10.2±2.3	0.433
Inter-atrial septum			
Total septal length (TSL), mm	53.5±13.0	44.9±6.4	0.001
Atrial septal aneurysm	8 (22.9%)	3 (10.0%)	0.201
Occluder size			
Occluder diameter, mm	20.4±6.5	25.4±2.8	<0.001
Occluder-BSA ratio, cm/m^2	11.1±3.8	13.4±1.8	0.003
Occluder-TSL ratio	0.41±0.19	0.57±0.09	<0.001

Data are presented as mean ± SD or frequencies (%). ASD= Atrial septal defect; PFO= Patent foramen ovale; SOV= Sinus of Valsalva; D= Diameter; max= Maximum.

The indication for PFO closure was paradoxical embolism in 27 patients (90%) and platypnea orthodeoxia symptoms in three. PFO tunnel length was in average 10.4±3.3 mm. The Amplatzer PFO Occluder diameter was 25.4±2.8 mm (18 mm in 2 patients, 25 mm in 23, and 30 mm in 5), the occluder-BSA ratio was 13.4±1.8 cm/m^2, and the occluder-TSL ratio was 0.57±0.09.

Compared to PFO patients, those with an ASD were more likely females (86% vs. 53%, p=0.006) and hypertensive (34% vs. 3%, p=0.002), and more often had atrial fibrillation

(40% vs. 0%, p<0.001). Both groups were comparable regarding aortic root dimensions. TSL was smaller while occluder diameter, occluder-BSA ratio, and occluder-TSL ratio were larger in PFO than in ASD patients (Table 1).

The occluder-aorta relationship on 3D-TEE:

As shown in Table 2, the vast majority of occluders (93.8%) were in contact with the aortic root (ASD, 91.4%; PFO, 96.7%). The contact was continuous throughout the cardiac cycle in 73.8% of patients, and was intermittent in 20%. In patients with an ASD, occluder-aorta contact was very common not only in those with an aortic rim <5 mm (100%), but also in patients with an aortic rim ≥5 mm (79%). However, patients with an aortic rim <5 mm had a higher likelihood of a continuous occluder-aorta contact as compared to

Table 2. Occluder contact with the aortic root.

	Device contact		
	No contact	**Intermittent contact**	**Continuous contact**
Total	4 (6.2%)	13 (20.0%)	48 (73.8%)
ASD	3 (8.6%)	5 (14.3%)	27 (77.1%)
Aortic rim ≥5mm	3 (21.4%)	4 (28.6%)	7 (50.0%)
Aortic rim <5mm	0	1 (4.8%)	20 (95.2%)
PFO	1 (3.3%)	8 (26.7%)	21 (70.0%)

The relationship of the closure device and the aortic root for the total study cohort and for ASD (n=35) and PFO (n=30) separately. ASDs are divided into aortic rim ≥5mm (n=14) and <5mm (n=21).

Table 3. Comparison of anatomical and occluder characteristics in patients with vs. without continuous occluder-aorta contact

	No/intermittent occluder-aorta contact (n=17)	**Continuous occluder-aorta contact (n=48)**	**p value***
Body surface area (BSA), m^2	1.91 (1.74 - 1.98)	1.88 (1.73 - 2.03)	0.858
ASD vs. PFO			0.579
ASD	8 (47.1%)	27 (56.3%)	
Deficient AoR[§]	*1 (12.5%)*	*20 (74.1%)*	0.003
Deficient non-AoR[§]	*1 (12.5%)*	*7 (25.9%)*	0.642
PFO	9 (52.9%)	21 (43.8%)	
Total septal length (TSL), mm	52.0 (39.0 - 60.5)	47.0 (44.0 – 54.0)	0.897
SOV systolic D_{mean}, mm	30.3 (27.3 - 31.7)	30.8 (28.2 – 33.0)	0.403
Occluder diameter, mm	25.0 (19.0 - 25.0)	25.0 (18.0 - 25.0)	0.759
Occluder-BSA ratio	12.3 (10.0 - 14.9)	12.1 (9.5 - 14.6)	0.846
Occluder-TSL ratio	0.45 (0.37 - 0.63)	0.51 (0.34 - 0.57)	0.820

*Mann-Whitney U or chi square tests.
[§]Among ASD patients
SOV, sinus of Valsalva

patients with an aortic rim ≥5 mm (no contact: 0 vs. 21%; intermittent contact: 5% vs. 29%; and continuous contact: 95% vs. 50%; in patients with aortic rim <5 mm vs. ≥5 mm, respectively; p=0.007) (Table 2). On the other hand, neither deficiency of a non-aortic rim (in ASD patients) nor tunnel length (in case of PFO) had a significant influence on the pattern of occluder-aorta relationship. Table 3 summarizes the anatomical and occluder characteristics in patients without vs. with continuous occluder-aorta contact.

The point of occluder-aorta interface was above the level of the SOV Dmax in the majority of cases, and was in average 14.1±5.8 mm above the aortic valve annulus plane (13.9±6.7 mm in ASD vs. 14.3±4.5 mm in PFO, p=0.74) (Figure 5).

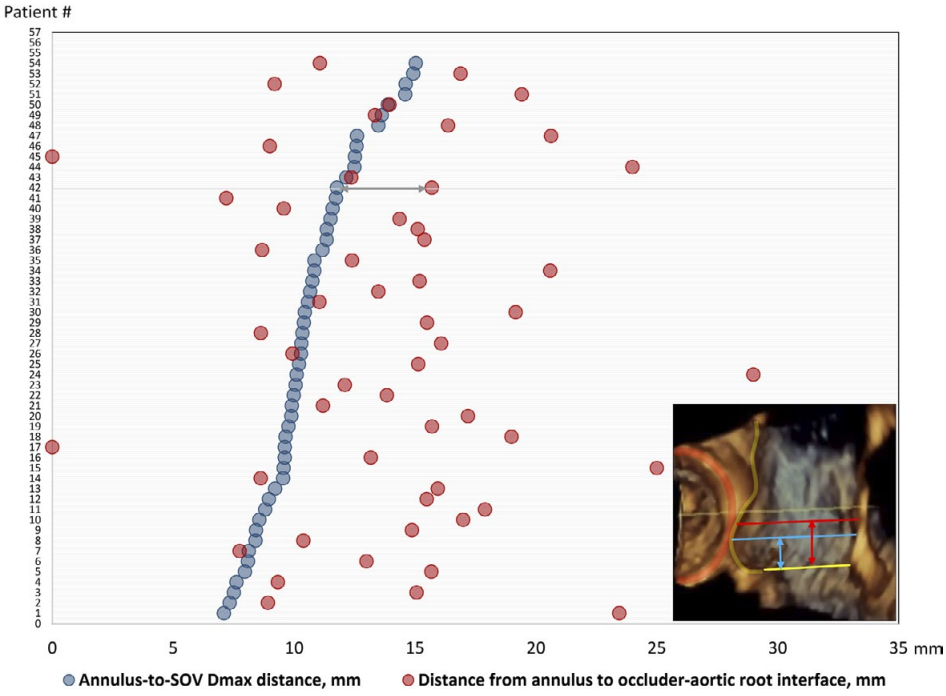


Figure 5. The distance from the annulus to the SOV Dmax and to the occluder-aorta interface. The figure displays data from 57 patients with adequate images for both parameters. Patients (number on y axis) are ordered according to the annulus-to-SOV Dmax distance (blue dots), where patient #1 has the shortest distance and patient #57 has the largest. The distance from the annulus to the occluder-aorta interface (red dots) was greater than the annulus-to-Dmax distance (i.e. occluder-aorta interface at a higher level than SOV Dmax) in the majority of cases. In two patients (both received a 14 mm Amplatzer septal occluder), the device came in contact with the aortic root low at the level of the annulus (distance = 0; patients #17 and #45). The right lower panel displays an example (patient #42) where the occluder-aorta interface (15.7 mm above the annulus plane) is higher than the SOV Dmax level (11.8 mm above the annulus plane). The distance between the two levels is represented by the double-head grey arrow.

Changes in aortic root geometry and mechanics after occluder implantation:

An example case of the 3D analysis of aortic root geometry is shown in Figure S2. As shown in Table S1, aortic root dimensions did not significantly differ from before to after closure of ASD with an aortic rim ≥5 mm. On the other hand, patients with an ASD and an aortic rim <5 mm and those with a PFO showed a small, yet significant, increase in diastolic SOV antero-posterior Dmax.

For 2D-ST analysis, the average number of analyzed segments was 5.0±1.3 per echocardiogram, the left-posterior segment being the least trackable. Overall, the segmental values of circumferential and radial strain (Figure 6) as well as GCS (Table S2) did not change significantly after occluder implantation. However, radial strain tended to decrease in the segments closest to the atrial septum while circumferential strain tended

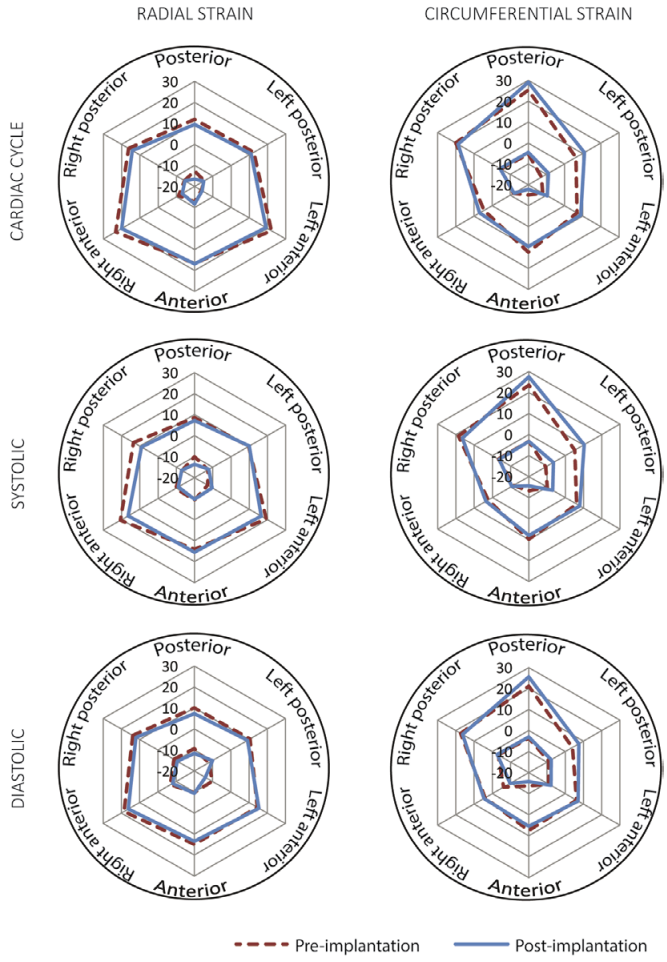


Figure 6. Radial and circumferential strain for the six aortic wall segments. Strain is given as percentages. The outer and inner circles represent peak and minimal strain respectively.

to increase in the contralateral segments (Figure 6). As shown in Table S3, GCS was not different between ASD and PFO patients neither at baseline nor after closure. On the other hand, the pattern of occluder-aorta contact was associated with a differential pattern of GCS change. While minimum GCS decreased in patients with no/intermittent occluder-aorta contact, it increased in those with a continuous contact (Table S4). Consequently, post-closure minimum GCS was significantly higher in patients with continuous vs. no/intermittent occluder-aorta contact, while it was similar at baseline.

In ASD patients, post-closure peak diastolic GCS correlated negatively with the occluder size (Spearman correlation coefficient = −0.52, p=0.015) and with the occluder-BSA ratio (Spearman correlation coefficient = −0.68, p=0.001) (Table 4). Post-closure 2D-ST parameters did not correlate with occluder characteristics in PFO patients.

Table 4. Correlation between post-closure global circumferential strain and occluder characteristics.

	Occluder size	Occluder/ defect ratio	Occluder/ BSA ratio	Occluder/ TSL ratio
Atrial septal defect (n=21)				
Maximum GCS				
Cardiac cycle	-0.282	0.130	-0.390	-0.260
Systolic	-0.105	0.198	-0.202	0.137
Diastolic	**-0.522***	0.262	**-0.684****	-0.391
Minimum GCS				
Cardiac cycle	-0.031	0.147	-0.231	0.029
Systolic	0.014	0.227	-0.235	0.090
Diastolic	-0.126	-0.037	-0.275	0.054
Patent foramen ovale (n=19)				
Maximum GCS				
Cardiac cycle	0.025	NA	-0.220	-0.120
Systolic	-0.021	NA	-0.288	-0.172
Diastolic	-0.164	NA	-0.429	-0.343
Minimum GCS				
Cardiac cycle	-0.022	NA	-0.248	-0.374
Systolic	0.231	NA	-0.104	-0.275
Diastolic	0.084	NA	-0.230	-0.449

Data are the Spearman correlation coefficient.
*P≤0.01. **P=0.001.
GCS= global circumferential strain

Clinical outcomes:

At latest clinical follow up (mean 354 days; median[IQR]: 204[181-512] days), all ASD patients with dyspnea symptoms at baseline -but one- demonstrated improvement of

the functional status after closure (from NYHA II to I in 8 and from NYHA III to II in 3). No patients in the PFO group presented with recurrent cerebrovascular accidents during follow up. Five patients required hospitalization due to cardiac causes (n=1 elective PCI, n=4 atrial fibrillation/ flutter). One 69-year-old ASD patient had new-onset paroxysmal atrial fibrillation after closure. Throughout follow up, no cases of device erosion, cardiac tamponade, or unexplained death were documented.

DISCUSSION

The main findings of the present study can be summarized as follows: 1) a precise assessment of the occluder-aorta relationship can be achieved by 3D-TEE; 2) a close mechanical contact between interatrial occluders and the aortic root is more common than previously thought and is not confined to patients with ASD and a deficient aortic rim; 3) in spite of the occluder-aorta contact in the majority of cases, no gross changes of the aortic root geometry/mechanics were seen after occluder implantation; and 4) the pattern of occluder-aorta contact and the occluder-BSA ratio influence aortic root strain after occluder implantation.

Since this is the first study to evaluate the changes in aortic root 3D geometry and mechanics in relation to septal occluder implantation, there are no established methods to apply in this field. 3D-TEE has been shown to yield an assessment of aortic root geometry that is comparable to computed tomography[19,20] and 2D-ST has been shown effective in assessing aortic root mechanics in a number of cardiovascular conditions[17,21]. Therefore, we used these two modalities in our study.

3D-TEE findings:

We detected a direct contact of the septal occluder with the aorta in all patients with an ASD and a deficient aortic rim. Unexpectedly, occluder-aorta contact was also observed in the majority of patients with an ASD and an adequate aortic rim as well as in patients with a PFO. While it is important to know that the occluder touches the aorta in the majority of patients after ASD/PFO closure, more importantly this contact should not be considered per se as a risk factor for device erosion, being very common and being not associated with clinical erosions in our cohort at a mean follow up of 354 days. Other aspects of the occluder-aorta interaction (e.g. malalignment and indentation) as well as the pattern of contact (continuous vs. intermittent) could be more specific surrogates of erosion risk and should be further explored in future studies. Although "continuous contact" pattern has been observed more frequently in patients with ASD and a deficient aortic rim, the "intermittent" pattern has been suggested by some experts as a risk factor for device erosion[15].

Freedom from an occluder-aorta contact was 21% in patients with an ASD and a sufficient aortic rim, but was rare in patients with a PFO (3%) and lacking (0%) in patients with an ASD and a deficient aortic rim. In these two latter groups, the antero-posterior SOV diameter (measured in diastole) showed an increase as compared to pre-closure measurement. This expansion seems to compensate for the constrained motion in the medio-lateral axis by the occluder. Put together, an ASD with a sufficient aortic rim seems to be the most favorable scenario where a continuous occluder-aorta contact is least likely and no measurable change in aortic root dimensions is seen after closure. On the other hand, ASDs with deficient aortic rims as well as PFOs are characterized by a higher likelihood of continuous occluder-aorta contact and of measurable geometrical change of the aorta after closure. Although one may assume that PFO occluder placement would have similar effect to placement of an occluder in patients with an ASD and a sufficient aortic rim, the observations listed in Table 1 (i.e. shorter septal length together with larger absolute and relative occluder diameters in PFO cases) suggest that a relatively large PFO occluder is commonly "constrained" by a non-capacious landing zone. In line with our findings, previous reports have indeed documented early and late device erosion after device closure of ASD with sufficient rims as well as after PFO closure[30-32].

Determining the level at which the occluder-aorta interface is maximum was possible thanks to 3D imaging. The cropping mode enabled manipulation of the imaging plane to cut through the occluder discs at the level of their maximum interface with the aorta. The level of this interface was in average 14 mm above the aortic valve annulus, but varied considerably from patient to patient. In the majority of cases, the occluder-aorta interface was at a higher plane than the SOV Dmax; while it was lower than the SOV Dmax level in few cases. From these data, a certain level in the aortic root that is particularly exposed to the occluder-induced stresses cannot be identified. In two of our patients, the occluder-aorta interface was very low lying at the annulus plane (Figure 5). This contact between the occluder and the aortic valve annulus could be the mechanism of new/worsening aortic valve regurgitation (AR) described in previous studies as a complication of ASD/PFO percutaneous closure[11,22]. Interestingly, in both cases (both had an ASD), the occluder size was relatively small (14 mm). Although such occluder-annulus contact could be a logical mechanism of new/worsening AR, this explanation remains speculative and should be explored in future studies. In our cohort, validation of this concept was not possible as we observed no cases of new >mild AR after ASD/PFO closure.

It should be kept in mind that our observations describe the occluder-aorta relationship early after the procedure. Thereafter, atrial and device remodeling[23] could lead to a change in this relationship, especially after ASD closure. Notwithstanding, according to the largest series of cardiac erosion after ASD device closure, one third of erosion cases

takes place within 24 hours after occluder implantation[10], emphasizing the importance of this early post-closure period. Moreover, the time directly after implantation is important for the decision to leave the device in place or to remove it and evaluation at a later time point is less relevant to this decision.

2D-ST findings:

The aortic root is known to have conformational changes during the cardiac cycle that contribute to a normal function of the aortic valve[24-26]. Therefore, derangements of aortic root mechanics could alter the physiology of the aortic valve complex.

2D-ST has been shown to be a feasible and reproducible method to assess the ascending aortic wall deformation[17]. The major finding of this analysis was that, in spite of the close occluder-aorta contact in the majority of cases, no gross change in aortic wall strain was detected after occluder implantation. However, some modest changes have been observed and should be interpreted with caution until further confirmed in future studies. Although did not reach statistical significance, the aortic wall thinned out (radial strain reduced) in the segments adjacent to the occluder, and expanded (circumferential strain increased) at the contralateral side of the aortic wall after occluder implantation (Figure 6), possibly as a result of device impingement on aortic wall. Additionally, minimum GCS tended to increase in patients with a continuous occluder-aorta contact and to decrease in patients with other patterns of occluder-aorta relationship, denoting that the pattern of occluder-aorta relationship has an impact on aortic root mechanics. In addition to the occluder-aorta relationship, occluder size was found to influence aortic root strain. Peak diastolic GCS displayed a negative correlation with the occluder size. Indexing the occluder size to the BSA correlated even more strongly with peak diastolic GCS. On the other hand, the occluder-TSL ratio did not display a significant correlation with GCS.

Relative risk factors of cardiac erosion by atrial septal occluders:

Most device erosions occur early after implantation, but the risk of erosion continues up to years after device implantation[27]. The most frequently reported potential risk factor is a deficient aortic (anterior-superior) rim[10,13,27,28]. Since a large proportion of patients eligible for ASD closure (40-60%) have insufficient aortic rim[14,29], a causal relationship with occluder erosion remains uncertain. We found in patients with an ASD that a "sufficient" aortic rim did not guarantee freedom from occluder-aorta interface, and that a "deficient" aortic rim was associated with a higher likelihood of occluder-aorta contact, especially the "continuous" pattern. These results, on the one hand, further supports that an aortic rim <5 mm should be considered "deficient", but, on the other hand, challenges considering that aortic rims ≥5 mm are always "sufficient" to keep the occluder and the aorta apart.

In the largest series of cardiac erosions after ASD closure[10], the location of erosion was most commonly the aortic root (54%) and seven out of nine deaths occurred as a result of erosion into the aortic root. On echocardiography, the occluder was remote from the SOV wall in 13% of patients with no erosion but in no single case in the erosion group. Additionally, SOV wall was more often indented by the occluder in the erosion group than in the control group. However, this finding (aortic wall indentation by the occluder) was relatively common in the control group as well. Put together with our findings, it can be suggested that patients with adequate rim(s) and no obvious occluder-aorta contact have a negligible risk of erosion. However, the risk of erosion in those with one or more of these criteria remains low, denoting that these criteria have a high sensitivity but a poor specificity to predict erosion. The authors[10] also indexed the occluder size to the body weight (BSA being not available for analysis), and a larger occluder size relative to body weight was an independent predictor of the risk of erosion. Put together with our observation of a reduced aortic wall strain in patients with a large occluder-BSA ratio, the patient's body size (BSA and weight) should be considered when choosing the occluder size, bearing in mind that the larger the occluder relative to the patient's body size, the more it will impact on aortic root mechanics.

Limitations

The major limitation of this study is the small cohort size and its descriptive nature, even though this is a hypothesis-generating study. Percutaneous closure of ASD causes instantaneous hemodynamic changes resulting from shunt closure. Therefore, the results of the impact of occluder implantation on aortic root geometry and mechanics may have been confounded by the simultaneously changing hemodynamic circumstances. Only direct post-closure changes were studied; aortic root geometry and mechanics may change during longer-term follow-up post-closure, as a result of device repositioning from device/atrial remodeling especially after ASD closure. However, immediate post-implantation evaluation is important for the decision to leave the device in place or to remove it. Finally, our 3D echocardiographic imaging was focused on the occluder-aorta interface. The relationship between the occluder and other nearby structures (e.g. valves and venous structures) should be explored in future research.

CONCLUSIONS

This exploratory study shows that the spatial relationship between inter-atrial septal occluders and the aortic root can be precisely evaluated using 3D-TEE. Most occluders are in close contact with the aortic root even in patients with an ASD and an adequate aortic rim and those with a PFO. The most important factor determining the pattern

of occluder-aorta contact was a deficient aortic rim, causing a characteristic pattern of aortic root strain change. Although not powered for clinical endpoints, the study results pave the way to understanding the mechanisms behind erosion and suggest routine acquisition of 3D-TEE images during all closure procedures, followed by case-control analysis of images when erosions occur.

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SUPPLEMENTAL DATA

Table S1. Aortic root geometric changes after occluder implantation.

	Baseline	Mean difference (95% CI)	P-value*
Atrial septal defect			
ASD with aortic rim ≥5mm			
Systolic			
SOV height, mm	19.0 ±2.7	−0.59 (−2.00 - 0.82)	0.364
SOV antero-posterior Dmax, mm	28.7 ±2.1	0.15 (−0.66 - 0.97)	0.692
SOV medio-lateral Dmax, mm	29.4 ±2.8	0.47 (−0.65 - 1.60)	0.378
SOV Dmean, mm	29.0 ±2.3	0.31 (−0.56 - 1.18)	0.455
SOV eccentricity	0.92 ±1.4	−0.23 (−0.85 - 0.39)	0.431
Annulus-to-Dmax distance, mm	11.0 ±1.3	−1.16 (−2.42 - 0.10)	0.067
Diastolic			
SOV height, mm	18.3 ±3.7	−0.52 (−2.08 - 1.04)	0.473
SOV antero-posterior Dmax, mm	28.1 ±2.1	−0.56 (−1.17 - 0.05)	0.069
SOV medio-lateral Dmax, mm	28.5 ±3.0	0.19 (−0.84 - 1.23)	0.692
SOV Dmean, mm	28.3 ±2.5	−0.16 (−0.82 - 0.49)	0.600
SOV eccentricity	0.63 ±1.1	0.44 (−0.37 - 1.25)	0.259
Annulus-to-Dmax distance, mm	10.1 ±1.8	−1.14 (−2.31 - 0.03)	0.056
ASD with aortic rim <5mm			
Systolic			
SOV height, mm	20.2 ±3.3	0.31 (−0.56 - 1.19)	0.461
SOV antero-posterior Dmax, mm	30.6 ±3.1	0.06 (−0.56 - 0.67)	0.853
SOV medio-lateral Dmax, mm	30.9 ±2.9	−0.62 (−1.26 - 0.01)	0.053
SOV Dmean, mm	30.6 ±2.8	−0.25 (−0.70 - 0.20)	0.262
SOV eccentricity	1.6 ±1.5	−0.75 (−1.64 - 0.14)	0.095
Annulus-to-Dmax distance, mm	11.1 ±2.3	−0.14 (−1.23 - 0.94)	0.789
Diastolic			
SOV height, mm	20.3 ±3.2	−0.19 (−1.10 - 0.72)	0.660
SOV antero-posterior Dmax, mm	29.7 ±2.8	0.48 (0.07 - 0.90)	0.025
SOV medio-lateral Dmax, mm	29.8 ±2.7	0.29 (−0.32 - 0.90)	0.333
SOV Dmean, mm	29.7 ±2.6	0.38 (−0.04 - 0.81)	0.075
SOV eccentricity	1.3 ±1.2	−0.19 (−0.82 - 0.45)	0.551
Annulus-to-Dmax distance, mm	10.7 ±2.4	−0.23 (−1.15 - 0.68)	0.599
Patent foramen ovale			
Systolic			
SOV height, mm	21.2 ±4.6	0.29 (−0.84 - 1.42)	0.600
SOV antero-posterior Dmax, mm	31.5 ±4.4	0.19 (−0.29 - 0.67)	0.421
SOV medio-lateral Dmax, mm	31.2 ±3.9	0.13 (−0.47 - 0.73)	0.667

Table S1. (*continued*)

	Baseline	Mean difference (95% CI)	P-value*
SOV Dmean, mm	31.3 ±4.0	0.16 (–0.21 - 0.53)	0.387
SOV eccentricity	0.71 ±2.1	–0.07 (–0.86 - 0.73)	0.867
Annulus-to-Dmax distance, mm	10.8 ±2.2	0.26 (–0.51 - 1.04)	0.490
Diastolic			
SOV height, mm	20.9 ±4.9	–0.02 (–0.70 - 0.67)	0.963
SOV antero-posterior Dmax, mm	30.5 ±4.0	0.34 (0.01 - 0.67)	0.045
SOV medio-lateral Dmax, mm	30.5 ±3.7	0.22 (–0.36 - 0.80)	0.441
SOV Dmean, mm	30.5 ±3.7	0.27 (–0.11 - 0.66)	0.159
SOV eccentricity	1.03 ±2.0	–0.10 (–0.66 - 0.46)	0.709
Annulus-to-Dmax distance, mm	10.2 ±2.3	0.13 (–0.37 - 0.63)	0.590

*Pre- vs. post-closure
SOV= Sinus of Valsalva; D= Diameter; max= Maximum.

Table S2. Global circumferential strain before and after occluder implantation in the overall population with available 2D-ST (n=40).

	Pre-closure	Post-closure	*p* value
Maximum GCS			
Cardiac cycle	2.38 (1.29 - 4.06)	2.81 (0.34 – 4.22)	0.754
Systolic	2.06 (0.00 – 3.67)	2.50 (0.00 – 4.00)	0.858
Diastolic	1.71 (0.63 – 2.66)	0.84 (0.00 – 3.22)	0.706
Minimum GCS			
Cardiac cycle	–2.09 (–5.74 - –0.92)	–2.25 (–6.25 - –0.94)	0.856
Systolic	–1.79 (–5.00 - –0.61)	–1.19 (–5.53 - 0.00)	0.892
Diastolic	–1.92 (–4.75 - –0.69)	–1.75 (–5.50 - –0.55)	0.545

Data are presented as median (25th-75th percentile).
GCS= global circumferential strain.

Table S3. Global circumferential strain before and after occluder implantation in ASD vs. PFO.

	Pre-closure			Post-closure		
	ASD (n=21)	**PFO (n=19)**	***p* value**	**ASD (n=21)**	**PFO (n=19)**	***p* value**
Maximum GCS						
Cardiac cycle	2.50 (0.87 - 5.50)	2.19 (1.81 - 3.67)	0.251	2.88 (0.22 - 4.06)	1.88 (1.16 - 4.08)	0.471
Systolic	1.75 (0.00 - 4.50)	2.06 (0.82 - 3.50)	0.509	2.81 (0.16 - 3.91)	1.69 (0.00 - 3.91)	0.593
Diastolic	2.00 (0.81 - 3.91)	1.69 (0.31 - 2.24)	0.097	0.00 (0.00 - 2.81)	1.13 (0.47 - 3.22)	0.859
Minimum GCS						
Cardiac cycle	−2.12 (-6.13 - −0.81)	−2.06 (−5.17 - −1.08)	0.984	−2.25 (−4.50 - −0.88)	−2.25 (−6.53 - −1.13)	0.665
Systolic	−1.69 (−5.50 - −0.81)	−1.88 (−4.16 - −0.28)	0.878	−1.13 (−3.94 - 0.00)	−1.25 (−6.53 - 0.00)	0.556
Diastolic	−2.12 (−4.50 - −0.81)	−1.63 (−4.33 - −0.54)	0.729	−1.75 (−3.59 - −0.81)	−1.75 (−6.30 - −0.30)	0.460

Table S4. Global circumferential strain before and after occluder implantation stratified by the pattern of occluder-aorta contact.

	Pre-closure			Post-closure		
	No continuous occluder-aorta contact (n=9)	**Continuous occluder-aorta contact (n=31)**	***p* value**	**No continuous occluder-aorta contact (n=9)**	**Continuous occluder-aorta contact (n=31)**	***p* value**
Maximum GCS						
Cardiac cycle	2.06 (0.94 - 3.56)	2.50 (1.69 - 4.16)	0.330	1.88 (1.31 - 3.50)	2.81 (0.30 - 4.94)	0.370
Systolic	0.94 (0.00 - 2.44)	2.19 (0.00 - 3.86)	0.249	1.31 (0.31 - 3.44)	2.75 (0.00 - 4.63)	0.354
Diastolic	1.72 (0.81 - 2.84)	1.69 (0.63 - 2.47)	0.908	0.62 (0.00 - 0.87)	1.13 (0.00 - 3.69)	0.250
Minimum GCS						
Cardiac cycle	−2.41 (−5.00 - −1.19)	−2.06 (−5.91 - −0.92)	0.781	−1.31 (−2.19 - −0.81)	−2.81 (−6.84 - −1.13)	0.014
Systolic	−2.41 (−4.38 - −0.81)	−1.63 (−5.00 - −0.61)	0.811	−0.88 (−1.25 - 0.00)	−1.63 (−6.28 - 0.00)	0.028
Diastolic	−2.06 (−5.00 - −1.19)	−1.78 (−4.13 - −0.69)	0.642	−1.31 (−1.75 - −0.81)	−2.50 (−6.05 - −0.55)	0.059

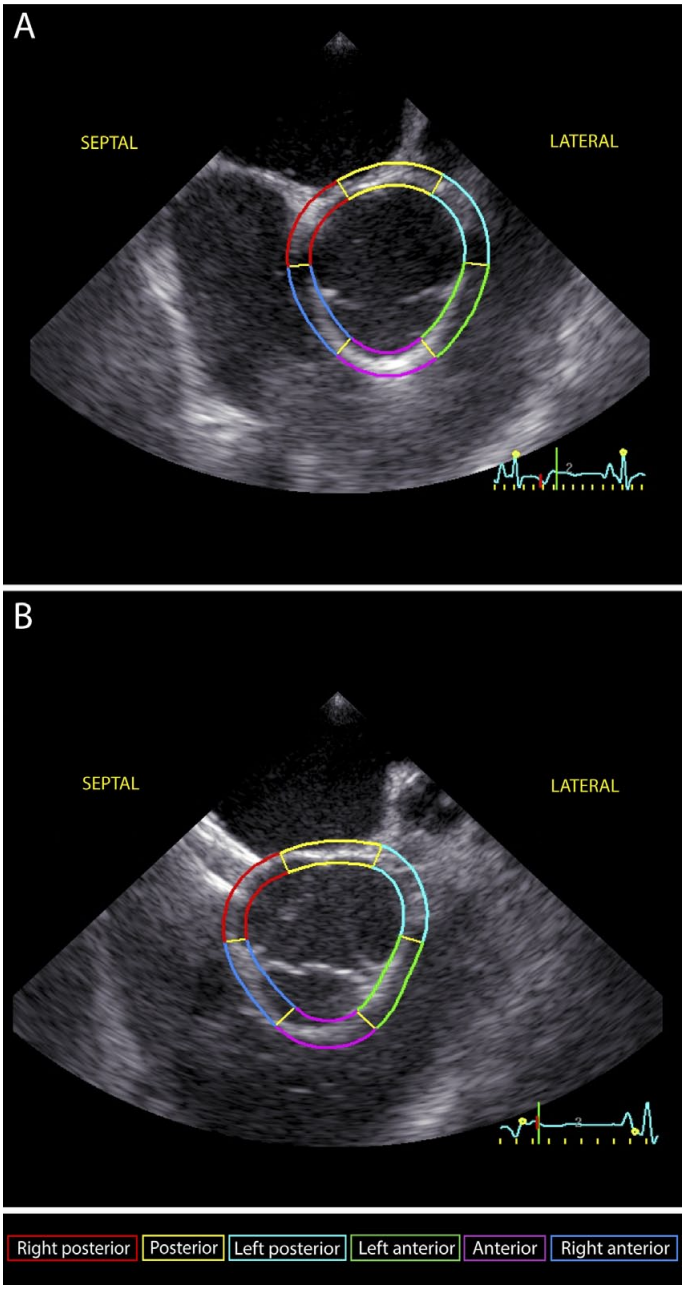


Figure S1. Tracing of the aortic wall in a PFO patient just before (**panel A**) and directly after (**panel B**) occluder implantation automatically divided into six equidistant segments.

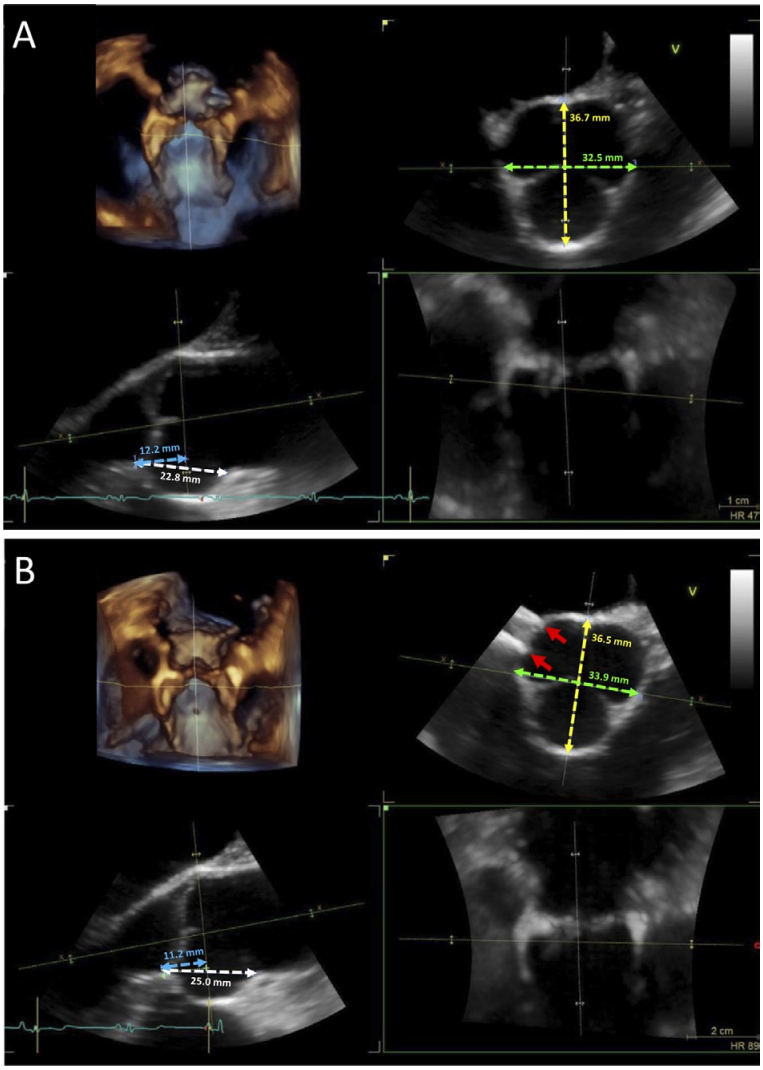


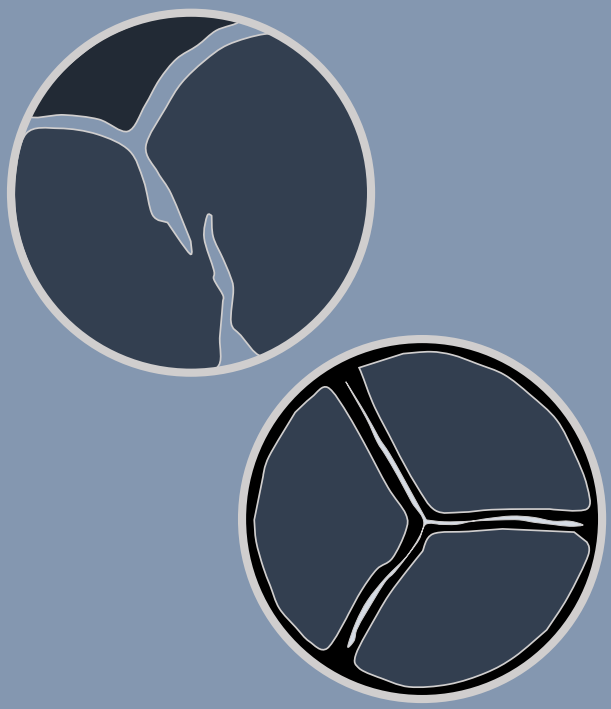
Figure S2. 3D-TEE analysis of the aortic root dimensions before (**A**) and after (**B**) Amplatzer PFO occluder implantation (the same case as in Figure 3). In spite of an overt occluder impingement on the aortic wall (red arrows in **B**) and a marked reduction of aortic wall strain after occluder implantation (Figure 3), aortic root dimensions did not show a substantial change.

Video 1. 3D-TEE dataset of the aortic root after Amplatzer septal occluder (22 mm) implantation in a 44 years old female patient with an ASD.

Video 2. 3D-TEE dataset of the aortic root after Amplatzer septal occluder (18 mm) implantation in a 38 years old female patient with an ASD.

PART D

Summary and conclusions



SAMENVATTING EN CONCLUSIES

In dit proefschrift wordt een spectrum van cardiale interventies besproken voor patiënten met structurele hartziekten: 1) uitgebreide beoordeling van de klinische toestand van de patiënt om in aanmerking te komen voor een bepaalde interventie, zowel als de waarschijnlijkheid op een significante verbetering van de klinische toestand na de procedure en 2) de centrale rol die multimodale beeldvorming speelt in de voorbereiding als wel in de bepaling van het klinische succes van de interventie.

Deel A: Transcatheter implantatie van de aortaklep: van haalbaarheid tot optimaal resultaat

Zestien jaar na de eerste transcatheter implantatie van een Aortaklep (TAVI) bij de mens door Alain Cribier is TAVI nu een gevestigde catheter techniek geworden voor een breed spectrum van patiënten met Aoklep ziekten. Haalbaarheid van de techniek is nu bereikt zelfs in de context van een uitdagende anatomie (bijv. bicuspide Aoklep ziekten). Wanneer we de grenzen van onze techniek opzoeken zijn in deel A gerichte verfijningen van de techniek beschreven met het doel de selectie van de ideale kandidaat patiënt voor TAVI te vinden (Sectie A.1), verbetering van de bepaling van de functie van de bioprothese klep (Sectie A.2) en documenteren van de late resultaten van de techniek (Sectie A.3).

Sectie A.1. Besluitvorming en verruiming van de indicaties voor TAVI

Hoofdstuk 2. Dit hoofdstuk gaat uitgebreid in op de beoordeling van de juiste indicatie voor TAVI voor de individuele patiënt. De beoordeling van de juiste klinische indicatie zoals bepaald in en door het "Hartteam" bevat de volgende criteria. 1) leeftijd, 2) waarschijnlijkheid van klinische verbetering, 3) anatomische mogelijkheden, zowel voor de toegangs weg van de catheter perifeer als cardiaal op klepniveau.

Hoofdstuk 3. In hoofdstuk 3 worden de off-label indicatie van TAVI besproken.(hooggradige Aortainsufficiëntie met valvulaire Aortastenose). Ondanks een toegenomen risico op lekkage van de prothese wordt met TAVI een klinische verbetering gezien te vergelijken met patiënten met pure valvulaire Aortastenose. Dit wordt verklaard door een vermindering van de insufficiëntie tgv de prothese., in deze subgroep waarschijnlijk tgv preconditioning van de linkerkamer. Een recente studie bevestigt onze vermoedens door dat lagere waarden van insufficiëntie worden bereikt in de nieuwe generatie prothesen (Seeger et al. Structural, Heart 1;3-4,162-167).

Sectie A.2. Beoordeling van paravalvulaire lekkage na TAVI

Dit is een sectie gericht op nadeel van TAVI dat lang werd beschouwd als de achilleshiel van deze technologie. Kwantificering van de insufficiëntie van de prothese (PVL), in

het bijzonder in het cathlab (interventiekamer) wanneer er nog steeds plaats is voor corrigerende maatregelen, is vereist maar wel een uitdaging. **Hoofdstuk 4** geeft een overzicht van gevestigde en opkomende technieken om PVL na TAVI te beoordelen. **Hoofdstuk 5** is gericht op het optimaliseren van de consistentie tussen de twee meest gebruikte methoden van PVL-beoordeling; echocardiografie en angiografie. De studie heeft een speciaal echocardiografisch algoritme voorgesteld dat steunt op multiplane en opnames uit verschillende transducerposities met kleuren-Doppler-beeldvorming. Deze aanpak correleerde beter dan de bestaande technieken met de angiografische beoordeling. **Hoofdstukken 6 en 7** introduceren een nieuw angiografisch hulpmiddel om PVL met videodensitometrie te beoordelen. De technologie is gevalideerd in een in vitro model tegen de regurgitatiefractie gemeten door een Doppler flow catheter. De studie (**hoofdstuk 6**) toonde aan dat dit middel accuraat is en suggereert enkele technische tips om dit middel praktischer en preciezer te maken. Namelijk; het beperken van het gebied van interesse tot een apart deel van -in plaats van het gehele linkerventrikel en de opname van ten minste drie hartcycli in de analyse. In **hoofdstuk 7** wordt verdere in vivo validatie (tegen CMR) aangetoond. De studie heeft echter de belangrijkste beperking van deze techniek benadrukt; beperkte klinische haalbaarheid. Een van de laatste activiteiten van de auteur van dit proefschrift voor het afronden van zijn PhD-programma, was de deelname aan de lancering van een multicenter prospectieve studie gericht op het verbeteren van de haalbaarheid van deze techniek. Voorlopige bemoedigende resultaten zijn gepresenteerd in TCT 2018 (Abdel-Wahab et al. JACC Sep 2018, 72 (13 supplement) B179) en impliceren dat een gestandaardiseerde acquisitie deze analyse in> 90% van de gevallen haalbaar kan maken.

Sectie A.3. Langdurige klinische en hemodynamische resultaten na TAVI

Gegevens over de lange termijn van klinische en hemodynamische resultaten na TAVI zijn schaars. In deze sectie worden gegevens voor de middellange tot lange termijn gepresenteerd. **Hoofdstuk 8** richt zich op symptomatische verbetering en identificeert een aantal belangrijke determinanten van een dergelijke verbetering. Hoewel de functionele klasse van NYHA significant verbeterde bij de meerderheid van de patiënten na TAVI, bleven de resterende symptomen bij een derde van de patiënten aanwezig en hadden ze een verminderd prognose. De studie benadrukt het concept van "futiliteit", waarbij het technische succes van de procedure niet resulteert in een adequate verlichting van de symptomen van de patiënt. Factoren die verband hielden met restfunctiestoornissen van de functionele capaciteit omvatten atriale fibrillatie, low-flow lage gradiënt AS, COPD en anemie. Een vervolgstudie door de groep (van Mourik et al, Open Heart, 2018; 5 (2): e000879) heeft echter de overweging van dit gebrek aan objectieve functionele capaciteitsverbetering aangevochten als "futiliteit". De studie documenteerde dat in de meerderheid van de patiënten (zelfs die met resterende symptomen) nog steeds

gunstige door de patiënt gerapporteerde uitkomstmaten gaf. **Hoofdstuk 9** is een van de weinige lange termijn uitkomststudies na TAVI. De hemodynamische prestaties op lange termijn van de zelfexpanderende THV van de oudere generatie waren gunstig op een mediaan van 6 jaar en tot 9 jaar na TAVI.

Deel B: Transcatheterinterventies voor andere hart kleppen

Naast TAVI is implantatie van andere kleppen met Cathetergebonden techniek ook een optie. Elk van deze toepassingen heeft echter zijn specifieke uitdagingen en in dit deel van het proefschrift worden twee voorbeelden gegeven. Transkatheter mitralisklep implantatie vormt een uitdaging door de complexe geometrie van de annulus van de mitralisklep. Een vereenvoudigde op MSCT-gebaseerde methodologie van annulus metingen wordt beschreven in **hoofdstuk 10**. Dmean (het gemiddelde van inter-commissurale en antero-posterieure diameters) is een eenvoudige en reproduceerbare index die in deze studie is weergegeven om de effectieve mitrale annulusomvang weer te geven.

In september 2000 voerde Philipp Bonhoeffer de eerste cathertergebonden pulmonale klepimplantatie uit bij de mens. Tien jaar later keurde de Amerikaanse Food and Drug Administration de Melody-klep goed (een aangepaste versie van het originele apparaat van Bonhoeffer et al vervaardigd door Medtronic Inc., Minneapolis, MN). Sindsdien is pulmonaire klepimplantatie met behulp van de Melody-bioprothese een gevestigde interventie geworden, maar er zijn recentelijk toenemende zorgen ontstaan, die worden aangewakkerd door signalen van een hoog risico op endocarditis. Omdat het aantal Melody-klepimplantaten per centrum meestal klein is en endocarditis een zeldzame ziekte blijft, hebben we geprobeerd de incidentie en de natuurlijke geschiedenis van melodieklep-endocarditis te onderzoeken door systematisch de gepubliceerde gegevens in **hoofdstuk 11** te bekijken. Het risico lijkt aanzienlijk hoog (ten opzichte van de chirurgische tegenhanger) en de diagnose is een uitdaging, waarbij wordt opgeroepen tot specifieke diagnostische criteria en meer vertrouwen op PET-scan bij de diagnose van deze aandoening.

Deel C: Transcatheter sluiting van inter-atrische communicatie

Percutane sluiting is de voorkeursbehandeling voor atriumseptumdefect (ASD). Het is een veilige interventie die de verslechtering van de structuur en functie van het rechter hart, veroorzaakt door chronische volumebelasting, tot staan brengt. Hoewel deze twee kenmerken (veiligheid en effectiviteit) over het algemeen goed zijn ingeburgerd, moeten nog enkele openstaande vragen worden beantwoord. In **hoofdstuk 12** hebben we onderzocht of de verlichting van volumeoverbelasting zou leiden tot verbetering van tricuspidalisklep regurgitatie bij patiënten die transkatheter-ASD-sluiting ondergaan. Matig-ernstige TR was aanwezig in 64 patiënten vóór en in 36 patiënten 6 maanden na ASD-sluiting, en resterende TR was geassocieerd met cardiovasculaire sterfte en/of

ziekenhuisopname voor hartfalen. Voorspellers van post-procedureel matig-ernstige TR waren leeftijd, rechter atriaal eind-diastolisch oppervlak, rechterventrikel systolische druk en TAPSE (tricuspidalisring systolische excursie). In **hoofdstuk 13** wordt aandacht besteed aan het zorgwekkende probleem van erosie van het inter-atriale septumapparaat in de aortawortel. Vanwege de uiterst zeldzame incidentie is er onvoldoende onderzoek op dit gebied. Omdat de mechanische relatie tussen deze apparaten en de aortawortel niet bekend is, hebben we een mechanistische studie van deze relatie uitgevoerd met behulp van geavanceerde echocardiografische technieken. Dankzij 3D-echocardiografie kunnen we met behulp van het interface van het apparaat door de aorta scrollen om het punt van maximale benadering tussen aortawortel en interatriaal septum te identificeren. In de overgrote meerderheid van de gevallen werd een mechanisch contact tussen het device/de klep en de aorta waargenomen, en dit was niet beperkt tot patiënten met een beschadigde aortarand (zoals intuïtief werd verwacht). Zelfs bij mensen met een PFO of een ASD met een voldoende aorta-rand, was een direct intraatrieel septum -aorta-contact gedocumenteerd. Met behulp van een andere echocardiografische modaliteit (speckle tracking), bleek de verhouding tussen de diameter van het device en het lichaamsoppervlak invloed te hebben op de vervorming van de aortawortel, en werd gepleit om rekening te houden met deze parameter bij het kiezen van de klepgrootte/devicegrootte.

Conclusies

Interventies voor de behandeling van structurele hartziekten nemen enorm toe. Terwijl er waardevol onderzoek wordt uitgevoerd om nieuwe technologieën te introduceren, richt dit proefschrift zich op het verfijnen van bestaande technieken. De concepten die werden benadrukt waren: 1) optimalisatie van de selectie van patiënten om de uitkomsten te verbeteren, 2) toepassing van wetenschappelijk gerechtvaardigde benaderingen om de waarschijnlijkheid van adequate en duurzame klinische verbetering en reverse cardiale remodellering te voorspellen, 3) gebruik van multimodaliteit imaging om de anatomische planning te optimaliseren, en 4) inzichtelijke studie van de interactie tussen device en patiënt met behulp van speciale beeldvormingsmethoden. Drie patronen van nadelige interactie tussen het apparaat en de patiënt werden besproken, nl. niet correcte aanpassing van de anatomie van de landingszone, welke kan leiden tot lekkage van de aortaklep prothese, infectieuze endocarditis van de ingebrachte pulmonaal kleppen, en inter-atriale mechanische interactie van de aorta en de prothese in het atriumseptum de aorta. In hoofdstuk 14 wordt een futuristische technologie beschreven die gericht is op minimalisatie van deze nadelige interactie tussen prothese en de patiënt.

SUMMARY AND CONCLUSIONS

This thesis addresses in a spectrum of SHD interventions two prerequisites to optimize outcomes: 1) comprehensive patient assessment to decide upon eligibility for a given intervention, as well as the likelihood of a significant clinical benefit after the procedure; and 2) the central role of multimodality imaging in planning as well as assessing the device-host interaction.

Part A: Transcatheter aortic valve implantation; beyond feasibility towards optimization

Sixteen years after the first-in-man TAVI by Alain Cribier, TAVI has now become an established treatment for a large spectrum of patients with aortic valve disease. Feasibility has been established even in challenging anatomical contexts (e.g. bicuspid aortic valve disease). Moving to the next frontier, **Part A** of the thesis has focused on further refinements aiming at optimization of patient selection (**Section A.1**), improving the assessment of bioprosthetic valve function (**Section A.2**), and documenting the long-term results (**Section A.3**).

Section A.1. Decision-making and expanding the indications of TAVI

Chapter 2 has focused on a comprehensive assessment of the patient's eligibility for TAVI. The assessment of patient's eligibility for TAVI as assessed by the "Heart Team" comprises the following criteria: 1) patient's age, life expectancy, and operative risk; 2) the likelihood of a measurable clinical benefit; and 3) anatomical suitability (on the access and the valve levels). **Chapter 3** addressed one of the so-far off-label anatomical indications for TAVI (high grade regurgitation combined with AS). In spite of an increased risk of PVL in this anatomical context, TAVI provided a clinical benefit comparable to that achieved in patients with pure AS. This was explained by a lower prognostic penalty of PVL in this subgroup, likely because of left ventricular preconditioning. Further reassuring, a subsequent study has shown that lower PVR rates can be achieved in this patient subset using next generation THVs (Seeger et al. Structural Heart, 1:3-4, 162-167).

Section A.2. Assessment of paravalvular leakage after TAVI

This is a focused section on a downside of TAVI that has long been considered the Achilles' heel of this technology. Quantification of PVL, especially within the cath lab when there is still a place for corrective measures, is required but challenging. **Chapter 4** gives an overview of established and upcoming techniques to assess PVL after TAVI. **Chapter 5** aimed at optimizing the consistency between the two most commonly used methods of PVL assessment; echocardiography and angiography. The study has proposed a dedicated echocardiographic algorithm that relies on multi-window multi-plane color Dop-

pler imaging. This approach correlated more strongly with the angiographic assessment. **Chapters 6 and 7** introduce a novel angiographic tool to assess PVL (videodensitometry). The technology has been validated in an in vitro model against the regurgitation fraction measured by a transonic flow probe. The study (**Chapter 6**) showed that this tool is accurate and provided some technical tips to make this tool more practical and precise, namely; confining the region of interest to the subaortic part of –rather than the entire- left ventricle, and the inclusion of at least three cardiac cycles in the analysis. In **Chapter 7**, further in vivo validation (against CMR) is demonstrated. The study has, however, highlighted the main limitation of this technique; limited clinical feasibility. One of the last activities of the author of this thesis before finishing his PhD program, was participation in launching a multicenter prospective study aiming at improving the feasibility of this technique. Provisional encouraging results have been presented in TCT 2018 (Abdel-Wahab et al. JACC Sep 2018, 72 (13 Supplement) B179) and imply that a standardized acquisition can make this analysis feasible in >90% of cases.

Section A.3. Long-term clinical and hemodynamic outcomes after TAVI

Data on the long-term clinical and hemodynamic outcomes after TAVI are scarce. In this section, mid- to long-term data are presented. **Chapter 8** focuses on symptomatic improvement and identifies some important determinants of such an improvement. Although NYHA functional class improved significantly in the majority of patients after TAVI, residual symptoms persisted in one third of patients and carried a negative prognostic signal. The study highlights the concept of "futility", where the technical success of the procedure does not translate into adequate alleviation of patient's symptoms. Factors associated with residual impairment of functional capacity included atrial fibrillation, low-flow low-gradient AS, COPD, and anemia. A subsequent study by the group (van Mourik et al, Open Heart. 2018; 5(2): e000879) has however challenged the consideration of this lack of objective functional capacity improvement as "futility". The study documented that the majority of patients (even those with residual symptoms) still report favorable patient-reported outcome measures. **Chapter 9** represents one of very few long term outcome studies after TAVI. The long-term hemodynamic performance of the older generation self-expanding THV was favorable at a median of 6 years, and up to 9 years after TAVI.

Part B: Transcatheter interventions for other cardiac valves

Beyond TAVI, transcatheter valve implantation is an option in other valve positions. However, each of these applications has its specific challenges, and two examples are presented in this part of the thesis. Transcatheter mitral valve implantation is challenged by the complex geometry of the mitral valve annulus, and a simplified MSCT-based methodology of annulus sizing is described in **Chapter 10**. Dmean (the average of inter-

commissural and antero-posterior diameters) is a simple and reproducible index that has been shown in this study to reflect the effective mitral annulus size.

In September 2000, Philipp Bonhoeffer performed the first-in-man transcatheter pulmonary valve implantation. Ten years later, the US Food and Drug Administration approved the Melody valve (a modified version of the original device of Bonhoeffer et al manufactured by Medtronic Inc, Minneapolis, MN). Since then, pulmonary valve implantation using the Melody bioprosthesis became an established intervention but increasing concerns have recently arisen, sparked by signals of a high endocarditis risk. As the number of Melody valve implants per center is usually small and endocarditis remains an uncommon disease, we sought to explore the incidence and the natural history of Melody valve endocarditis by systematically reviewing published data in **Chapter 11**. The risk appears significantly high (relative to the surgical counterpart) and the diagnosis is challenging, calling for dedicated diagnostic criteria and more reliance on PET-scan in the diagnosis of this condition.

Part C: Transcatheter closure of inter-atrial communications

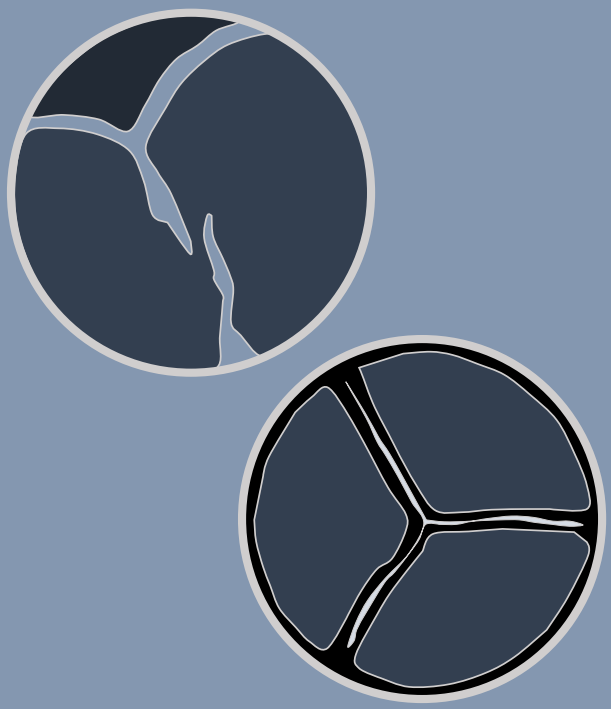
Percutaneous closure is the treatment of choice for ASD. It is a safe intervention that halts the deterioration in right heart structure and function induced by chronic volume overload. Although these two features (safety and effectiveness) are generally well-established, some pending questions are yet to be answered. In **Chapter 12**, we sought to explore whether the relief of volume overload would translate into improvement of tricuspid regurgitation in patients undergoing transcatheter ASD closure. Moderate-severe TR was present in 64 patients before and in 36 patients 6 month after ASD closure, and residual TR was associated with the composite of cardiovascular death or hospitalization for heart failure. Predictors of post-procedural moderate-severe TR were age, right atrial end-diastolic area, right ventricular systolic pressure, and tricuspid annular plane systolic excursion. In **Chapter 13**, the worrisome problem of inter-atrial septal device erosion into the aortic root is indirectly addressed. Due to the extremely rare incidence, there is no sufficient research in this field. As the mechanical relationship between those devices and the aortic root is not known, we conducted a mechanistic study of this relationship using advanced echocardiographic techniques. Thanks to 3D echocardiography, we could scroll through the device-aorta interface to identify the point of their maximum approximation. In the vast majority of cases, a mechanical contact between the device and the aorta was observed, and this was not confined to patients with deficient aortic rim (as intuitively expected). Even in those with a PFO or an ASD with an adequate aortic rim, a direct device-aorta contact was document. Using another echocardiographic modality (speckle tracking), the ratio of the device diameter to the body surface area was found to impact on aortic root deformation, calling for considering this parameter when choosing the device size.

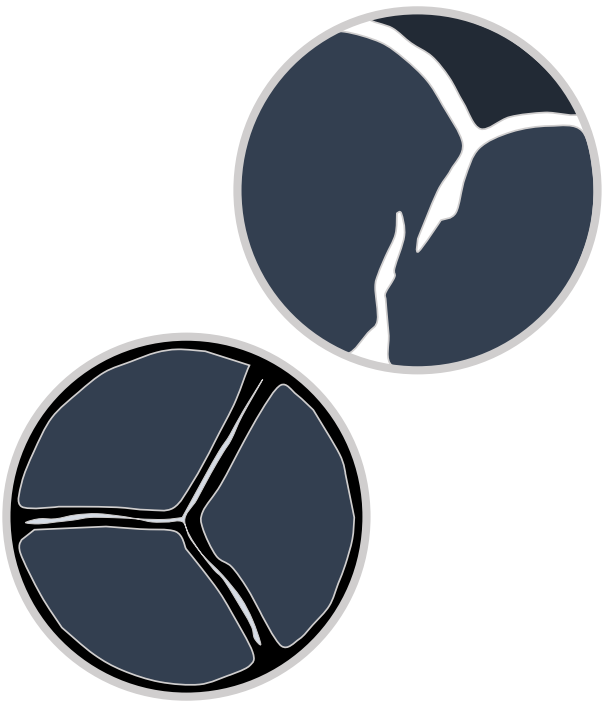
CONCLUSIONS

Interventions to treat structural heart diseases are widely expanding. While valuable research is running to introduce new technologies, this thesis aimed at refinement of established techniques. The concepts sought to be emphasized were: 1) optimizing patient selection to improve outcomes, 2) applying evidence-based approaches to predict the likelihood of adequate and durable clinical improvement and reverse cardiac remodeling, 3) using multimodality imaging to optimize anatomical planning, and 4) insightful studying of the device-host interaction using dedicated imaging methods. Three patterns of adverse device-host interaction were addressed, namely: improper adaptation to the landing zone anatomy leading to paravalvular leakage of transcatheter aortic valves, infective endocarditis of transcatheter pulmonary valves, and inter-atrial device mechanical interaction with the aorta. In **Chapter 14**, a futuristic technology is being described which aims at minimization of these adverse device-host interaction.

PART E

Future perspective



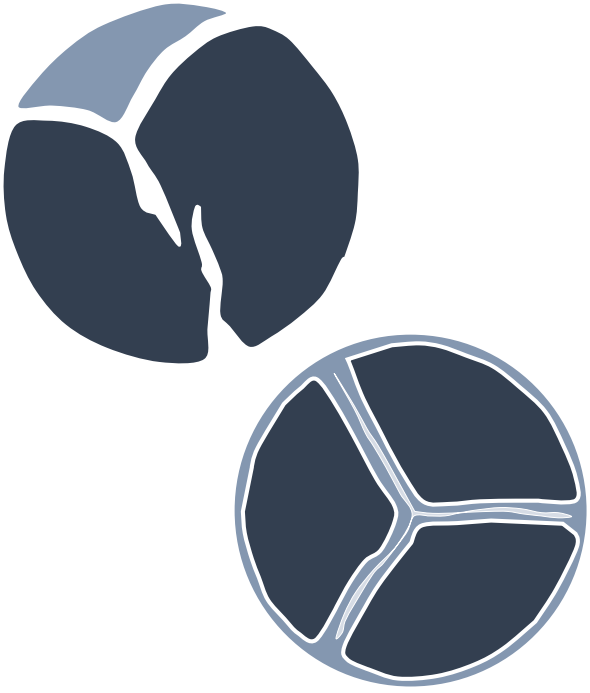


Chapter 14

Acute performance of a novel restorative transcatheter aortic valve: preclinical results

Miyazaki Y, Soliman OII, Abdelghani M, Katsikis A, Naz C, Lopes S, Warnack B, Cox M, Onuma Y, Serruys PW

EuroIntervention. 2017;13(12):e1410-e1417.



ABSTRACT

Aim:

The XELTIS aortic valve leaflets are made from a bioabsorbable supramolecular polymer that guides the tissue to restoring itself. It is mounted on a self-expandable nitinol frame that includes three feelers and a native leaflet clipping mechanism. We sought to investigate the acute valve performance in a preclinical setting.

Methods and results:

In 33 sheep, 26 mm XELTIS aortic valve were transapically implanted in a 23 mm native annulus. Aortography (analysable, n=28) and echocardiography (analysable, n=20) were acquired immediately after implantation of the XELTIS aortic valve to assess the acute device performance. On echocardiography, transvalvular peak pressure gradient (PG) was 7.4[IQR: 6.0-8.9] mmHg, mean PG was 4.0[IQR: 3.0-5.0] mmHg, and effective orifice area was 2.2[IQR: 1.6-2.5] cm^2. Trace (n=6) and mild (n=2) and no (n=12) transvalvular aortic regurgitation (AR) were seen. Likewise, no paravalvular AR was detected in 7 cases, whereas trace, mild and moderate were seen in 7, 5 and 1 case, respectively. On quantitative Videodensitometric-AR (VD-AR) assessment, a median value of 6% [IQR: 1-12%] of AR was seen. Three cases had a VD-AR superior to 17%, which has a prognostic significance. Out of these three cases 2 had echocardiographic assessment available, and showed mild and moderate paravalvular regurgitation, due to inadequate leaflets clipping.

Conclusions:

In a transapical ovine model, the novel restorative transcatheter aortic valve with bioabsorbable leaflets demonstrated good hemodynamic performances comparable to commercially available devices. The highly porous polymeric leaflets demonstrated good competence immediately after implantation with no cases having >mild transvalvular AR.

INTRODUCTION

Transcatheter Aortic Valve Implantation (TAVI) is an established treatment of aortic stenosis with expanding indications towards younger and lower risk patients. However, durability concerns emerge related to signals of an accelerated degeneration of transcatheter aortic valves leaflets, which represents the major barrier limiting TAVI expansion to new patients' strata[1,2]. Current bioprosthetic valves are made of animal-derived glutaraldehyde-fixed foreign material, which raises several issues, such as durability, thromboembolism, infection, stenosis and regurgitation. Tissue of animal origin tends to degenerate and becomes calcified with time, so that in the span of a life time, re-intervention (re-operation) is frequent after one or two decades in the patient who received bio-prostheses implanted surgically or percutaneously[3].

A restorative valve was developed based on a novel technology named "endogenous tissue restoration (ETR)". The principle of ETR is that a leaflet of a bioabsorbable material will be progressively replaced by endogenous tissue[4]. As schematically shown in **Figure 1**, the implant is created by electrospinning a bioabsorbable polymer to form a three dimensional construct, such as a heart valve. The construct is implanted without adding any cells or growth factors, and is functional upon implantation. The porous microstructure of the implant allows cells to migrate into the construct, after which these cells start to produce neotissue that fills the pores and gradually takes over functionality from the gradually absorbing polymer. This new technology could potentially overcome the issues of the current available valves caused by the use of foreign material. Paediatric conduit (Fontan) and pulmonary valved conduit with this technology were investigated in-vitro, in preclinical setting and are currently tested in clinical setting[5,6]. With regard to the extension of this technology to aortic valve, this is the first report to investigate the acute performance of the XELTIS aortic valve.

METHOD

Study design

This preclinical study included 33 Ile de France sheep that received the XELTIS aortic valve by transapical approach. The first seven sheep were used for iterative design optimizations after which 26 sheep were implanted the XELTIS aortic valve. This study reports the acute performance of the XELTIS aortic valve implanted in these 33 sheep. Post implantation aortography was performed at the end of procedure to evaluate the acute performance of the valve. Echocardiography was obtained after procedure. The study was conducted in compliance with ISO 10993-2. The Animal Care and Use Committee of the testing facility is registered at the CNREEA under the Ethics Committee n° 37.

Design of the XELTIS aortic valve and implantation of the XELTIS aortic valve

The XELTIS aortic valve (Xeltis BV, Eindhoven, The Netherlands) is made from a bioabsorbable supramolecular polymer. More specifically, polyester-urethanes were used that contained the ureidopyrimidinone (UPy) supramolecular binding motif [7]. A key attribute of this class of materials is that mechanical properties and absorption characteristics can be changed and tuned independently, thus allowing selection of the appropriate material configuration through a process of elimination and optimization. Three polymer configurations were used to construct the XELTIS aortic valve in this study. The supramolecular polymers were used to synthesize the leaflets (through an electrospinning process) and the leaflets were mounted on a self-expandable nitinol frame that included three feelers and a native leaflet clipping mechanism. Extremities of the feelers

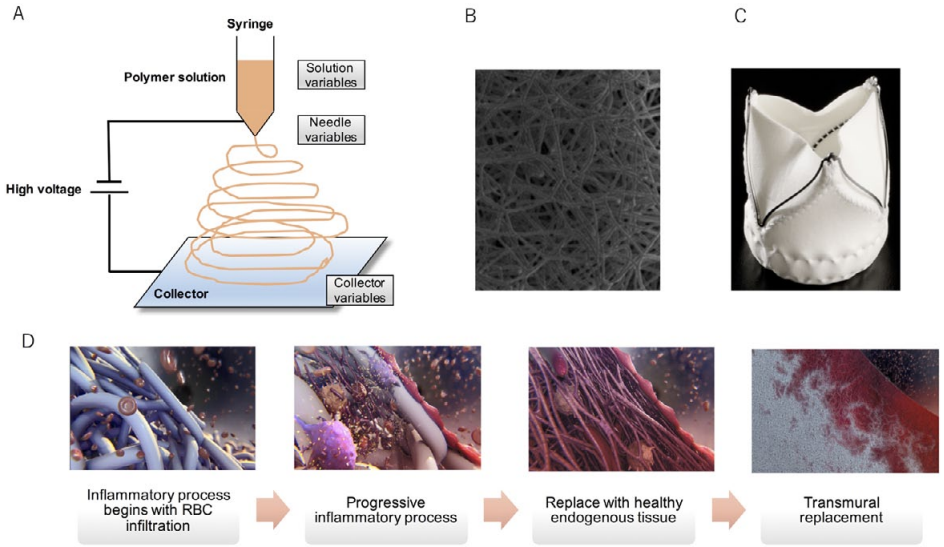


Figure 1. The principle of electrospinning and ETR of the XELTIS aortic valve

A) The principle of electrospinning: Electrospinning is a widely used technique for the electrostatic production of nanofibers, during which electric power is used to make polymer fibers with diameters ranging from 2 nm to several micrometres from polymer solutions or melts. This process is a major focus of attention because of its versatility and ability to continuously produce fibers on a scale of nanometres, which is difficult to achieve using other standard technologies. Electrospinning is a relatively simple way of creating nanofiber materials, but there are several parameters that can significantly influence the formation and structure of produced nanofibers. These parameters such as solution variables, needle variables or collector variables could be manipulated to produce the desired material.

B) Electron microscopic images of the product of electrospinning.

Reproduce and adopted with permission from Leo A. Bockeria et al.[5]

C) Leaflets with a porous microstructure made through electrospinning process were mounted on a self-expandable nitinol frame that included three feelers and a native leaflet clipping mechanism.

D) The principle of ETR: The XELTIS aortic valve is gradually infiltrated by blood elements (red cells, platelets, macrophages), myoblasts, fibroblasts with subsequent enzymatic bioabsorption of the fibers, and gradually replaced by endogenous tissue.

were encapsulated with bioabsorbable materials to avoid damage to the leaflet as seen in the first series of seven implants (**Figure 1**).

Implantation procedure of the XELTIS aortic valve

All procedures were performed under general anaesthesia. The XELTIS aortic valves were implanted by a trans-apical approach under the guidance of echocardiography, fluoroscopy and aortography. A pigtail catheter is introduced transfemorally and placed in the native aortic valve cusp as reference for positioning. The valve is delivered transapically using fluoroscopy guidance. The distal end of the valve is deployed first after which the delivery system is pulled gently to anchor the 3 device arms into the sinuses of Valsalva, prior to full deployment and release of the device (**Figure 2**).

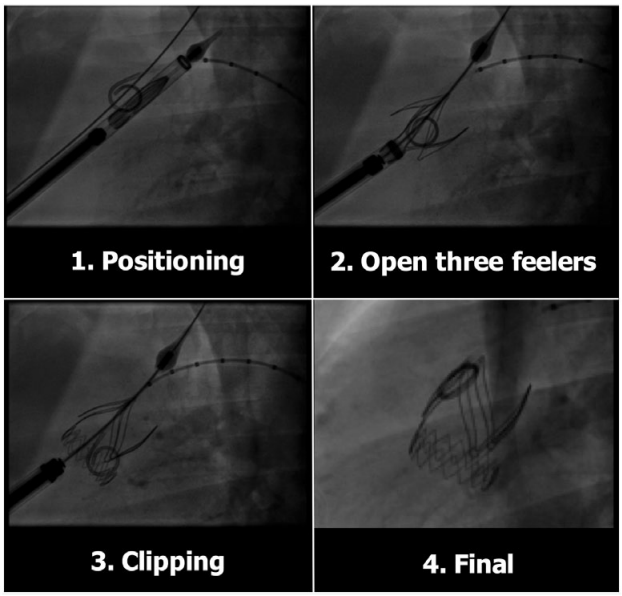


Figure 2. Implantation of the XELTIS aortic valve.

Quantification of aortic regurgitation assessment by aortography using videodensitometric technology

Videodensitometric-AR (VD-AR) was analysed at an independent core laboratory (Cardialysis Clinical Trials Management and Core Laboratories, Rotterdam, The Netherlands) by experienced observers who were blinded to echocardiogram results. A dedicated software (CAAS A-Valve 2.0.2; Pie Medical Imaging, Maastricht, The Netherlands) was used to quantify the regurgitation from angiograms. The details of this technique have been described elsewhere[8-14]. After delineating the aortic root (i.e. reference area) and the subaortic one third of the left ventricle (i.e. region of interest [ROI]), the contrast

time-density curves (TDCs) are analysed both in the ROI (in the LV) and the reference region (the aortic root) during at least three cardiac cycles after contrast injection. The area under the curve (AUC) is automatically calculated and represent time-density integrals. VD-AR is automatically calculated as the ratio of the AUC of the time-density integrals measured in the ROI and the reference area. Theoretically, the value of VD-AR ranges from 0 to 1 (**Figure 3**).

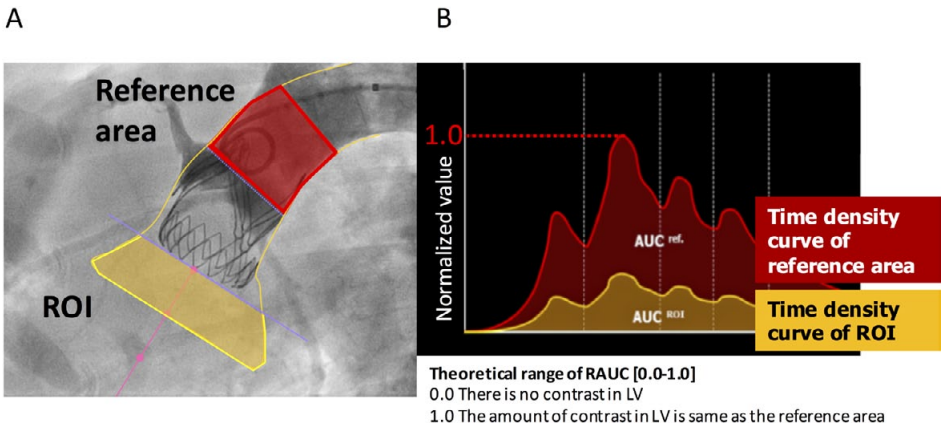


Figure 3. Videodensitometric assessment of aortic regurgitation
A) Delineation of the aortic root (reference area: red area in the aortography) and the subaortic one third of LV (ROI: yellow area in the aortography) are shown by the analyzer. **B)** The time density curves are provided for both the ROI (yellow TDC) and the reference region (red TDC) and the AUC is automatically computed by the software time-density integrals. VD-AR corresponds to the relative AUC, which is automatically calculated as the ratio of the relative AUC (ROI [yellow] and reference area [red]). Theoretically, the value of VD-AR ranges from 0 to 1.
Reproduce and adopted from Tateishi et al. EuroIntervention 2016.[13]

Aortic regurgitation and hemodynamic data assessment by echocardiography

Echocardiographic data were analysed in accordance with the recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging[15-17]. Mean and peak pressure gradient (PG) across the XELTIS aortic valve were derived from continuous wave Doppler evaluation of blood flow in the left ventricle outflow tract (LVOT) and across the prosthetic device by manual tracing of the timed integration of the velocity curve. Aortic valve area was calculated by continuity equation using following measurements: 1) Velocity-time-integral (VTI) from LVOT level measured by pulsed-wave Doppler, 2) Velocity-time-integral (VTI) across aortic valve prosthesis level measured by continuous wave Doppler, and 3) diameter of the LVOT at the same location of pulsed-wave Doppler sample in the LVOT. For the assessment of aortic regurgitation (AR) severity and the origin of AR, Core Lab used a standard methodology as described earlier in several Core Lab publications[18-20].

Statistics

When continuous variables were normally distributed, we summarized data as mean ± standard deviation (SD). If they were not normally distributed, median and inter-quartile range [IQR] were used.

RESULTS

Between April 25, 2016 and October 10, 2016, 33 devices with a diameter of 26 mm were implanted transapically in native annulus with an approximate diameter of 23 mm. Aortography was performed after implantation of the XELTIS aortic valve in all 33 sheep. In order to assess the acute device performance, echocardiography was performed immediately after the procedure in twenty consecutive cases after the initial and purely angiographic assessment of the first 13 cases.

Procedural success

Overall, there were no major complications in the majority of cases after TAVI procedure. However, two cases suffered from complications during the procedure because one of the feelers did not deploy well. Few cases showed issues in the subacute phase (>24hrs and <2 weeks), which were mainly related to 1) perforation of the native cusps due to improper coverage of the stent feelers and 2) abrasion of the mitral valve against the aortic valve stent frame resulting in mitral insufficiency. In most cases mitral valve abrasion was a consequence of stent migration due to perforation of the native cusps. Small improvements to the strut and frame protection were made during the study, which successfully eliminated these subacute issues.

Quantification of aortic regurgitation after implantation of XELTIS aortic valve

Aortic regurgitation (AR) after implantation of the XELTIS aortic valve was quantified by video-densitometric assessment. Five animals were not analysable due to the following reasons: 1) the ROI moved by deep breath (n=3) and 2) the ROI was not included in the aortography (n=2). Twenty-eight animals were analysable for this assessment. The median and IQR of VD-AR was 6%[1-12%] (**Figure 4**). We compared the VD-AR in the first 7 iterative cases with the next 26 cases. There were 6 (86%) versus 22 (79%) analyzable cases for VD-AR in the first 7 cases and the next 26 sheep, respectively. Median [IQR] VD-AR was 8% [1.8-9.8%] versus 5.5% [1.0-14.0%] in the first 7 iterative cases and the next 26 sheep (p=0.89), respectively. Three cases showed a regurgitation superior to 17%, a value which is has a prognostic significance in clinical practice[13].

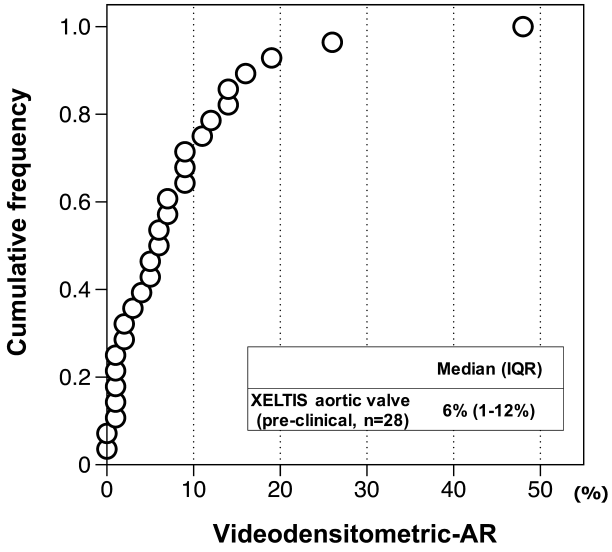


Figure 4. Cumulative frequency distribution curves of quantitative aortic regurgitation assessment (VD-AR) after implantation of the XELTIS aortic valve by videodensitometry.
Cumulative frequency and median value of VD-AR immediately after implantation of the XELTIS aortic valve was shown.

Acute hemodynamic performance of the XELTIS aortic valve

Hemodynamic performance was assessed immediately after implantation of the XELTIS aortic valve in 20 cases. Trans-valvular peak pressure gradient (PG) was 7.4 [6.0-8.9] mmHg, mean PG was 4.0 [3.0-5.0] mmHg, and effective orifice area was 2.2 [1.6-2.5] cm^2. (**Figure 5**).

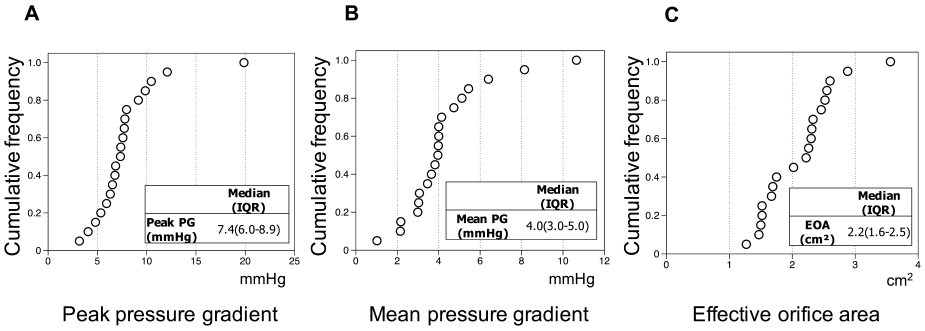


Figure 5. Hemodynamic performance after implantation of the XELTIS aortic valve
Cumulative frequency and median value of **A)** peak pressure gradient across the valve, **B)** mean pressure gradient across the valve, and **C)** effective orifice area immediately after implantation of the XELTIS aortic valve were shown.

Severity of aortic regurgitation by echocardiography

Twenty cases were analysable for the severity of paravalvular regurgitation (PVR) and transvalvular regurgitation by echocardiography. Seven cases were observed without any PVR. Seven cases had trace, 5 cases mild and 1 case moderate PVR. In terms of transvalvular regurgitation, 12 cases had none, 6 cases trace and 2 cases mild transvalvular regurgitation. Out of the three cases with video-densitometric assessment superior to 17%, 2 had echocardiographic assessment available, and showed mild and moderate paravalvular regurgitation. These cases were attributed to a inappropriate clipping of the leaflets.

DISCUSSION

The main findings of this study are as follows: 1) the XELTIS aortic valves were implanted safely via trans-apical approach, 2) hemodynamic performance immediately after implantation of the XELTIS aortic valve was excellent compared to the objective performance indices of the current commercially available bioprosthetic valves, 3) substantial regurgitation was observed in three cases, however those paravalvular regurgitation were due to the inadequate clipping of the leaflets and 4) otherwise, only less than mild transvalvular regurgitation were observed.

Added value of the XELTIS aortic valve

TAVI was primarily introduced for treating elderly high-risk patients with severe aortic stenosis. Because of the limited life expectancy, there was a less focus on the long-term durability[21]. However, patient selection of TAVI has been increasingly expanded to younger patients and/or lower surgical risk[22]. Therefore, the long-term durability of TAVI prosthesis became important. Although most of the current available studies have not shown significant deterioration-related problems, longer term data in large cohorts is needed to conclude[21].

Current bioprosthetic valves are based on animal-derived glutaraldehyde-fixed pericardial tissue, which have known to lead the biocompatibility concerns due to chronic inflammatory responses. The chronic inflammation could lead to calcification through secretion of cytokines by macrophages, such as osteopontin[23-25]. As clinical consequences, there is a need for adjunctive pharmacotherapy (long term aspirin therapy and short-term systemic anticoagulation) [26-28] and repeat hospitalizations with or without re-interventions. ETR technology is based on the fact that a leaflet of a bioabsorbable material will be progressively replaced by endogenous tissue. Therefore, ETR could improve biocompatibility resulting in less leaflet thickening. In addition, less valve leaflet thrombosis and thus less need for antithrombotic therapy. Thus, this valve

could potentially overcome the issues of the current available valves caused by the use of foreign material.

Angiographic aortic regurgitation after implantation of the XELTIS aortic valve

The leaflets of the XELTIS aortic valve are constructed by electrospinning, so that the leaflet has a porous texture due to the random assembly of microfibers (**Figure 1**). Therefore, the concern that transvalvular (trans-leaflet) AR could be initially present, existed. In fact, in the large majority of cases the videodensitometry of the outflow tract just detected trace of contrast medium. During surgical reconstruction of RVOT in clinical cases, the surgical operator uses to witness oozing of the blood through the wall of the conduit, but almost instantaneously the hemostasis is achieved. Red cell, fibrin and protein get caught in the fiber network and render the leaflets competent and no longer permeable to the angiographic contrast medium.

Echocardiographic aortic regurgitation after implantation of the XELTIS aortic valve

More than mild transvalvular regurgitation was not observed by echocardiography. Although quantitative assessment of regurgitation by aortography indicated that 3 cases had a regurgitation superior to the critical level of 17%, AR of 2 of these cases by echocardiography was shown to originate from paravalvular leaks due to inadequate clipping of native leaflet.

Comparison with current available bioprosthesis valves

Spethmann et al. reported the hemodynamic performance after implantation of Edwards Sapien and CoreValve, and Soliman et al. reported the hemodynamic data after implantation of Lotus and Sapien3 based on echocardiogram[18,29] (Table 1). The severity of AR after implantation of the XELTIS aortic valve quantified by videodensitometry using aortography was compared to that of current commercially available valves, which were assessed in the Brazilian TAVI registry. VD-AR of the XELTIS aortic valve (6% [1-12])

Table 1. Comparison of hemodynamic data between current commercially available valve and XELTIS aortic valve

	Human data from clinical trial				Preclinical data from normal sheep
	Edwards Sapien (26mm)[29]	**CoreValve (26mm)**[29]	**Lotus**[18]	**Sapien 3**[18]	**XELTIS**
Peak pressure gradient (mmHg)	15.8	15.5	20	18	7.4
Mean pressure gradient (mmHg)	8.5	8.4	11	10	4.0
THV EOA (cm^2)	1.82	1.78	1.84	1.99	2.2

was less than that of Sapien XT (10% [5-14]) and CoreValve (13% [7-22]), and was similar with that of Lotus bioprosthesis valve (3% [1-7]) (unpublished data). Although the current study is performed in a preclinical setting, and compared to the hemodynamic parameters reported in a clinical setting, the acute hemodynamic performance was excellent.

Limitations

First of all, although there was an attempt to make a large animal model with aortic stenosis[30], there are no well-standardized large animal models of aortic stenosis. Furthermore, while reasonable efforts should be made to mimic the human situation, it should be realized that there will always be differences between human and animal models. In our specific case, there were several challenges specific to the use of the sheep model that we were successful in solving. First, sheep have a very short aortic root, and therefore limited space for positioning the valve. In addition, the sheep aortic and mitral valve are very close to each other and reside in the same plane. These challenges might lead to an ill-positioned or too long aortic valve prosthesis, which may cause mitral valve damage because of abrasion against the aortic valve prosthesis. We were able to solve this by using a short design of the prosthesis and appropriate cushioning of parts that are at risk of causing abrasion. Another challenge relates to the absence of stenosis and calcification, which means that the sheep aortic valve cusps are very thin and fragile, compared to human aortic valve cusps, which are typically thick and calcified in cases of severe aortic stenosis. Since, the position of our valve is based on feelers that sit on the native cusps, further cushioning was required to avoid perforation of these thin native cusps by the feelers. For the purpose of assessing the XELTIS aortic valve leaflets, a reasonable effort in developing and optimizing the ovine model have been done. However, taking into account that the usage of normal animal for the current experiments, the acute performance of XELTIS aortic valve could be different in between non- aortic stenosis recipient and aortic stenosis recipient, suggesting further investigations are needed for the confirmation.

CONCLUSION

In a transapical ovine model, the novel transcatheter aortic valve with restorative leaflets demonstrated good hemodynamic performance. The hemodynamics of the valve is comparable to the commercially available valves implanted in clinical cases. The highly porous polymeric leaflets demonstrated very good competence immediately after implantation with no cases having a more than mild transvalvular AR.

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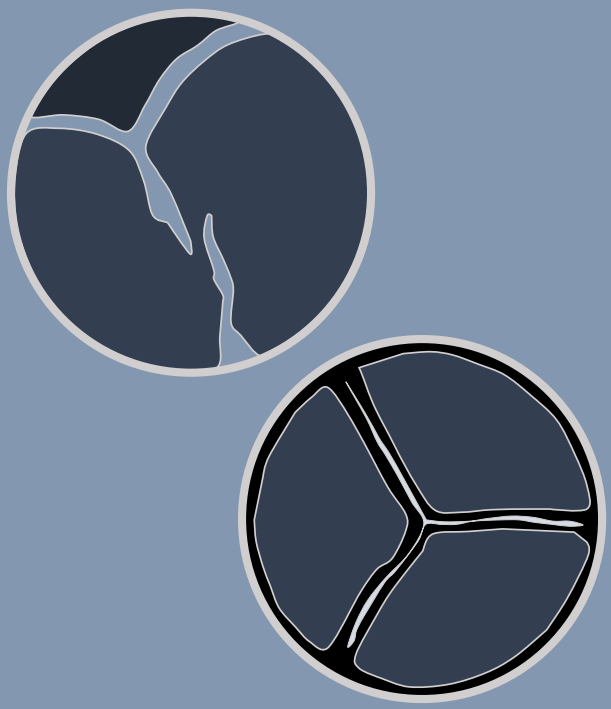
PART F

Appendices

Authors and affiliations
Curriculum vitae
Portfolio
List of publications
Acknowledgement



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PhD training	Year	ECTS
Courses		
Practical Biostatistics, Graduate School, AMC	2015	2.0
Expert Management of Medical Literature, Graduate School, AMC	2015	2.0
Systematic Reviews, Graduate School, AMC	2016	2.0
Presentations and international conferences		
EuroPCR, Paris, France (attendant)	2015	1.0
EuroPCR, Paris, France (1 oral presentation)	2016	2.0
PCR London Valves, London, UK (1 oral presentation)	2016	2.0
European Society of Cardiology (ESC) Congress, Rome, Italy (1 poster presentation)	2016	2.0
EuroPCR, Paris, France (1 oral presentation)	2017	2.0
ESC Congress, Barcelona, Spain (1 oral and 1 poster presentation)	2017	2.0
Other academic activities		
Local associated editor for EuroIntervention	2015-2017	4.0
Regular reviewer for EuroIntervention and Catheterization and Cardiovascular Interventions journals	2015-2017	4.0

LIST OF PUBLICATIONS

Included in this thesis

1. Abdelghani M, Cavalcante R, Miyazaki M, de Winter RJ, Tijssen JG, Sarmento-Leite R, Mangione JA, Abizaid A, Lemos PA, Serruys PW, de Brito Jr FS. Transcatheter aortic valve implantation for mixed versus pure stenotic aortic valve disease. EuroIntervention 2017;13(10):1157-1165.
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