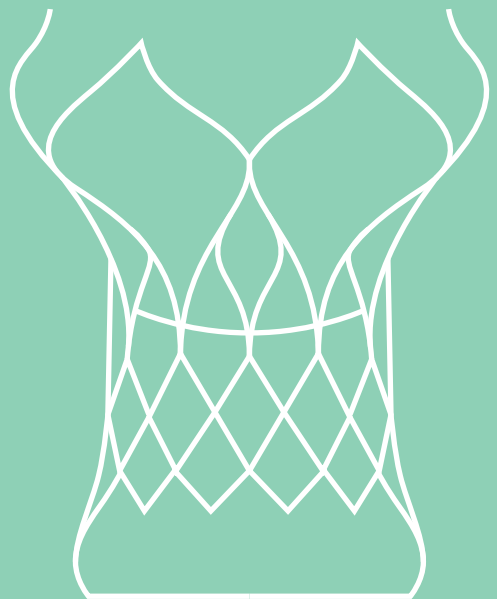


Darren Mylotte

The Evolution of Transcatheter Heart Valve Technology

Refining Aortic and Defining Mitral Valve Implantation



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**Evolution of Transcatheter Heart Valve Technology:
Refining Aortic and Defining Mitral Valve Implantation**

**Evolutie van Transkatheter Hartklep Technologie:
Het Verfijnen Van Aortaklep- en Definiëren Van Mitralisklepimplantatie**

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the rector magnificus

Prof. dr. R.C.M.E. Engles

and in accordance with decision of the Doctorate Board.
The public defence shall be held on

Tuesday the 15th of January 2019 at 15.30

by

Darren Mylotte
born in Birmingham, the United Kingdom

Erasmus University Rotterdam



DOCTORAL COMMITTEE

Promotor: Professor A.P. Kappetein

Co Promoter: Dr Nicolo Piazza

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INTRODUCTION



Chapter 1 General Introduction, Aims and Outline

Chapter 2 Cardiac Anatomy for Transcatheter Aortic Valve Implantation

Anatomy of the Aortic Valvar Complex

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JACC Cardiovasc Interv. 2014;7:652-61.

**GENERAL INTRODUCTION,
AIMS, AND OUTLINE**

1

GENERAL INTRODUCTION

In 2002, Professor Alain Cribier performed the first human transcatheter aortic valve implantation (TAVI) in a 57 year-old patient with severe aortic stenosis and refractory cardiogenic shock, who had been refused conventional surgical aortic valve replacement (SAVR).¹ The ensuing decade has witnessed immense progress in the field of structural heart intervention, and in particular in the development of TAVI. This novel technology is now firmly established in international societal guidelines,^{2,3} and is considered to be the standard of care for patients with severe symptomatic aortic stenosis at high or excessive operative risk for conventional surgery (**Figure 1**).^{4,5}

TAVI vs. Medical Therapy: 5-Year All-Cause Mortality

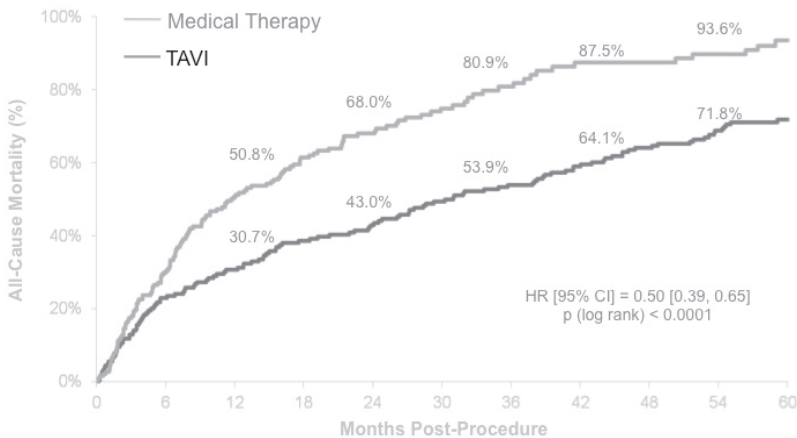


Figure 1. Transcatheter aortic valve implantation reduces all-cause mortality compared to medical therapy. Adapted from Kapadia S *et al.* 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015. 20;385:2485-9

While the field of transcatheter heart valve therapies has developed rapidly, there remain important unresolved issues that may affect the widespread dispersion of this technology. The application of TAVI to younger and lower risk patients, more complex anatomy, bicuspid aortic valve stenosis, and in failing surgical bioprosthetic heart valves, mandates good quality clinical research studies to better inform medical-decision making among interested physicians and surgeons. More recently, transcatheter mitral valve implantation (TMVI) has been introduced as a potential alternative to surgical intervention among inoperable patients with severe symptomatic mitral regurgitation.⁶ This technology is in its infancy with less than 100 patients treated worldwide, though there are important lessons from the TAVI experience,

that can be applied to this novel therapy. Pre-procedural imaging for TMVI with multislice computed tomography is one such lesson that will be extrapolated in this thesis.

“We look for medicine to be an orderly field of knowledge and procedure. But it is not. It is an imperfect science, an enterprise of constantly changing knowledge, uncertain information, fallible individuals, and at the same time lives on the line. There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing. The gap between what we know and what we aim for persists. And this gap complicates everything we do.”

Atul Gawande, Complications: A Surgeon's Notes on an Imperfect Science

AIMS

The aims of this thesis are to study the development of transcatheter aortic valve implantation (TAVI), including pre-procedural imaging, novel adaptations and failure of the technology, and to draw on these experiences to explore some basic principles of transcatheter mitral valve implantation (TMVI).

Specific goals include:

1. To review the anatomy of the aortic valve complex, principles of patient selection, and key procedural steps in TAVI.
2. To investigate the importance of non-invasive imaging in TAVI, with specific focus on pre-procedural multislice computed tomography.
3. To appraise the prevalence of aortic stenosis and adoption of TAVI in Europe.
4. To assess clinical outcomes associated with novel adaptations of TAVI technology.
5. To apply knowledge gained from the aortic valve arena, and apply it to describe a standardized methodology for the assessment of the mitral valve complex using multislice computed tomography for the purposes of transcatheter mitral valve implantation.

OUTLINE

The foreword aims to familiarize the reader with the anatomy of the aortic valvar complex and its associated structures (**Chapter 2**), to introduce the concept of patient selection for TAVI (**Chapter 3**), and to discuss the key technical steps (**Chapter 4**) in the performance of transfemoral TAVI. The importance of appropriate pre-procedural multi-modal imaging (**Chapters 5**) is examined.

Part II. TAVI Candidates and Technology Adoption

Part two of this thesis describes the prevalence of severe aortic stenosis, and attempts to establish the number of potential TAVI candidates in Europe and North America (**Chapter 6**). Subsequently, the actual adoption of TAVI technology in Western Europe is studied, and factors that may affect utilization in individual nations are investigated (**Chapters 7**). Finally, we discuss clinical trial design for approval of THVs in the U.S, and suggest the use of Objective Performance Criteria for new device approval under certain circumstances (**Chapter 8**).

Part III. Novel Applications of TAVI Technology

Herein, we describe the adaptation of TAVI technology for the treatment of failing surgical bioprosthetic aortic and mitral valves (**Chapters 9, 10, 11 and 12**). Thereafter, the use of self-expandable and balloon-expandable TAVI systems in bicuspid aortic valve morphology is evaluated (**Chapter 13**). The technical details of a first-in-human implant of a new transcatheter heart valve system are described (**Chapter 14**). Finally, the development of transcarotid vascular access for TAVI is then investigated (**Chapter 15**).

Part IV. Transcatheter Heart Valve Failure

In this section, we explore the subject of transcatheter heart valve failure, and identify valve failure modes that are typical of surgical bioprosthetic valves, and failure modes that are unique to TAVI (**Chapter 16**).

Part V. Transcatheter Mitral Valve Implantation

The final section in this thesis introduces the concept of transcatheter mitral valve replacement (**Chapter 17**). We then describe for the first time a systematic measurement methodology for assessing the mitral valvar complex for the purposes of TMVI (**Chapter 18**) and provide results from applying this methodology to a potential patient population (**Chapter 19**).

REFERENCES

1. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Sebah L, Bash A, Nusimovici D, Litzler PY, Bessou JP and Leon MB. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. *J Am Coll Cardiol*. 2004;43:698-703.
2. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL and Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33:2451-96.
3. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd and Thomas JD. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63: 2438-88.
4. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, Webb JG, Mack MJ, Douglas PS, Thourani VH, Babaliaros VC, Herrmann HC, Szeto WY, Pichard AD, Williams MR, Fontana GP, Miller DC, Anderson WN, Smith CR, Akin JJ and Davidson MJ. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2485-91.
5. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Jr., Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S and Oh JK. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790-8.

THE ANATOMY OF THE AORTIC VALVAR COMPLEX

2

Adapted from:

The Anatomy of the Aortic Valvar Complex

Mylotte D, Spicer DE, Sarwark AE, Backer CL, Anderson RH, Piazza N.

The Clinical Atlas of Transcatheter Aortic Valve Therapies, First Edition. Edited by Serruys PW, Windecker S, Thomas M, Bax J, Piazza N, van Mieghem N, Leon M.

2014 Europa Digital & Publishing.

INTRODUCTION

Half a millennium ago, Renaissance artist and scientist Leonardo da Vinci (1513) provided the first description of the structure and function of the aortic valvar complex.¹ da Vinci described how eddy currents generated by the sinuses of Valsalva approximated the aortic valvar leaflets in preparation for valvar closure. Some 500 years later, renewed interest in the anatomy of the aortic valvar complex has emerged in the light of the development and widespread adoption of transcatheter aortic valve implantation (TAVI). While there are several publications describing the anatomy of the aortic valvar complex,²⁻⁴ few specifically focus on the unique challenges presented by TAVI.⁵ Herein, we provide a detailed and comprehensive description of the anatomy of the aortic valvar complex as it pertains to TAVI.

ATTITUDINALLY APPROPRIATE NOMENCLATURE

In this chapter, we will describe all relevant cardiac structures according to their anatomical position within the chest, rather than the more traditional and somewhat confusing Valentine description.⁶ Attitudinal anatomy becomes even more important when one considers that it corresponds to the 3-dimensional imaging techniques currently used to assess the aortic root for the purposes of TAVI.

THE AORTIC ROOT

The 'aortic root' refers to the aortic outflow tract from its entrance at the left ventricular outlet to its junction with the ascending portion of the aorta.⁷ It is demarcated inferiorly by a virtual plane created by joining the basal attachment of the aortic valvar leaflets within the left ventricular outflow tract, and superiorly by the distal attachment of the leaflets at the sinutubular junction (**Figure 1**).⁸ Within the root as thus defined, it is possible to recognise the sinuses of Valsalva, the sinutubular junction, the fibrous interleaflet triangles, and the semilunar valvar leaflets with their attachments in part to the ventricular and aortic walls, and in part to the aortic or anterior leaflet of the mitral valve (**Figure 2**). The root lies posterior and rightward relative to the subpulmonary infundibulum, with its circumference bordered anteriorly by the muscular left ventricle, and posteriorly by the orifices of the atrioventricular valves.

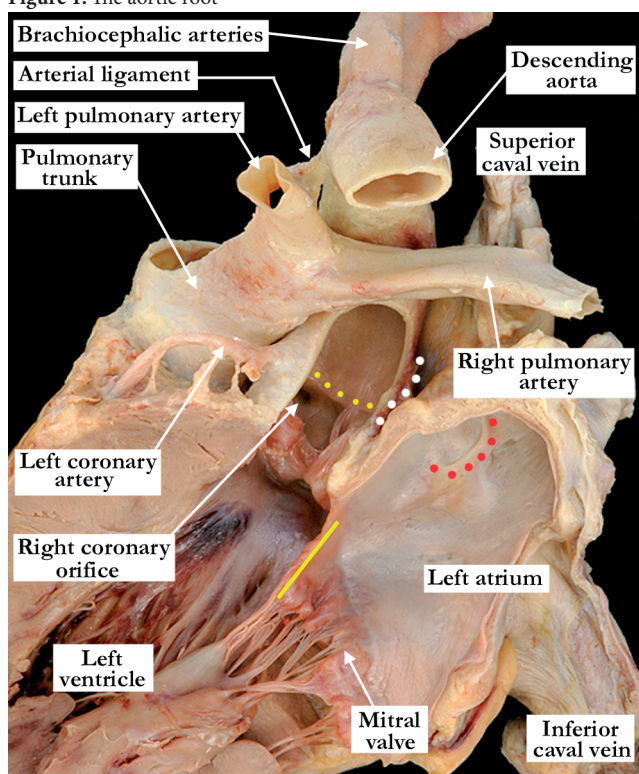
Figure 1. The aortic root

Figure 1. The left atrial and left ventricular walls along with the posterior wall of the aortic root have been removed to show the relationships of the structures surrounding the aortic root. Anteriorly the aortic root is bordered by the pulmonary trunk, the two arterial trunks spiralling as they leave the ventricular mass and exit the pericardial cavity. The pulmonary trunk bifurcates into the right and left pulmonary arteries and the arterial ligament extends from the base of the left pulmonary artery to the underside of the aortic arch. Adjacent to the pulmonary trunk and along its left posterior aspect, the left coronary artery arises from the aortic root and from the left facing or left coronary aortic sinus. The right facing or right coronary aortic sinus gives rise to the right coronary artery with the right coronary orifice arising just below the sinotubular junction in this specimen. The aortic root extends posterior and to the right of the pulmonary trunk with the distal most extension of the root marked by the sinotubular junction (yellow dots) and giving way to the tubular or ascending aorta. The ascending aorta then becomes the transverse aortic arch from which the brachiocephalic arteries arise. The area between the left subclavian artery, the most distal of the brachiocephalic arteries, and the arterial ligament is the aortic isthmus. The aortic isthmus then continues as the descending aorta. The right pulmonary artery crosses behind the ascending aorta on its way to the root of the right lung. The superior caval vein flanks the ascending aorta on the right. Within the left atrium, the horseshoe-like structure (red dots) marks the posterior aspect of the flap valve of the oval fossa where it overlaps the superior interatrial fold. The anterior wall of the right and left atrium lie adjacent to the aortic root and the space separating them is intrapericardial, known as the transverse sinus (white dots). The inlet of the left ventricle is guarded by the mitral valve with the anterior or aortic leaflet separating the inlet from the outlet component. This leaflet (yellow line) is in fibrous continuity with the aortic valve and forms an integral component of the supporting structures for the aortic root.

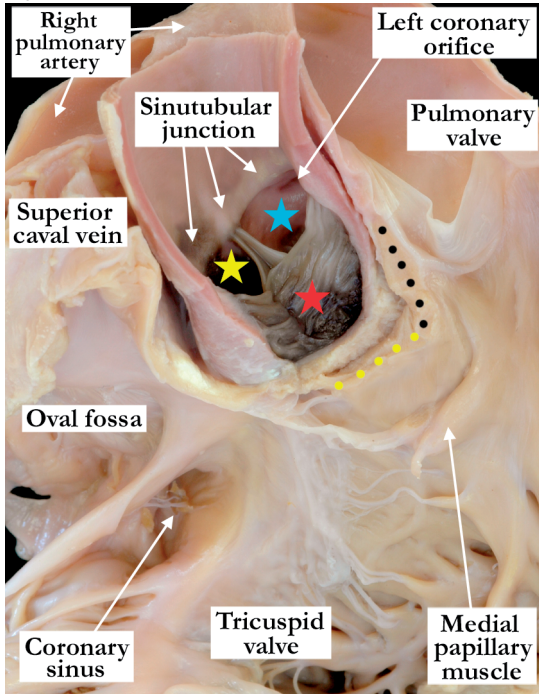
Figure 2. Aortic root

Figure 2. This is a simulated, oblique, subcostal echocardiographic view demonstrating the central position of the aortic root relative to the other cardiac valves. The aortic valve is to the right and posterior to the pulmonary valve that is supported by a complete, subpulmonary muscular infundibulum (black dots). Two leaflets of the aortic valve are immediately adjacent to the pulmonary trunk with those aortic sinuses typically giving rise to the coronary arteries. The red star marks the right hand facing sinus and gives origin to the right coronary artery while the left hand facing sinus (blue star) gives origin to the left main coronary artery. The yellow star marks the non-adjacent aortic sinus that has been referred to in the past as the non-coronary aortic sinus. Although rare, coronary arteries have been known to arise from this sinus, so the best reference to this sinus is non-adjacent. The leaflets of the aortic valve attach to the aortic wall at the sinutubular junction which is the distal most margin of the aortic root. On the anterior aspect of the aortic root lies the inner heart curvature which is at the junction of the subpulmonary infundibulum (black dots) and the parietal wall of the right ventricle, this area sometimes referred to as the ventriculo-infundibular fold (yellow dots). Note the close proximity of the right atrial musculature to the right of the aortic root.

AORTIC SINUSES

The regions corresponding to the luminal surface of the three bulges of the aortic root, which support their respective valvar leaflets, are known as the aortic sinuses of Valsalva (**Figure 3**). Usually, the right and left sinuses give rise to coronary arteries (right and left), while the third sinus does not. Because of this, the third sinus is usually described as the non-coronary sinus. On rare occasions, nonetheless, a coronary artery can arise from this third sinus. We prefer, therefore, to describe the sinuses as being right coronary; left coronary; and non-

adjacent. The “non-adjacency” is considered relative to the sinuses of the pulmonary trunk. When considered attitudinally, the sinuses are located anteriorly (right coronary), leftward and posteriorly (left coronary), and rightward and posteriorly (non-adjacent) ⁷. The mean diameter of the sinuses of Valsalva as measured with multidetector computed tomography (MDCT) was 32.4 ± 4.0 mm,⁹ and was not significantly different between patients with and without aortic stenosis.¹⁰

Figure 3. Aortic sinuses

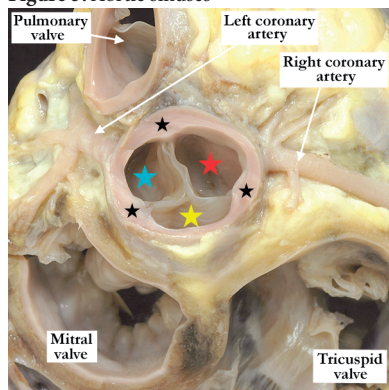


Figure 3. This close up view of the aortic root from the base of the heart demonstrates the relationship between the atrioventricular valves, the anterior wall of the atriums and the pulmonary trunk. The aortic root is located at the centre of the heart and is deeply wedged between the atrioventricular valves. The subpulmonary muscular infundibulum and the pulmonary trunk wrap around the anterior aspect of the aortic root. The two aortic sinuses that lie adjacent to the pulmonary trunk are called the right (red star) and left (blue star) facing sinuses, the right facing sinus typically giving rise to the right coronary artery and the left facing sinus the left coronary artery. The sinus marked by the yellow star is the non-adjacent sinus and is farthest from the pulmonary trunk. The zones of apposition between the three aortic valvar leaflets extend from the thickened areas within the aortic wall (black stars) to the central portion of the valvar orifice, this entire area marked as the commissure. In the past, only the areas at the black stars marking the attachment of the leaflets to the sinutubular junction were referred to as the commissures.

As the aortic root is a centrally located cardiac structure within the pericardial sac, rupture of the root or one of its sinuses during TAVI can result in direct communication with several different cardiac chambers.⁷

- Non-adjacent sinus: potential communication with the right or left atrium
- Left coronary sinus: potential communication with the left atrium or the transverse sinus (pericardial space).
- Right coronary sinus: potential communication with the right atrium or the right ventricular outflow tract.

As it exits the left ventricle, the aortic root angulates slightly towards the right and therefore overlies the superior aspect of the muscular ventricular septum and the right ventricle. Thus, aortic root rupture during TAVI can potentially also produce an interventricular septal communication.

SINUTUBULAR JUNCTION

The superior attachments of the aortic valvar leaflets demarcate the level of the sinutubular junction. This junction marks the exit of the aortic root, and the beginning of the ascending aorta (**Figures 2, 4**). Echocardiographic studies have demonstrated that the diameter of the sinutubular junction is significantly larger in patients with aortic stenosis than in normal patients.¹⁰ MDCT data demonstrate that the maximal diameter of the sinutubular junction is 28.2 ± 3.2 mm, and that the mean distance between the basal attachment of the valvar leaflets and the sinutubular junction (sinutubular height) is 20.3 ± 3.3 mm.⁹ The sinutubular ridge is prone to age-related atherosclerotic change and calcification.¹¹ The extent and location of such calcification should be considered when planning TAVI.

Figure 4. Sinutubular junction

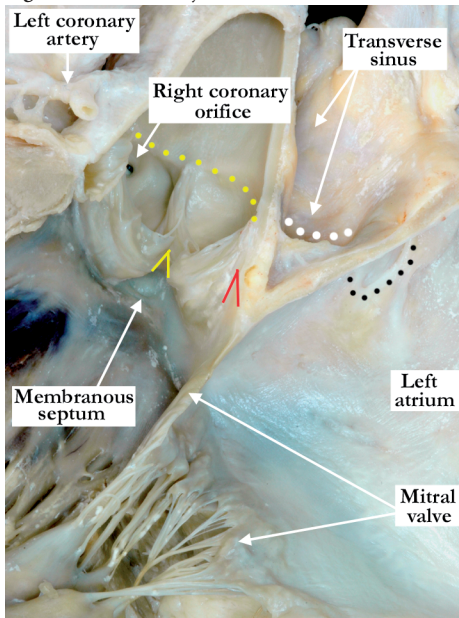


Figure 4. This long axis, close up view of the inlet and outlet components of the left ventricle highlights the relationship of the interleaflet triangles to the outside of the heart. The apex of the interleaflet triangles is the distal most extent of where the semilunar hinges of the leaflets join the sinutubular junction (yellow dots). The interleaflet triangle between the non-adjacent and the right coronary aortic sinus is illustrated with yellow lines. The red lines mark the interleaflet triangle between the non-adjacent and the left coronary aortic sinus, showing nicely how the distal extension of the interleaflet triangles separates the cranial extension of the aortic root from the pericardial cavity. The white dots mark the margin of the serous pericardium lining the transverse sinus. The serous pericardium reflects from the epicardial surface of the tubular aorta onto the anterior wall of the atrial chambers and incorporates a small area outside the heart, but within the pericardial cavity. The proximal aspect of two of the interleaflet triangles are in direct contact with the area of aorta to mitral fibrous continuity and are an integral part of the left and right fibrous trigones. Note the black dots which mark the horseshoe-like structure representing the overlapping of the flap valve of the oval fossa with the superior interatrial fold.

AORTIC LEAFLETS

The normal aortic valve is trifoliate (**Figure 5 A, B**). Each of the three leaflets has a semilunar attachment within the aortic root, and a free margin for coaptation with the other leaflets. At the level of the sinutubular junction, the semilunar hinges of adjacent leaflets come together to form the so-called commissures. If used literally, however, a “commissure” is a zone of apposition between adjacent structures. The true “commissures” within the valvar root, therefore, are the three zones of apposition between the leaflets extending from the so-called “commissures” to the valvar centroid. The leaflets themselves are slightly thicker towards their free margins. Interindividual and intraindividual variability with respect to the width and height of the leaflets is common.¹² The average width, measured between the peripheral zones of attachment along the sinus ridge, is 25.5 mm (**Figure 6**). The average height, measured from the base of the center of the leaflet to its free edge, is 14.1 mm (**Figure 5**). Coaptation along the zones of apposition occurs on the ventricular aspect of the leaflets, and involves the entire length of the free margin, taking place along approximately one third of the total leaflet depth. The central point of coaptation is thickened, and is known as the lunule. The leaflets are comprised of a fibrous core and underlying subendothelial fibroelastic layers. In the setting of severe aortic stenosis the

Figure 5. Normal trileaflet aortic valve leaflets

5A. Aortic view

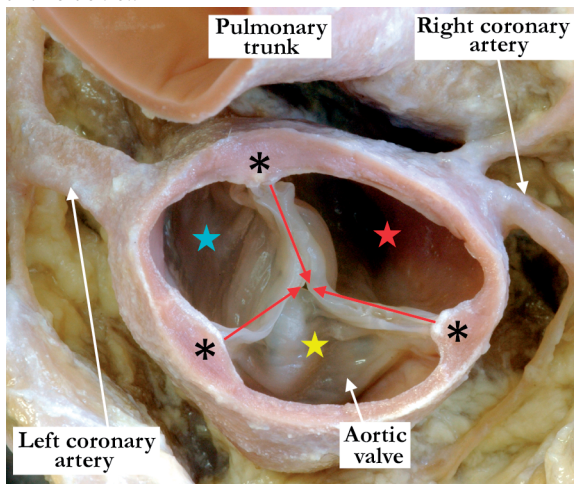


Figure 5A. This close up, short axis view from the base of the heart shows the normal aortic valve with two of the leaflets and aortic sinuses adjacent to the pulmonary trunk, the right (red star) aortic sinus typically gives rise to the right coronary artery and the left (blue star) aortic sinus the left coronary artery. The non-adjacent aortic sinus is represented by the yellow star. The zones of apposition (red arrows) between the leaflets extend from their attachments at the sinutubular junction (black stars) to the centre of the valvar orifice. Historically, it was only the peripheral attachments that were referred to as the commissures. Actually, it is the entirety of the zone of apposition that is the commissure.

5B. Ventricular view

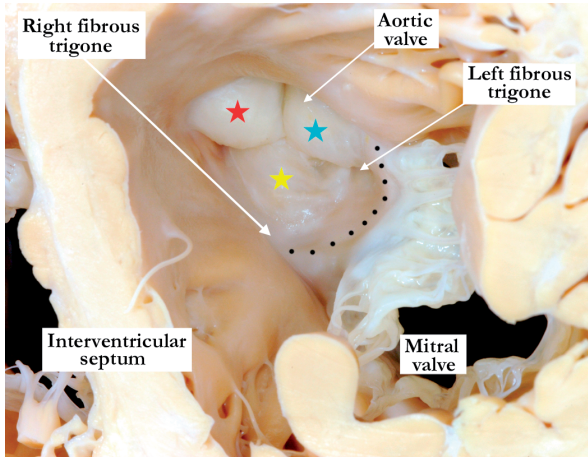


Figure 5B. The aortic to mitral fibrous continuity (black dots) and the aortic valve are viewed from the apex of the left ventricle. The mitral valve is supported by tendinous cords arising from the paired papillary muscles with no attachments to the ventricular septum. Within the left ventricle, the aortic root interposes between the mitral valve and the interventricular septum. The left ventricular outlet has a partially fibrous and partially muscular wall. Two of the leaflets that guard the outlet or aortic root are in fibrous continuity with the anterior or left coronary leaflet of the mitral valve. These are the non-adjacent (yellow star) and the left (blue star) facing or left coronary leaflet with the third leaflet, the right (red star) facing or right coronary leaflet. The right and left fibrous trigones form the two ends of this fibrous continuity. The aortic root and mitral valve are anchored within the roof of the left ventricle where the fibrous trigones attach to the crest of the muscular ventricular septum. The fibrous trigones are thickened areas within the aortic to mitral fibrous continuity and the right fibrous trigone is continuous with the membranous septum. The right fibrous trigone and the membranous septum together form the central fibrous body.

Figure 6. Dimensions of aortic leaflets

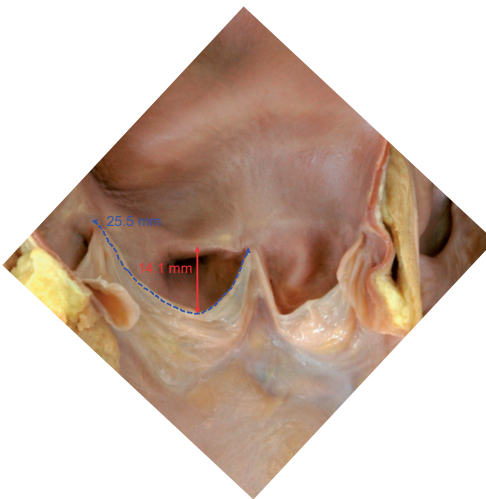


Figure 6. The average length and height of the aortic valve leaflets are 25.5 and 14.1 mm, respectively.

leaflets become thickened, heavily calcified, and non-compliant, with a resultant reduction in the orificial area for the systolic ejection of blood by the left ventricle (**Figure 7 A, B**).

Figure 7. Calcific aortic stenosis

7A. Aortic view

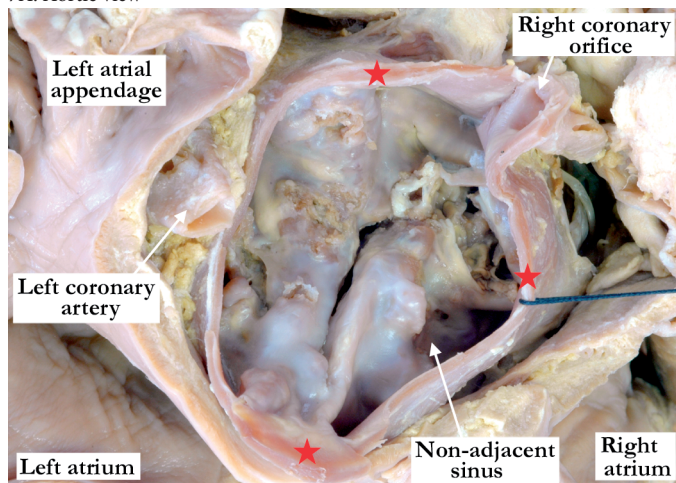


Figure 7A. The aortic root is viewed from the base of the heart and has been transected just below the sinutubular junction along the anterior most aspect. The aortic valvar leaflets are extremely thickened and are entirely calcified. The leaflets are non-compliant with only a small, slit-like, eccentric opening.

7B. Ventricular view.

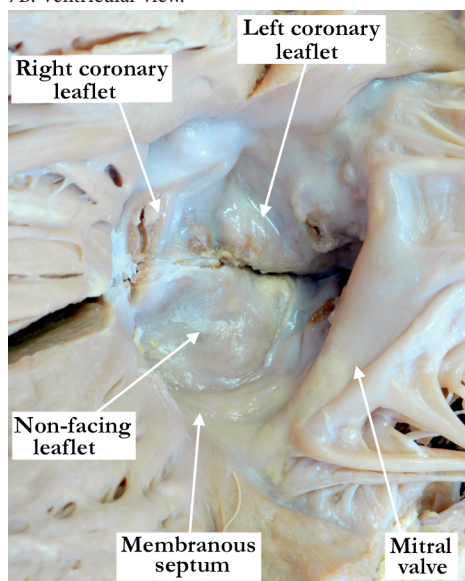


Figure 7B. This view is looking into the left ventricular outflow from the apex. The aorta to mitral fibrous continuity is thickened and has a redundant, shelf-like appearance secondary to the calcific nature of the aortic valvar leaflets. The leaflets are focally nodular and ulcerated with a slit-like, slightly eccentric opening. The normal semilunar nature of the leaflets and the overall anatomy of the aortic root have been disrupted.

The non-adjacent leaflet, and part of the left coronary leaflet, are in fibrous continuity with the aortic or anterior leaflet of the mitral valve. At either end, this area of fibrous continuity thickens to form the right and left fibrous trigones. The right fibrous trigone itself is then continuous with the membranous septum, and together these structures form the central fibrous body. When considered together, the fibrous trigones serve to anchor the aorto-mitral valvar unit to the roof of the left ventricle (**Figure 8**). Inadvertent low implantation of a transcatheter valve can therefore impinge on the aortic leaflet of the mitral valve, and yield mitral valve dysfunction.¹³

Figure 8. Ventricular aspect of aortic and mitral valves

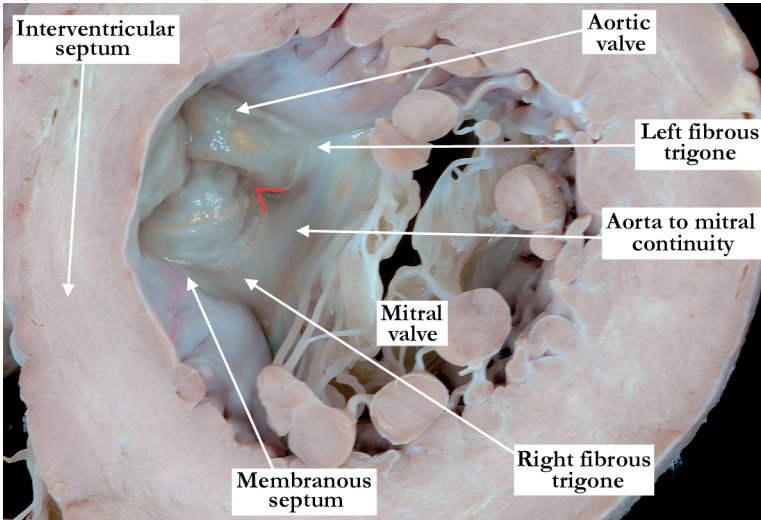


Figure 8. In this simulated, short axis, apical, echocardiographic view, the aortic root lies within the central portion of the heart and lifts the mitral valve away from the muscular, interventricular septum. The mitral valve is a bifoliate structure and is supported by paired papillary muscles with no cordal attachments to the septum. The aorta to mitral fibrous continuity supports approximately one third of the aortic root with the remaining two thirds supported by muscle. This area of fibrous continuity is quite strong and is supported by the thickened areas of the left and right fibrous trigones. The right and left fibrous trigones are easily seen at each end of the fibrous continuity with the interleaflet triangle (red lines) extending between the zones of apposition between the left aortic sinus and the non-adjacent aortic sinus. The non-adjacent sinus is entirely supported by the area of fibrous continuity between the aortic and mitral valves. The right fibrous trigone joins with the membranous septum at the base of the interleaflet triangle between the right aortic sinus and the non-adjacent sinus and forms the central fibrous body.

ANATOMY OF THE SO-CALLED “AORTIC ANNULUS”

The anatomic ventriculo-arterial junction is the transition point where left ventricular muscular tissue is replaced by the fibroelastic walls of the aortic valvar sinuses (**Figure 9**). Two of the aortic valvar leaflets cross this ventriculo-arterial junction, and take their basal origins from

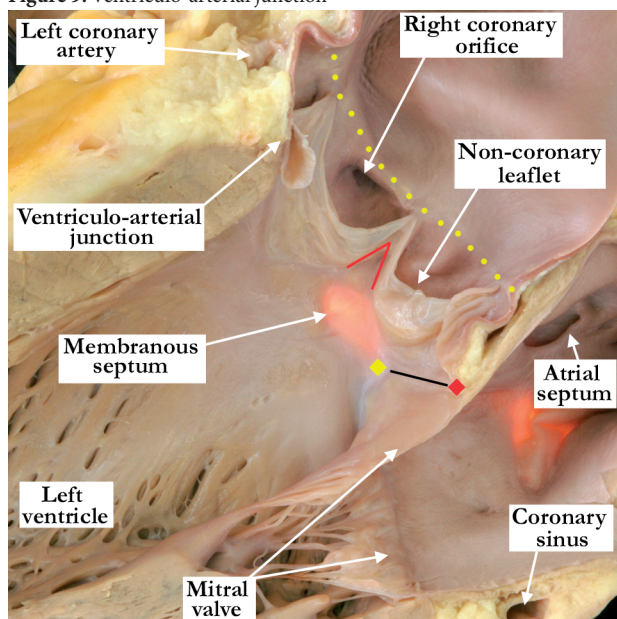
Figure 9. Ventriculo-arterial junction

Figure 9. This is a close up, long axis view of the left ventricle and the aortic root. The aortic root is supported by partially fibrous and partially muscular walls with the anterior or aortic leaflet of the mitral valve in fibrous continuity with the aortic valve. This area of fibrous continuity (black line) involves the left and non-adjacent leaflets. The ends of this area of fibrous continuity are thickened and form the right (yellow diamond) and left (red diamond) fibrous trigones with the right fibrous trigone continuous with the membranous septum. These two components then form the central fibrous body. The attachments of the fibrous trigones to the crest of the musculature of the ventricular septum are what anchors the aortic root and the mitral valve within in the roof of the left ventricle. In the left ventricle, the aortic root interposes between the mitral valve and the septum. The anatomic ventriculo-arterial junction is in the area where the fibrocollagenous wall of the aorta is supported by the musculature of the parietal wall of the ventriculo-arterial junction. There is epicardial fat marking the outer aspect of this junction. The yellow dots mark the sinutubular junction which is the distal most extent of the aortic root. This area is typically represented by a discrete ridge between the aortic valvar sinuses and the tubular component of the aorta. The red lines represent a fibrous triangle between the right and non-adjacent aortic leaflets. These fibrous triangles extend between the semilunar hinge lines of the three aortic valvar leaflets to become the most distal extension of the ventricular outflow tract.

the muscular walls of the left ventricle (**Figure 10**). The semilunar hinge line of the coronary aortic leaflets, therefore, incorporates a small crescent of ventricular myocardium within the aortic sinuses. It is the virtual plane created by joining together the basal attachments of the leaflets that demarcates the frequently described “aortic annulus”. It is this diameter of the entrance to the root that is important for the purposes of transcatheter aortic valve sizing.

There are three circular, and 1 crown-like, rings within the extent of the aortic root (**Figure 11**).⁸ Since the leaflets are attached throughout the length of the root, it is their semilunar hinges which, in 3-dimensions, form the crown-like structure. The base of this crown is not a distinct anatomical structure, but is the virtual ring formed by joining the basal attachments of

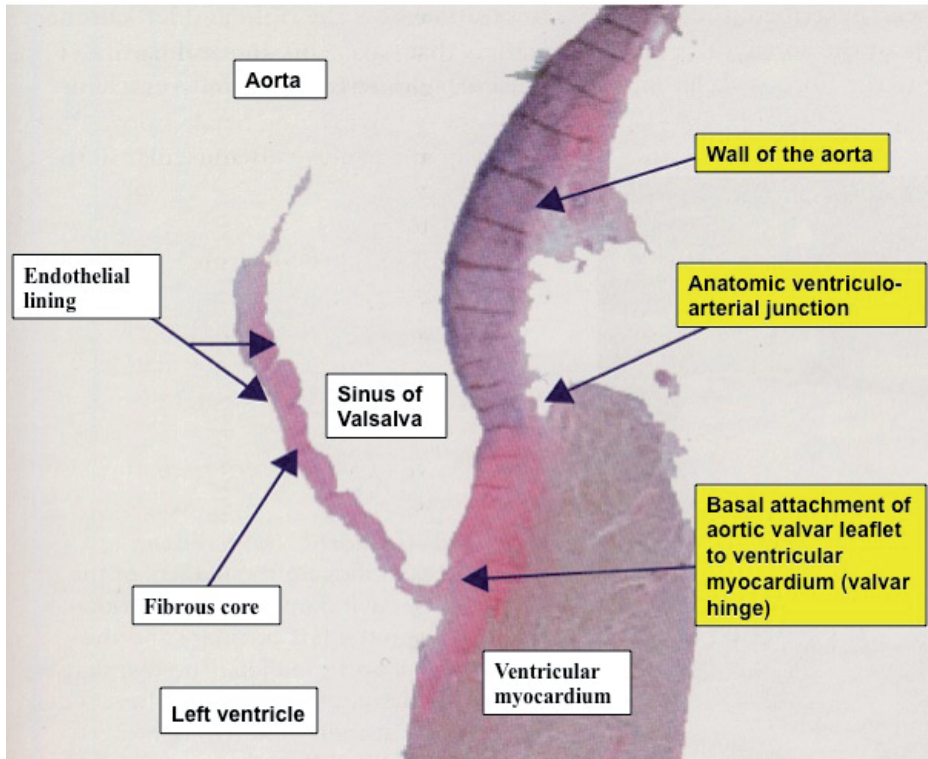
Figure 10. Histology of the aortic root

Figure 10. Histology of the aortic valvar complex shows the anatomic ventriculoarterial junction. Note that the basal attachment of the aortic valvar leaflets to the ventricular myocardium is proximal relative to the anatomic junction. The aortic leaflet displays an endothelial lining and a fibrous core.

the leaflets within the left ventricle. As discussed above, it is the diameter of this plane that is usually designated by echocardiographers as representing the valvar annulus. Many surgeons, in contrast, consider the crown-like construction to be the “annulus”. The sinutubular junction forms the superior aspect of the crown and is a true anatomical ring. It is demarcated by the sinus ridge, the distal attachment points of the leaflets to the aortic root, and represents the most distal apposition zone between the aortic valve leaflets. Despite its true annular morphology, however, it is rarely, if ever, defined as the “annulus”. The anatomic ventriculo-arterial junction also forms a ring between the base and superior aspects of the crown, but this locus is also not defined as the annulus.

Figure 11. The Aortic Rings

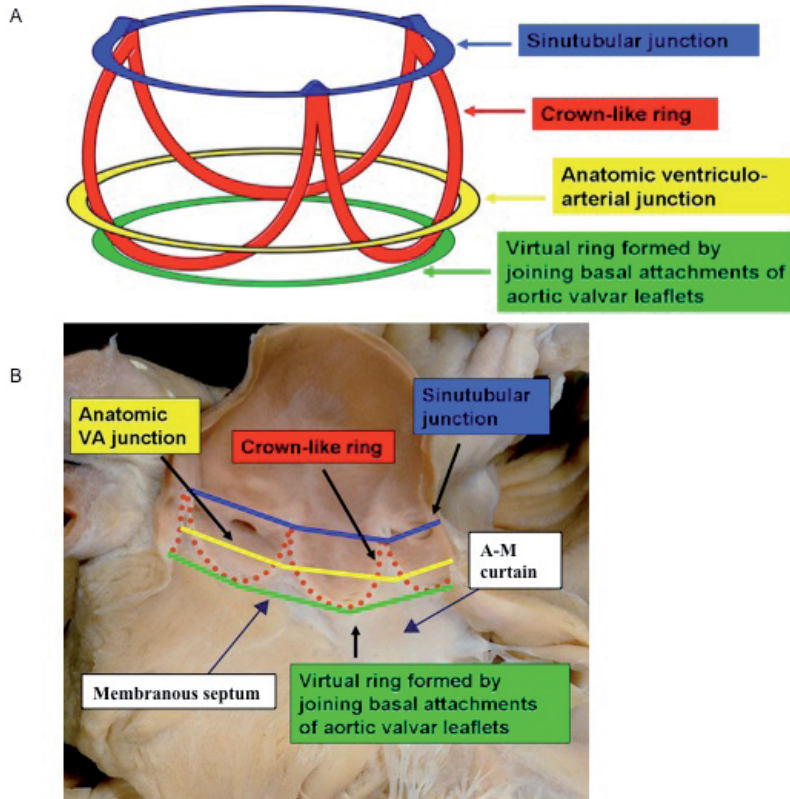


Figure 11. (A) Three-dimensional arrangement of the aortic root, which contains 3 circular “rings,” but with the leaflets suspended within the root in crown-like fashion. (B) The leaflets have been removed from this specimen of the aortic root, showing the location of the 3 rings relative to the crown-like hinges of the leaflets. VA indicates ventriculoarterial; A-M, aortic-mitral.

AORTIC ROOT DIAMETERS

The shape of the aortic root is consistent, though its diameter can vary considerably. The diameter at its outlet, which is the level of the sinutubular junction, exceeds that at the level of its inlet at the virtual ring formed by the basal attachments of the leaflets by a ratio of 1.34 to 1.¹⁴ Thus, the root has been described as a truncated cone. Importantly, the valvar complex is a dynamic structure, and its dimensions change according to the phases of the cardiac cycle, and with changes in pressure within the aortic root.^{15, 16} The diameter of its entrance, the so-called aortic annulus, in particular, increases in diameter and decreases in eccentricity during ventricular systole.

Accurate measurement of the dimensions of the root is a critical component of successful transcatheter aortic valve implantation. Erroneous measurement of the aortic root (**Figure 12**) can lead to malposition or embolization of the prosthesis, paravalvar leak, rupture of the entrance to the root, and the potential for early structural degeneration of the leaflets. Several imaging modalities can be used for assessing the dimensions of the so-called annulus. The measurements of relevance include.¹⁷

Dimensions: maximal diameter, minimal diameter, mean, area, perimeter (circumference)

- Width of the Sinuses of Valsalva
- Height of the Sinuses of Valsalva
- Take-off height of the coronary arteries
- Width of the ascending aorta

Figure 12. Erroneous measurement of the aortic annulus diameters.

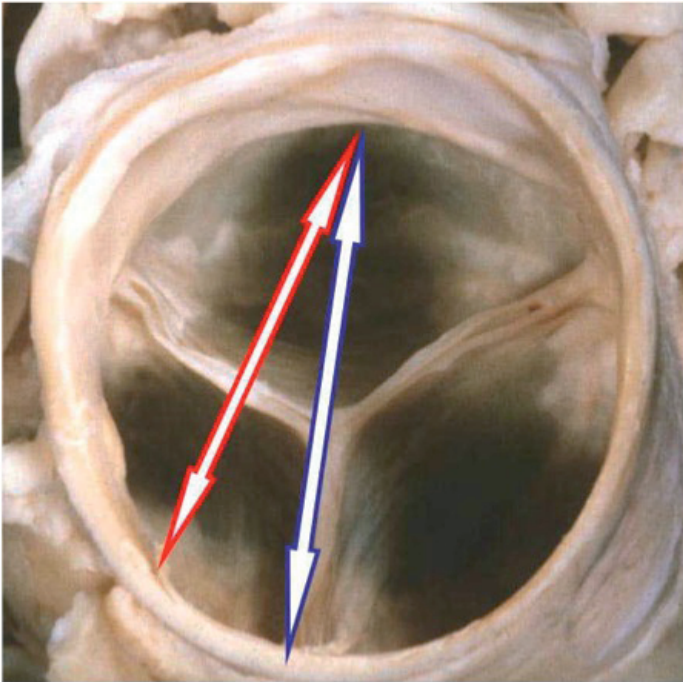


Figure 12. This basal short-axis view shows the closed aortic valve. The arrows demonstrate the potential hazard of 2-dimensional imaging techniques (echocardiography, contrast aortography) for measuring the “aortic valve annulus.” Measurements made using the basal attachment of the leaflets do not transect the full diameter of the outflow tract but instead a tangent cut across the root.¹⁸

THE INTERLEAFLET FIBROUS TRIANGLES AND TRIGONES

The aortic root has several important boundary structures: the muscular and membranous interventricular septal components, the aortic or anterior mitral valvar leaflet, the area of aortic-to-mitral valvar continuity, and the two fibrous trigones. Approximately two thirds of the circumference of the lower part of the aortic root is connected to the muscular ventricular septum, with the remaining one third in fibrous continuity with the aortic leaflet of the mitral valve. As the semilunar attachments of the valve leaflets cross the anatomic ventriculo-arterial junction and merge distally to form the commissures, they leave three triangular wedges of tissue between their arcs (**Figure 13**). These triangles are known as the interleaflet fibrous triangles. The triangles are thinner, and less collagenous, than the surrounding sinusal walls. They therefore represent potential sites of root rupture during transcatheter valve implantation. The triangle between the left and right coronary sinuses lies immediately behind the free-standing right ventricular muscular infundibulum. The triangle between the right and non-adjacent leaflets is confluent with the membranous septum. The triangle between the left and non-adjacent leaflets lies along the area of aortic-mitral fibrous continuity.

The ends of the area of fibrous continuity are thickened to form the left and right fibrous trigones, with the right fibrous trigone contiguous with the triangle between the right and the non-adjacent sinuses. The trigones support and hinge the aortic-mitral valvar unit, thereby allowing these structures to be displaced during the cardiac cycle. The right fibrous trigone and the membranous ventricular septum together form the central fibrous body of the heart. This is the area within the heart where the membranous septum, the atrioventricular valves, and the aortic valve join in fibrous continuity.

Figure 13. The interleaflet fibrous triangles

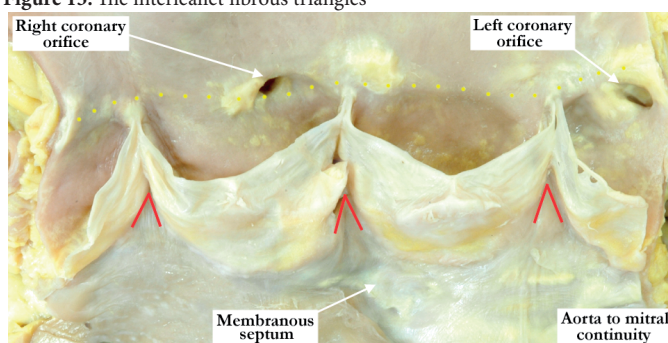


Figure 13. This diseased aortic valve has been opened through the mid portion of the left coronary aortic sinus. All of the aortic valve leaflets are thickened and focally calcified. There are calcific plaques at the sinutubular junction (yellow dots) and within the sinuses, especially in the area where the leaflets cross the anatomic ventriculo-arterial junction. The interleaflet triangles are marked with the red lines. The area of fibrous continuity between the aortic and mitral valves is thickened along with the membranous septum.

CORONARY ARTERIES

In the majority of cases, the coronary arteries arise from two separate orifices located within the left and right coronary aortic sinuses (**Figure 14**).^{14, 19} Most arise below the sinutubular junction, although take-off at (9%) or above (22%) the junction is not uncommon.²⁰ Knowledge of the height of the coronary arteries with respect to the basal attachment of the native valve leaflets is important for those undertaking TAVI. Post-mortem examination of normal hearts show that the left and right coronary arteries arise on average 12.6 ± 2.61 mm and 13.2 ± 2.64 mm from the basal attachment of their respective leaflets.²¹

Figure 14. Origins of the coronary arteries

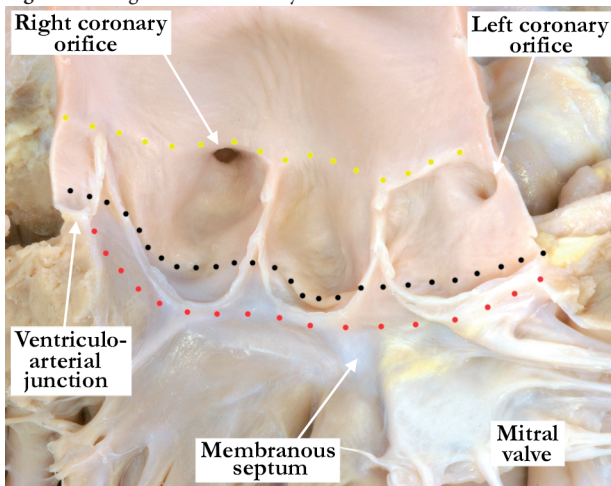


Figure 14. The aortic valvar leaflets have been removed from the intact aortic valve. This demonstrates three lines within the aortic root, the sinutubular junction (yellow dots), the anatomic ventriculo-arterial junction (black dots) and the line marking the most proximal portion of the aortic root (red dots). The sinutubular junction and the anatomic ventriculo-arterial junction form true lines within the aortic root. The line represented by the red dots is a virtual line and represents the proximal most attachment of the aortic valvar leaflets within the left ventricular outflow tract or aortic root. The aortic valvar leaflets cross the anatomic ventriculo-arterial junction at six points around the circumference of the valve, incorporating a crescent of muscle into the base of the sinus of the right coronary aortic leaflet and a portion of the left coronary aortic leaflet. Typically, the non-adjacent sinus has fibrous tissue in this area with fibrous tissue making up the remainder of the base of the left sinus. In this heart, the interleaflet triangle between the right coronary aortic sinus and the non-adjacent sinus is supported by muscle and does not reach the right fibrous trigone and the right-ward extent of the membranous septum.

Accurate assessment of the distance between the basal attachment point of the leaflets and the coronary arterial orifices is an important component of screening in advance of implantation, and procedural planning. All current prostheses available for transcatheter valve implantation are designed with a skirt of fabric or tissue sewn within the stent or frame in order to create a seal with the native aortic root and reduce paravalvar leak). If the origin of the coronary arteries is low within the sinuses of Valsalva, and/or the prosthesis is placed too high, the skirt

can obstruct the arterial orifices and rapidly induce myocardial ischemia and haemodynamic collapse. An identical situation can be observed if deployment of the prosthesis displaces the native leaflets such that they cover that arterial orifices in patients with low lying coronary arteries.

Consequently, the height of the orifices within the sinuses should be assessed using multislice computed tomography.⁹ According to the computed tomographic data, the mean distance from the basal attachment point of the leaflets to the orifices of the left coronary and right coronary arteries was 14.4 ± 2.9 mm and 17.2 ± 3.3 mm, respectively.⁹ Although these measurements were similar in those with and without aortic stenosis, there was important variability that underscores the need for assessment in individual patients, the more so since the height of the orifice of the left coronary artery ranged from 7.1 to 22.7 mm.⁹ The width of the sinuses of Valsalva has also been recognized to be an important determinant of potential arterial occlusion in the setting of transcatheter valve implantation. A minimum sinus width is recommended in order to accommodate the redundant native aortic leaflets.

In cases where transcatheter valve implantation is being considered for treatment of a failing surgical bioprosthesis, it is important to know both the position (annular or supra-annular implantation) and design characteristics of the surgical prosthesis, as coronary arterial occlusion is more commonly described than when native aortic valves are being replaced by transcatheter valve implantation.²²

RELATIONSHIP TO THE CONDUCTION SYSTEM

In the right atrium, the atrioventricular node is located within the triangle of Koch. The boundaries of this triangle are the tendon of Todaro, the orifice of the coronary sinus, and the attachment of the septal leaflet of the tricuspid valve (**Figure 15**). The hinge point of the septal leaflet of the tricuspid valve separates the membranous septum into its atrioventricular and interventricular components. It is the atrioventricular component of this membranous septum that forms the apex of the triangle of Koch, with the atrioventricular node found just inferior to the apex of this triangle.

The atrioventricular node continues as the bundle of His, which penetrates the atrioventricular component of the membranous septum, and runs superficially along the crest of the ventricular septum to give rise to the fascicles of the left bundle branch. The left bundle is closely related to the base of the interleaflet triangle between the right and non-adjacent and leaflets of the aortic valve, with the superior part of the bundle intimately related to the right coronary aortic leaflet (**Figure 16**).²³ Autopsy findings suggest that the average distance between the nadir of the non-adjacent aortic valve leaflet and the left bundle branch is 6.3 ± 2.7 mm. Thus, the conduction axis is closely related to the subaortic apparatus, and can be injured during or after transcatheter valve implantation.

Figure 15. Triangle of Koch

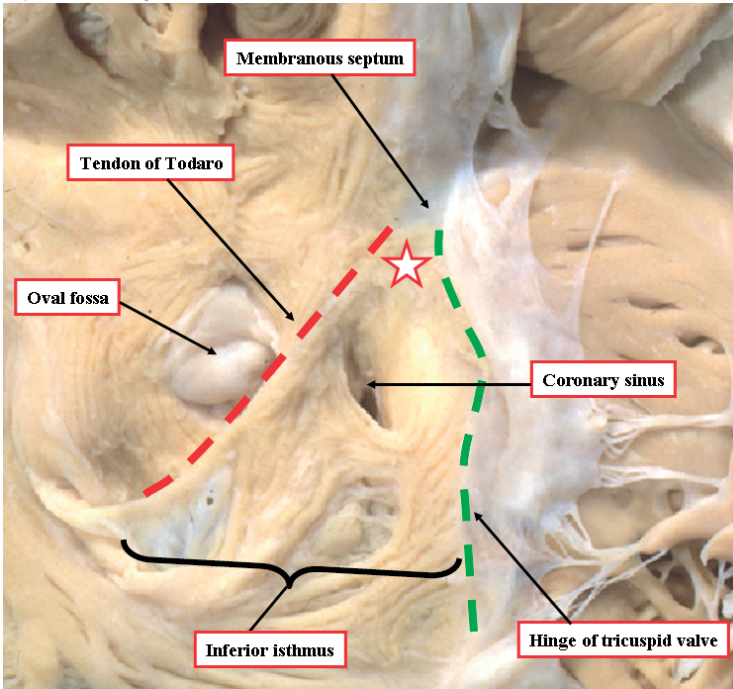


Figure 15. The heart is viewed from the right side, illustrating the component parts of the triangle of Koch.

Figure 16. Atrioventricular node

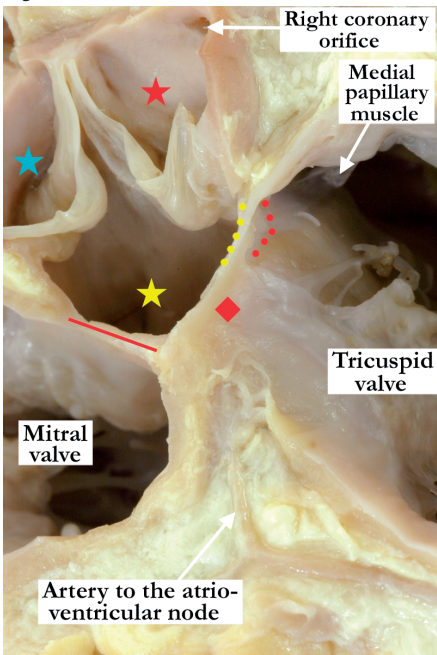


Figure 16. The atrial musculature has been removed along with the non-adjacent sinus of the aortic valve. The right (red star) and left (blue star) facing sinuses remain intact. The area of aortic to mitral fibrous continuity is marked by the red line and the image illustrates how the subaortic outflow tract is lifting the mitral valve away from the interventricular septum. On the opposite aspect a portion of the septal leaflet of the tricuspid valve has been removed to view the atrioventricular (yellow dots) and the interventricular (red dots) components of the membranous septum. This demonstrates the relationship between the base of the right interleaflet triangle, the right fibrous trigone and the membranous septum. The red diamond marks the site of the atrioventricular conduction axis. Note the artery to the atrioventricular node within the fat that interposes between the right and left atrial walls and the crest of the muscular ventricular septum at the base of the inferior interatrial fold.

ADDITIONAL SECTIONS

Bicuspid Aortic Valve

The aortic valve with two leaflets, usually said to be bicuspid, is the most commonly recognized form of adult congenital heart disease, estimated to occur in 1-2% of the general population^{12, 24} (Figure 17). Compared to valves with three leaflets, those with only two leaflets are more likely to develop mid-life aortic stenosis or regurgitation. The majority of patients with such bicuspid valves will require valvar replacement during their lifetime²⁵. This finding is thought to account for up to half of all surgical replacements of the aortic valve undertaken in adults²⁶. The procedure also accounts for over one-fifth of the indications for aortic valvar replacement in octogenarians²⁷. Traditionally, the finding of a valve with two leaflets has been considered a contraindication to transcatheter aortic valve implantation. The large and eccentric entrance of the root associated with the bicuspid valve, along with the extensive calcification and fibrosis of the aortic leaflets, and the not-infrequent requirement for replacement of the ascending aorta, all account for the reluctance to treating these patients percutaneously²⁸. Although viewed traditionally as a contraindication, however, patients with bicuspid valves have been successfully treated by transcatheter valve implantation²⁹.

Figure 17. Bicuspid aortic valve

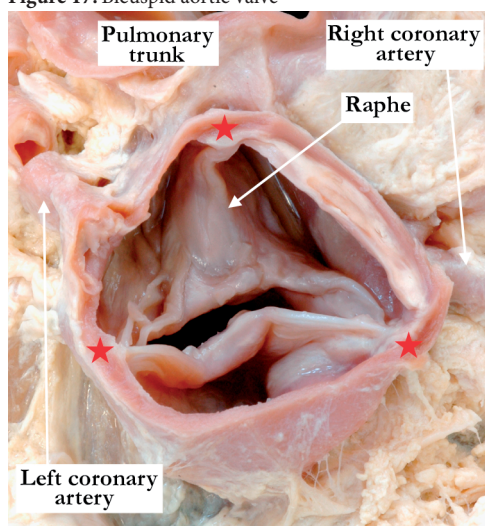


Figure 17. The aortic root is viewed from the arterial aspect and has been transected at the sinutubular junction. The aortic valve is bicuspid with an incomplete zone of apposition or raphe between the right and left facing sinuses. This area and the component parts of the aortic valvar leaflets, are thickened and somewhat rigid, preventing the leaflets from coapting in a normal fashion. The distal attachments of the zones of apposition are marked by the red stars and there is a plaque-like thickening within the aortic wall associated with the right facing sinus.

REFERENCES

1. Robicsek F. Leonardo da Vinci and the sinuses of Valsalva. *Ann Thorac Surg.* 1991;52:328-35.
2. Yacoub MH, Kilner PJ, Birks EJ and Misfeld M. The aortic outflow and root: a tale of dynamism and crosstalk. *Ann Thorac Surg.* 1999;68:S37-43.
3. Becker A. Surgical and pathological anatomy of the aortic valve and root. *Oper Tech Cardiac Thorac Surg* 1996;1:3-14.
4. Anderson RH, Razavi R and Taylor AM. Cardiac anatomy revisited. *J Anat.* 2004;205:159-77.
5. Piazza N, de Jaegere P, Schultz C, Becker AE, Serruys PW and Anderson RH. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. *Circ Cardiovasc Intervent.* 2008;1:74-81.
6. Anderson R and Kanani M. Mitral valve repair: critical analysis of the anatomy discussed. *Multimed Man Cardiothorac Surg.* 2007;2007.
7. Ho SY. Structure and anatomy of the aortic root. *Eur J Echocardiogr.* 2009;10:i3-10.
8. Anderson RH. Clinical anatomy of the aortic root. *Heart.* 2000;84:670-3.
9. Tops LF, Wood DA, Delgado V, Schuijff JD, Mayo JR, Pasupati S, Lamers FP, van der Wall EE, Schalij MJ, Webb JG and Bax JJ. Noninvasive evaluation of the aortic root with multislice computed tomography implications for transcatheter aortic valve replacement. *JACC Cardiovascular Imaging.* 2008;1:321-30.
10. Crawford MH and Roldan CA. Prevalence of aortic root dilatation and small aortic roots in valvular aortic stenosis. *Am J Cardiol.* 2001;87:1311-3.
11. Loukas M, Wartmann CT, Tubbs RS, Apaydin N, Louis RG, Jr., Easter L, Black B and Jordan R. The clinical anatomy of the sinutubular junction. *Anat Sci Int.* 2009;84:27-33.
12. Vollebergh FE and Becker AE. Minor congenital variations of cusp size in tricuspid aortic valves. Possible link with isolated aortic stenosis. *Br Heart J.* 1977;39:1006-11.
13. Wong DR, Boone RH, Thompson CR, Allard MF, Altwegg L, Carere RG, Cheung A, Ye J, Lichtenstein SV, Ling H and Webb JG. Mitral valve injury late after transcatheter aortic valve implantation. *J Thorac Cardiovasc Surg.* 2009;137:1547-9.
14. Reid K. The anatomy of the sinus of Valsalva. *Thorax.* 1970;25:79-85.
15. Swanson M and Clark RE. Dimensions and geometric relationships of the human aortic valve as a function of pressure. *Circ Res.* 1974;35:871-82.
16. Blanke P, Russe M, Leipsic J, Reinohl J, Ebersberger U, Suranyi P, Siepe M, Pache G, Langer M and Schoepf UJ. Conformational pulsatile changes of the aortic annulus: impact on prosthesis sizing by computed tomography for transcatheter aortic valve replacement. *JACC Cardiovasc Interv.* 2012;5: 984-94.
17. Buellesfeld L, Stortecky S, Kalesan B, Gloekler S, Khattab AA, Nietlispach F, Delfine V, Huber C, Eberle B, Meier B, Wenaweser P and Windecker S. Aortic root dimensions among patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv.* 2013;6:72-83.
18. Khaliq OK, Kodali S, Paradis JM, Nazif TM, Williams MR, Einstein AJ, Pearson GD, Harjai K, Grubb K, George I, Leon MB and Hahn RT. Aortic Annular Sizing Using a Novel 3-Dimensional Echocardiographic Method: Utility and Comparison to Cardiac Computed Tomography. *Circ Cardiovasc Imaging.* 2013.
19. Turner K and Navaratnam V. The positions of coronary arterial ostia. *Clin Anat.* 1996;9:376-80.
20. Muriago M, Sheppard MN, Ho SY and Anderson RH. Location of the coronary arterial orifices in the normal heart. *Clin Anat.* 1997;10:297-302.
21. Cavalcanti JS, de Melo NC and de Vasconcelos RS. Morphometric and topographic study of coronary ostia. *Arq Bras Cardiol.* 2003;81:359-62, 355-8.

22. Mylotte D, Lange R, Martucci G and Piazza N. Transcatheter heart valve implantation for failing surgical bioprostheses: technical considerations and evidence for valve-in-valve procedures. *Heart*. 2013; 99: 960-7.
23. Tawara S. *Das Reizleitungssystem de Saugetierherzens: Eine Anatomichhisologische Studie uber das Atrioventricularbündel und die Purkinjeschen Faden*. Jena, Germany; 1906.
24. Edwards JE. The congenital bicuspid aortic valve. *Circulation*. 1961;23:485-8.
25. Lewin MB and Otto CM. The bicuspid aortic valve: adverse outcomes from infancy to old age. *Circulation*. 2005;111:832-4.
26. Roberts WC and Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation*. 2005;111:920-5.
27. Roberts WC, Janning KG, Ko JM, Filardo G and Matter GJ. Frequency of congenitally bicuspid aortic valves in patients ≥ 80 years of age undergoing aortic valve replacement for aortic stenosis (with or without aortic regurgitation) and implications for transcatheter aortic valve implantation. *Am J Cardiol*. 2012;109:1632-6.
28. Himbert D, Pontnau F, Messika-Zeitoun D, Descoutures F, Detaint D, Cueff C, Sordi M, Laissy JP, Alkhoder S, Brochet E, Iung B, Depoix JP, Nataf P and Vahanian A. Feasibility and outcomes of transcatheter aortic valve implantation in high-risk patients with stenotic bicuspid aortic valves. *Am J Cardiol*. 2012;110:877-83.
29. Wijesinghe N, Ye J, Rodes-Cabau J, Cheung A, Velianou JL, Natarajan MK, Dumont E, Nietlispach F, Gurvitch R, Wood DA, Tay E and Webb JG. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. *JACC Cardiovasc Interv*. 2010;3:1122-5.

**PATIENT SELECTION FOR
TRANSCATHETER AORTIC
VALVE IMPLANTATION:
AN INTERVENTIONAL CARDIOLOGY
PERSPECTIVE**

Patient selection for transcatheter aortic valve implantation: An interventional cardiology perspective

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) has emerged as a highly effective minimally invasive treatment symptomatic for severe calcific aortic stenosis in patients at high or prohibitive surgical risk. The success of TAVI has been determined by a number of factors, but in particular by appropriate patient selection. Appropriate patient selection involves identifying patients with the potential to benefit most from TAVI and individualizing the bioprosthesis type and size, and the vascular access site for each case. We present herein, our critical appraisal on patient selection for TAVI: an interventional cardiology perspective.

Keywords: Aortic stenosis, transcatheter heart valve, transcatheter aortic valve implantation, TAVI, Edwards SAPIEN, Medtronic CoreValve, patient selection

INTRODUCTION

In April 2002, Alain Cribier performed the first-in-human transcatheter aortic valve implantation (TAVI). In the ensuing decade, this novel technique has evolved into a relatively mature widely accepted treatment for high or prohibitive surgical risk patients with symptomatic severe calcific aortic stenosis (AS) requiring aortic valve replacement (AVR). The Edwards SAPIEN transcatheter heart valve (THV) (Edwards LifeSciences, Irvine, CA) (*Figure 1*) and Medtronic CoreValve (Medtronic, Minneapolis, MN) (*Figure 2*) are licensed in Europe for implantation in selected patients, and in excess of 80,000 patients worldwide have undergone TAVI.

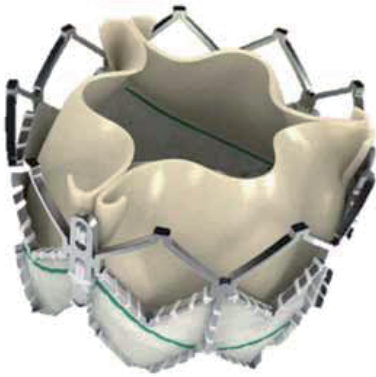


Figure 1 The Edwards SAPIEN XT. A balloon-expandable cobalt-chromium stent to which are sewn bovine pericardial leaflets in a trifoliate configuration



Figure 2 The Medtronic CoreValve. A self-expanding nitinol frame to which is sewn porcine pericardial leaflet in a trifoliate configuration

Careful, considered patient selection by a team of experienced interventional cardiologists, cardiac surgeons, anaesthetists, and imaging specialists (the heart team) has been at the core of the TAVI success story (1). Patient selection for TAVI continues to evolve however, as the almost daily publication of TAVI-related data defines and refines the patient, anatomical, and procedural factors that determine successful implantation. Put simply, appropriate patient selection implies identifying candidates who benefit most from TAVI, however, this can be a complex process (*Table 1*).

Table 1 Pre-procedure screening recommendations

Laboratory indices	Full blood count, serum urea, creatinine and electrolytes, C-reactive protein, serum transaminases, serum albumin, coagulation profile, blood culture, sputum culture, mid-stream urine, glycosylated haemoglobin, human immunodeficiency virus, hepatitis serology
Physical indices	Height, weight, body mass index
Clinical data to calculate logistic EuroSCORE or STS score	Detailed clinical history, examination and current medication list, 12 lead electrocardiography, echocardiography (transthoracic/transoesophageal), coronary angiography, peripheral vascular screening (contrast angiography/multidetector computed tomography), pulmonary function testing, right heart catheterization
Clinical parameters of comorbid conditions	Pulmonary function tests, carotid, vertebral and abdominal ultrasonography
Fragility and cognitive function*	Grip strength, graded exercise testing, walk test, physical activity level, mini-mental score
Confirmation of aortic stenosis severity and assessment of associated pathology	Echocardiography (transthoracic/transesophageal), exercise stress testing, stress echocardiography
Procedural planning	Multidetector computed tomography/transoesophageal echocardiography Aortic annulus: Dimensions (minimal, maximal and mean diameter; area; perimeter) and severity/distribution of calcification Other: Height of coronary arteries, Sinus of Valsalva dimensions, ascending aorta dimensions Iliofemoral vessels: Minimal luminal diameter, tortuosity, calcium distribution Aorta: Aortic plaque distribution, descending aortic tortuosity, proximal ascending aortic diameter

Legend: STS = Society of Thoracic Surgeons

* = Elements of the fried frailty index

TAVI ELIGIBILITY

Potential TAVI recipients must satisfy three essential criteria in order to be deemed “TAVI-eligible” (2,3): severe symptomatic AS, high or prohibitive surgical risk, and absence of contraindications to TAVI.

CONFIRMATION OF THE SEVERITY OF AORTIC STENOSIS

Transcatheter aortic valve implantation is indicated for selected patients with severe AS, thus confirmation of the AS severity is mandatory in all cases. Echocardiography is the gold standard method to assess AS, and yields both important anatomic and haemodynamic information. Doppler evaluation of the peak and mean transaortic gradients and determination of the aortic valve area (AVA) by the continuity equation are recommended. Current societal guidelines define severe AS as a mean aortic valve gradient of ≥ 40 mmHg or an AVA of ≤ 1 cm² (< 0.6 cm²/m²) (3,4). In patients with low transaortic gradients, despite an AVA consistent with severe AS, dobutamine stress echocardiography is recommended to distinguish between severe and pseudo-severe AS (5). The presence of symptoms is used to guide management of AS patients, however determining the nature of symptoms is not always straightforward. In cases of equivocal symptoms, exercise stress testing, and in particular stress echocardiography are advised (6).

SURGICAL RISK ELIGIBILITY

Transcatheter aortic valve implantation is indicated for selected patients at high or prohibitive surgical risk. Thus, the advent of TAVI has renewed interest in the use of surgical risk algorithms. Surgical risk has been quantified using the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) (7) and the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality score (8). However, these scores share important limitations in high-risk patient subsets, most notably a limited predictive capacity and an inability to capture significant comorbid conditions in what is a heterogeneous patient group. The logistic EuroSCORE for example, has a low discriminatory power in TAVI patients (C statistics 0.61 to 0.64) (9). As such, the applicability of these scores in patient selection for TAVI has been questioned (10–12). Despite these limitations, patient enrolment in TAVI trials has been determined by a EuroSCORE $> 15\%$ or an STS score $> 10\%$ (13–15). However, a number of comorbid illnesses associated with adverse surgical outcomes are not included in these risk calculation scores, including: chronic lung disease [forced expiratory volume in 1 second (FEV1) < 1 litre]; liver cirrhosis (Child class A or B); pulmonary hypertension (pulmonary artery systolic pressure > 60 mmHg); previous cardiac surgery; porcelain aorta; recurrent pulmonary emboli; right ventricular failure; contraindication to traditional open chest surgery (wide beam radiotherapy); or cachexia (body mass index < 18 kg/m²).

As such, we recommend these scores be used as a guide for patient selection, though they should not supersede clinical judgement. academic research consortium (VARC) major vascular complications and 30-day mortality (18). This ratio decreases to 1.00 in non-calcified vessels and increases to 1.10 in the presence of moderate to severe calcification.

MDCT is probably the gold standard test for screening the peripheral vasculature of potential TAVI recipients (*Figure 3*) (19). With MDCT, assessment of vessel tortuosity, calcification, and vessel size, is enhanced compared to contrast angiography; MDCT, however, is associated with increased iodinated contrast exposure. High-pitch spiral dual source CT with minimized contrast volume may overcome this limitation (20).

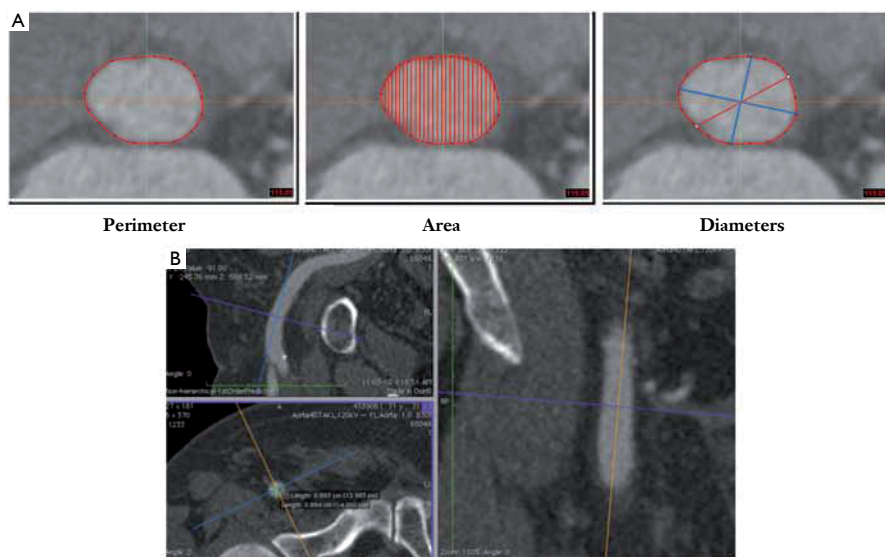


Figure 3 MDCT reconstructions of the aortic annulus and the iliofemoral tree. A. MDCT reconstructions of the aortic annulus can provide maximum/minimum diameters, and perimeter or area measurements; B. Orthogonal sagittal and coronal reconstructions of the peripheral vessels allow accurate proper cross-sectional measurements of the vessels

ANNULUS ASSESSMENT

Although not a distinct anatomic structure, the aortic valve annulus may be defined as the virtual ring formed at the junction of the basal attachment points of the aortic valve leaflets within the left ventricle (21). In this plane, the oval aortic annulus represents the transition point between the left ventricular outflow tract and the aortic root. Accurate measurement of the aortic annulus diameter is of critical importance for THV sizing and the short- and long-term success of the procedure. Valve oversizing risks catastrophic annulus rupture, while undersizing may result in valve migration or paravalvular regurgitation; which has been recognized as an independent predictor of long-term mortality (22).

Transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), MDCT, contrast aortography, and magnetic resonance imaging (MRI) can all be used to assess

the annulus dimensions. Although much debate surrounds the choice of imaging modality for optimal measurement of the non-circular annulus for the purposes of TAVI, MDCT is becoming recognized as the gold standard.

Although TEE is the most practical imaging modality, 2-dimensional (D) measurements of the 3-D aortic annulus, can lead to underestimation of the true dimensions of the annulus (23). It has been suggested that echocardiographic measurement of the annulus potentially results in valve undersizing, and consequently increases the risk of paravalvular aortic regurgitation (24). A recent publication noted that 3-D TEE may provide more accurate aortic annular measurements than 2-D TEE (25), however the use of 3-D TEE is not yet endorsed by societal guidelines (26).

MDCT reconstruction of the annulus orthogonal to the center-axis of the left ventricular outflow tract allows for the assessment of minimal and maximal diameter, circumference, and area measurements. MDCT data has confirmed that the majority of aortic annuli are oval, and has shown the mean difference between the maximum and minimum diameter of the aortic annulus to be 6.5 mm (95% confidence interval, 5.7-7.2) (27). Assessment of the aortic valvar structure with MDCT also facilitates assessment of cusp morphology, and the distribution of calcification. In the light of these advantages, MDCT is becoming the default imaging modality to assess aortic annular dimensions. It remains unclear how to exactly apply MDCT-based valve sizing to existing echocardiographic sizing criteria (27) - this will be further discussed below.

CONTRAINDICATIONS TO TAVI

Although many elderly patients with severe AS meet the “inclusion” criteria for TAVI, these procedures are not suitable for all. As the technology and physician experience evolves, some initial contraindications have been discounted, while others have emerged.

Recently, it has been recognised that frailty and futility are important concepts when selecting patients for TAVI. Frailty is considered to be a distinct clinical syndrome characterized by decreasing muscle mass, energy expenditure, and malnutrition, and imparts extreme vulnerability to adverse events (28). Futility implies that a patients’ condition is so advanced, that meaningful improvement will not be achieved despite a technically successful intervention. In this regard, the 2-year results of the Partner trials offer much food for thought. In inoperable patients (cohort B), two-year mortality following TAVI was 43.3%, the majority of whom died from cardiovascular causes (64.9%) (29). Similarly, two-year mortality was 33.9% in high operative risk patients that received TAVI in Partner cohort A (22). These data send a clear message: performing TAVI on patients who derive little long-term benefit due to irreversible coexisting conditions should be avoided, particularly in the current resource-limited environment. Preliminary analyses suggest that patients with lower surgical risk scores (Eu-

roSCORE, STS) derive the most benefit from TAVI (29,30), though further analysis of large patient populations is required before using risk score cut-off-points to define TAVI-ineligible patients. The role of specific risk scores to assess frailty, such as the Fried Frailty Index (28), is yet to be determined.

In borderline cases, where the decision to proceed to TAVI is not clear due to advanced age, co-morbid conditions or other factors, percutaneous balloon aortic valvuloplasty (BAV) can represent a useful additional selection tool (31). BAV strategy is associated with rapid functional improvement and thus, enhances the prediction of very frail patients who might benefit from TAVI, without incurring the risk or cost associated with a full TAVI procedure. In one study, re-evaluation of borderline patients 30-days after BAV, deemed 46% TAVI eligible, 28% surgical AVR eligible, while 21% demonstrated no functional improvement and were therefore assigned to medical therapy (31).

PROCEDURAL CONSIDERATIONS

Careful planning of the TAVI procedure itself is a critical component of the patient selection process. The vascular access site and the bioprosthesis type and size are crucial to procedural success.

VASCULAR ACCESS

Selection of the vascular access site is based on careful pre-procedural screening and should be individualized for each patient. Our preference is to select the least invasive route possible for TAVI. As such, all patients are evaluated for the feasibility of a transfemoral approach, and an alternative approach is only selected in the setting of a prohibitively small or diseased iliofemoral arterial system, the presence of mobile plaque, excessive calcification, or extreme tortuosity of the descending thoracic aorta. Alternative approaches in our order of preference are: subclavian (32–41); transaortic (42–48); and transapical (49–52). Importantly, we do not push the limits of the available technology and if the peripheral vasculature is unfavourable, an alternative access is selected. Feasibility does not equal safety.

The femoral artery is considered to be default vascular access site for TAVI. Theoretical advantages of the transfemoral approach include avoidance of general anaesthesia, thoracotomy, incision of the apex of the left ventricle, and potential complications such as delayed wound healing. Advantages to the non-transfemoral approaches include avoidance of peripheral vascular (except subclavian) and aortic complications. Importantly, the risk of periprocedural cerebral embolization and stroke appears to be similar between these different strategies (53,54).

To date, few studies have directly compared clinical outcomes between transfemoral and non-transfemoral TAVI (14,53,55,56). Compared to the femoral approach, non-transfemoral approaches (largely transapical) tends to be performed on higher risk patients, as assessed by EuroSCORE (largely driven by peripheral arterial disease). Transfemoral TAVI is associated with an increased risk of vascular complications, while non-transfemoral procedures have a higher risk of bleeding and surgical conversion (14,53). To date, non-transfemoral TAVI has been associated with increased 30-day and two-year mortality (14,53). Although this mortality difference may be due to the more advanced risk profile of the non-transfemoral patients, it is possible that these procedures themselves confer increased risk. General anaesthesia, thoracotomy, incision of the left ventricular apex and manipulation of a large catheter within the left ventricle are not without risk. However, it must be stated that as surgical experience with these devices improves, and dedicated transapical and transaortic devices are developed, improved outcomes are emerging with non-transfemoral TAVI (57). The advent of the trans-aortic approach is a particularly encouraging technique that avoids many of the theoretical complications associated with transapical TAVI (42–48).

BIOPROSTHESIS TYPE AND SIZE

Currently, two THV systems are available for implantation in Europe. The Edwards SAPIEN XT THV is a balloon-expandable valve that consists of a radiopaque cobalt-chromium frame, trileaflet bovine pericardial leaflets, and a polyethylene terephthalate fabric skirt. The Edwards SAPIEN XT THV is currently available in 4 sizes (20, 23, 26, and 29 mm) and can be implanted in native annuli with diameters of 16 to 27 mm. The Medtronic CoreValve bioprosthesis is a self-expandable valve manufactured from a radiopaque nitinol support frame, trileaflet porcine pericardial leaflets, and porcine pericardium fabric skirt. The CoreValve is available in 4 sizes (23, 26, 29, and 31 mm) and can be implanted in native annuli with diameters ranging from 17 to 29 mm.

Comparisons between the two available bioprosthesis types are few (58,59). To date, appreciable differences between the systems include a higher incidence of new pacemaker requirement with the CoreValve device (53). Approximately 15–47% (60–62) and 4–21% (63,64) of patients require a new permanent pacemaker after CoreValve and Edwards SAPIEN implantation, respectively. Importantly, new pacemaker implantation does not appear to be associated with long-term mortality (65). Therefore, the decision to implant a particular bioprosthesis depends largely on the availability of the devices, the experience of the operator with each device, and pre-procedural anatomical screening.

Operator experience is an important factor in determining TAVI outcomes (66–68). Therefore, the majority of individual operators tend to implant a single bioprosthesis type while many high volume TAVI centres implant both valves. In these centres, bioprosthesis

choice is dependant on the preprocedural assessment of the peripheral vasculature and the aortic annulus.

Manufacture sizing guidelines, based on echocardiographic annulus measurement, are available (69). For the Edwards Sapien XT valve, the 20 mm valve is designed for small annuli between 16-19 mm, the 23 mm valve is designed for 18-21 mm annuli, the 26 mm valve for 22-25 mm annuli, and the larger 29 mm valve for 25-27 mm annuli. For the Medtronic CoreValve 23, 26, 29, and 31 mm bioprosthesis sizes are designed for annuli between 17-20, 20-23, 24-27, and 26-29 mm respectively.

Personal perspective on transcatheter aortic valve sizing

Appropriate oversizing of transcatheter aortic valves relative to the aortic annulus is needed for (I) anchoring to prevent migration; (II) sealing to prevent paravalvular aortic regurgitation; and (III) proper valve functioning to prevent patient-prosthesis mismatch. Current echocardiographic sizing guidelines for the Medtronic CoreValve and Edwards SAPIEN XT would suggest an oversizing percentage between 7-30% and 4-27%, respectively (*Table 2*). Because self-expanding and balloon-expandable valves interfere differently with the aortic annulus, we should not expect similar oversizing principles. In our practice, MDCT dictates selection of the transcatheter aortic valve size. We compare the ratio of the aortic annulus perimeter obtained by MDCT to the perimeter of the transcatheter aortic valve (i.e. perimeter of the transcatheter aortic valve minus the perimeter of the aortic annulus then divided by the perimeter of the aortic annulus multiplied by 100). For self-expanding and balloon-expanding prostheses we aim for an oversizing percentage of 8-20% and 5-15%, respectively. Knowing that echocardiography underestimates the aortic annulus measurements, the actual oversizing obtained by echocardiography is less than expected. We believe that MDCT sizing allows a better approximation between the expected and actual oversizing than echocardiography.

Table 2 Transcatheter aortic valve echocardiographic sizing and oversizing principles

	Valve size	Aortic valve annulus criteria	Absolute oversizing	Relative oversizing
Medtronic coreValve	26 mm	20-23 mm	3-6 mm	13-30%
	29 mm	23-27 mm	2-6 mm	7-26%
Edwards SAPIEN	23 mm	18-22 mm	1-5 mm	4-27%
	26 mm	22-25 mm	1-4 mm	4-18%

Finally, the choice of bioprosthesis can be influenced by the iliofemoral anatomy. The minimal femoral dimensions for the available TAVI systems are based on the French (Fr) size of the access sheaths and catheters. According to manufacture guidelines, the 18 Fr CoreValve and 22/24 Fr Edwards SAPIEN delivery sheaths require 6 mm, 7 and 8 mm diameter femoral arteries respectively. The newer Edwards SAPIEN XT system requires 6 mm and 6.5 mm femoral artery diameters for the 18 Fr and 19 Fr systems respectively.

FUTURE PERSPECTIVES

It is likely that, similar to the evolution of drug-eluting stents, an initial conservative approach during the TAVI regulatory approval process will be followed by off-label case selection and treatment of lower risk patients. The move towards treating lower risk patients has already emerged in Europe (70,71). Future trials such as SURTAVI and Partner 2 will explore TAVI in patients at intermediate operative risk.

Although risk scores continue to play an important role in guiding patient selection for TAVI, they are poorly suited to this task. The development of alternative risk models designed specifically for high-risk TAVI recipients (72), and perhaps incorporating a measure of frailty, are required. Furthermore, the integration of MDCT in peripheral screening and most importantly, in annulus measurement for bioprosthesis sizing, is likely to improve outcomes in TAVI recipients.

CONCLUSIONS

Patient selection for TAVI is of considerable importance in optimizing procedural and long-term outcomes. The multi-disciplinary heart team approach, and the use of multimodal imaging is strongly advocated. Annulus sizing using MDCT is emerging as the modality of choice for assessment of annulus size and bioprosthesis sizing. Surgical risk scores must be refined to represent the unique challenge posed by high-risk TAVI populations, and incorporate a measure of frailty.

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REFERENCES

1. Piazza N, de Jaegere P, Manoharan G, et al. Patient Selection for the CoreValve ReValving System. In: Serruys P, Piazza N, Cribier A, et al, editors. *Transcatheter aortic valve implantation: Tips and tricks to avoid failure*. New York: Informa Healthcare, 2011:82.
2. Holmes DR Jr, Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement: Developed in collaboration with the American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Mended Hearts, Society of Cardiovascular Anesthesiologists, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *Ann Thorac Surg* 2012;93:1340-95.
3. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007;28:230-68.
4. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2008;118:e523-661.
5. Grayburn PA. Assessment of low-gradient aortic stenosis with dobutamine. *Circulation* 2006;113:604-6.
6. Lancellotti P, Lebois F, Simon M, et al. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation* 2005;112:1377-82.
7. Roques F, Nashef SA, Michel P. Risk factors for early mortality after valve surgery in Europe in the 1990s: lessons from the EuroSCORE pilot program. *J Heart Valve Dis* 2001;10:572-7, discussion 577-8.
8. Shroyer AL, Coombs LP, Peterson ED et al. The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg* 2003;75:1856-64; discussion 1864-5.
9. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2010;122:62-9.
10. Dewey TM, Brown D, Ryan WH, et al. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. *J Thorac Cardiovasc Surg* 2008;135:180-7.
11. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. *Ann Thorac Surg* 2009;88:S23-42.
12. Osswald BR, Gegouskov V, Badowski-Zyla D, et al. Overestimation of aortic valve replacement risk by EuroSCORE: implications for percutaneous valve replacement. *Eur Heart J* 2009;30:74-80.
13. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597-607.
14. Lefèvre T, Kappetein AP, Wolner E, et al. One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. *Eur Heart J* 2011;32:148-57.
15. Buellesfeld L, Gerckens U, Schuler G, et al. 2-year follow-up of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. *J Am Coll Cardiol* 2011;57:1650-7.
16. Delgado V, Ewe SH, Ng AC, et al. Multimodality imaging in transcatheter aortic valve implantation: key steps to assess procedural feasibility. *EuroIntervention* 2010;6:643-52.

17. Eltchaninoff H, Kerkeni M, Zajarias A, et al. Aorto-iliac angiography as a screening tool in selecting patients for transfemoral aortic valve implantation with the Edwards SAPIEN bioprosthesis. *EuroIntervention* 2009;5:438-42.
18. Hayashida K, Lefevre T, Chevalier B, et al. Transfemoral aortic valve implantation new criteria to predict vascular complications. *JACC Cardiovasc Interv* 2011;4:851-8.
19. Nietlispach F, Leipsic J, Al-Bugami S, et al. CT of the iliofemoral arteries using direct aortic contrast injection: proof of feasibility in patients screened towards percutaneous aortic valve replacement. *Swiss Med Wkly* 2009;139:458-62.
20. Wuest W, Anders K, Schuhbaeck A, et al. Dual source multidetector CT-angiography before Transcatheter Aortic Valve Implantation (TAVI) using a high-pitch spiral acquisition mode. *Eur Radiol* 2012;22:51-8.
21. Piazza N, de Jaegere P, Schultz C, et al. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. *Circ Cardiovasc Intervent* 2008;1:74-81.
22. Kodali SK, Williams MR, Smith CR, et al. Two-Year Outcomes after Transcatheter or Surgical Aortic Valve Replacement. *N Engl J Med* 2012;366:1686-95.
23. Messika-Zeitoun D, Serfaty JM, Brochet E, et al. Multimodal assessment of the aortic annulus diameter: implications for transcatheter aortic valve implantation. *J Am Coll Cardiol* 2010;55:186-94.
24. Tzikas A, Schultz CJ, Piazza N, et al. Assessment of the aortic annulus by multislice computed tomography, contrast aortography, and trans-thoracic echocardiography in patients referred for transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2011;77:868-75.
25. Husser O, Rauch S, Endemann DH, et al. Impact of three-dimensional transesophageal echocardiography on prosthesis sizing for transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2012;80:956-63.
26. Zamorano JL, Badano LP, Bruce C, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. *Eur Heart J* 2012;32:2189-214.
27. Schultz CJ, Moelker A, Piazza N, et al. Three dimensional evaluation of the aortic annulus using multislice computer tomography: are manufacturer's guidelines for sizing for percutaneous aortic valve replacement helpful? *Eur Heart J* 2010;31:849-56.
28. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146-56.
29. Makkar RR. Two-Year Outcomes of Transcatheter Aortic Valve Replacement (TAVR) in "Inoperable" Patients With Severe Aortic Stenosis: The PARTNER Trial. *Transcatheter Cardiovascular Therapeutics (TCT)*. San Francisco, California, 2011.
30. Eltchaninoff H, Prat A, Gilard M, et al. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. *Eur Heart J* 2011;32:191-7.
31. Saia F, Marrozzini C, Moretti C, et al. The role of percutaneous balloon aortic valvuloplasty as a bridge for transcatheter aortic valve implantation. *EuroIntervention* 2011;7:723-9.
32. Fraccaro C, Napodano M, Tarantini G, et al. Expanding the eligibility for transcatheter aortic valve implantation the trans-subclavian retrograde approach using: the III generation CoreValve revalving system. *JACC Cardiovasc Interv* 2009;2:828-33.
33. Bauernschmitt R, Schreiber C, Bleiziffer S, et al. Transcatheter aortic valve implantation through the ascending aorta: an alternative option for no-access patients. *Heart Surg Forum* 2009;12:E63-4.
34. Taramasso M, Giacomini A, Maisano F. Transcatheter aortic valve implantation through the left subclavian artery with a patent LIMA graft. *Catheter Cardiovasc Interv* 2010;76:153-5.

35. Petronio AS, De Carlo M, Bedogni F, et al. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. *Circ Cardiovasc Interv* 2010;3: 359-66.
36. Sharp AS, Michev I, Colombo A. First trans-axillary implantation of Edwards Sapien valve to treat an incompetent aortic bioprosthesis. *Catheter Cardiovasc Interv* 2010;75:507-10.
37. Bruschi G, Fratto P, De Marco F, et al. The trans-subclavian retrograde approach for transcatheter aortic valve replacement: single-center experience. *J Thorac Cardiovasc Surg* 2010;140:911-5, 915,e1-2.
38. De Marco F, Bruschi G, Klugmann S. Transcatheter aortic valve implantation by left subclavian access in the presence of a patent LIMA to LAD graft. *Catheter Cardiovasc Interv* 2011;77:430-4.
39. Modine T, Obadia JF, Choukroun E, et al. Transcatheter aortic valve implantation using the axillary/subclavian access: feasibility and early clinical outcomes. *J Thorac Cardiovasc Surg* 2011;141:487-91, 491, e1.
40. Vavuranakis M, Vrachatis DA, Filis K, et al. Trans-catheter aortic-valve implantation by the subclavian approach complicated with vessel dissection and transient left-arm paralysis. *Eur J Cardiothorac Surg* 2011;39:127-9.
41. Guarracino F, Covello RD, Landoni G, et al. Anesthetic management of transcatheter aortic valve implantation with transaxillary approach. *J Cardiothorac Vasc Anesth* 2011;25:437-43.
42. Bapat V, Thomas M, Hancock J, et al. First successful trans-catheter aortic valve implantation through ascending aorta using Edwards SAPIEN THV system. *Eur J Cardiothorac Surg* 2010;38:811-3.
43. Bruschi G, De Marco F, Fratto P, et al. Direct aortic access through right minithoracotomy for implantation of self-expanding aortic bioprosthetic valves. *J Thorac Cardiovasc Surg* 2010;140:715-7.
44. Latsios G, Gerckens U, Grube E. Transaortic transcatheter aortic valve implantation: a novel approach for the truly "no-access option" patients. *Catheter Cardiovasc Interv* 2010;75:1129-36.
45. Bruschi G, De Marco F, Fratto P, et al. Alternative approaches for trans-catheter self-expanding aortic bioprosthetic valves implantation: single-center experience. *Eur J Cardiothorac Surg* 2011;39:e151-8.
46. Etienne PY, Papadatos S, El Khoury E, et al. Transaortic transcatheter aortic valve implantation with the Edwards SAPIEN valve: feasibility, technical considerations, and clinical advantages. *Ann Thorac Surg* 2011;92:746-8.
47. Etienne PY, Papadatos S, Pieters D, et al. Embol-x intraaortic filter and transaortic approach for improved cerebral protection in transcatheter aortic valve implantation. *Ann Thorac Surg* 2011;92:e95-6.
48. Cockburn J, Trivedi U, Hildick-Smith D. Transaortic transcatheter aortic valve implantation within a previous bioprosthetic aortic valve replacement. *Catheter Cardiovasc Interv* 2011;78:479-84.
49. Kempfert J, Rastan A, Holzhey D, et al. Transapical aortic valve implantation: analysis of risk factors and learning experience in 299 patients. *Circulation* 2011;124:S124-9.
50. D'Onofrio A, Rubino P, Fusari M, et al. Clinical and hemodynamic outcomes of "all-comers" undergoing transapical aortic valve implantation: results from the Italian Registry of Trans-Apical Aortic Valve Implantation (I-TA). *J Thorac Cardiovasc Surg* 2011;142:768-75.
51. Falk V, Walther T, Schwammenthal E, et al. Transapical aortic valve implantation with a self-expanding anatomically oriented valve. *Eur Heart J* 2011;32:878-87.
52. Kempfert J, Rastan AJ, Mohr FW, et al. A new self-expanding transcatheter aortic valve for transapical implantation - first in man implantation of the JenaValve. *Eur J Cardiothorac Surg* 2011;40:761-3.
53. Moat NE, Ludman P, de Belder MA, et al. Long-Term Outcomes After Transcatheter Aortic Valve Implantation in High-Risk Patients With Severe Aortic Stenosis: The U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol* 2011;58:2130-8.

54. Erdoes G, Basciani R, Huber C, et al. Transcranial Doppler-detected cerebral embolic load during transcatheter aortic valve implantation. *European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery* 2012;41:778-84.
55. Himbert D, Descoutures F, Al-Attar N, et al. Results of transfemoral or transapical aortic valve implantation following a uniform assessment in high-risk patients with aortic stenosis. *J Am Coll Cardiol* 2009;54:303-11.
56. Ewe SH, Delgado V, Ng AC, et al. Outcomes after transcatheter aortic valve implantation: transfemoral versus transapical approach. *Ann Thorac Surg* 2011;92:1244-51.
57. Dewey TM, Thourani V, Bavaria JE, et al. Transapical aortic-valve replacement for critical aortic stenosis: Results from the nonrandomized continued-access cohort of the PARTNER trial. *Society of Thoracic Surgeons Annual Meeting. Ft Lauderdale, FL., 2012.*
58. Bosmans JM, Kefer J, De Bruyne B, et al. Procedural, 30-day and one year outcome following CoreValve or Edwards transcatheter aortic valve implantation: results of the Belgian national registry. *Interact Cardiovasc Thorac Surg* 2011;12:762-7.
59. Jilaihawi H, Chakravarty T, Weiss RE, et al. Meta-analysis of complications in aortic valve replacement: Comparison of Medtronic-Corevalve, Edwards-Sapien and surgical aortic valve replacement in 8,536 patients. *Catheter Cardiovasc inter* 2012;80:128-38.
60. Bleiziffer S, Ruge H, Horer J, et al. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2010;3:524-30.
61. Jilaihawi H, Chin D, Vasa-Nicotera M, et al. Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. *Am Heart J* 2009;157:860-6.
62. Piazza N, Onuma Y, Jesserun E, et al. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. *JACC Cardiovasc Interv* 2008;1:310-6.
63. Gutiérrez M, Rodés-Cabau J, Bagur R, et al. Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. *Am Heart J* 2009;158:302-8.
64. Sinhal A, Altwegg A, Pasupati S, et al. Atrioventricular block after transcatheter balloon expandable aortic valve implantation. *JACC Cardiovasc Interv* 2008;1:305-9.
65. D'Ancona G, Pasic M, Unbehaun A, et al. Permanent pacemaker implantation after transapical transcatheter aortic valve implantation. *Interact Cardiovasc Thorac Surg* 2011;13:373-6.
66. Nuis RJ, van Mieghem NM, van der Boon RM, et al. Effect of experience on results of transcatheter aortic valve implantation using a Medtronic CoreValve System. *Am J Cardiol* 2011;107:1824-9.
67. Webb JG, Altwegg L, Boone RH, et al. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. *Circulation* 2009;119:3009-16.
68. Grube E, Buellesfeld L, Mueller R, et al. Progress and Current Status of Percutaneous Aortic Valve Replacement: Results of Three Device Generations of the CoreValve Revalving System. *Circ Cardiovasc Intervent* 2008;1:167-75.
69. Jilaihawi H, Bonan R, Asgar A, et al. Anatomic suitability for present and next generation transcatheter aortic valve prostheses: evidence for a complementary multidevice approach to treatment. *JACC Cardiovasc Interv* 2010;3:859-66.
70. Piazza N, Otten A, Schultz C, et al. Adherence to patient selection criteria using the third generation 18F CoreValve ReValving System. *Heart* 2010;96:19-26.
71. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2012;59:280-7.
72. Van Mieghem NM, Head SJ, van der Boon RM, et al. The SURTAVI model: proposal for a pragmatic risk stratification for patients with severe aortic stenosis. *EuroIntervention* 2012;8:258-266.

4

TRANSFEMORAL TRANSCATHETER AORTIC VALVE REPLACEMENT

Adapted from:

Transfemoral transcatheter aortic valve replacement

Mylotte D, Martucci G, Lange R, Piazza N. Endovascular and Hybrid Therapies for Structural Heart and Aortic Disease, First Edition. Edited by Jacques Kpodonu and Raoul Bonan.

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INTRODUCTION

Somewhat surprisingly, transcatheter treatment of valvular heart disease was first conceived as far back as 1965. Davies devised a catheter-mounted cone-shaped valve as a potential therapy for aortic insufficiency [1], and paved the way for the development of a variety of transcatheter devices for the treatment of aortic insufficiency over the next 25–30 years [2–4]. Real progress in the field was not realized until 1986, when Professor Alain Cribier performed the first balloon aortic valvuloplasty (BAV) for the treatment of severe aortic stenosis [5]. Unfortunately, the impressive acute hemodynamic outcomes were diminished by valve restenosis, and symptoms typically recurred within 6–8 months of therapy [6–12]. Nevertheless, BAV demonstrated, for the first time, that transcatheter treatment of aortic stenosis was feasible, and with refinement could be an effective treatment for the 30–60% of patients who are refused surgery [13–16].

In 2002, some 15 years after performing the first BAV, Cribier implanted the first in-human balloon-expandable transcatheter heart valve. A first generation 23 mm bovine pericardial stent valve developed by Percutaneous Valve Technologies (Fort Lee, NJ), was implanted using a 24 Fr catheter delivery system [17]. The recipient was a 57-year-old man with refractory cardiogenic shock secondary to severe aortic stenosis, who was denied traditional aortic valve surgery (Fig. 14.1). Significant peripheral arterial disease necessitated antegrade implantation using a transvenous approach and transeptal puncture. After valve implantation, the transvalvular aortic gradient was <10 mmHg and the aortic valve area increased to 1.7 cm². Based on this initial success, the first series of 40 patients underwent implantation of a modified heart valve, the Cribier–Edwards valve, using an antegrade transeptal approach [18].

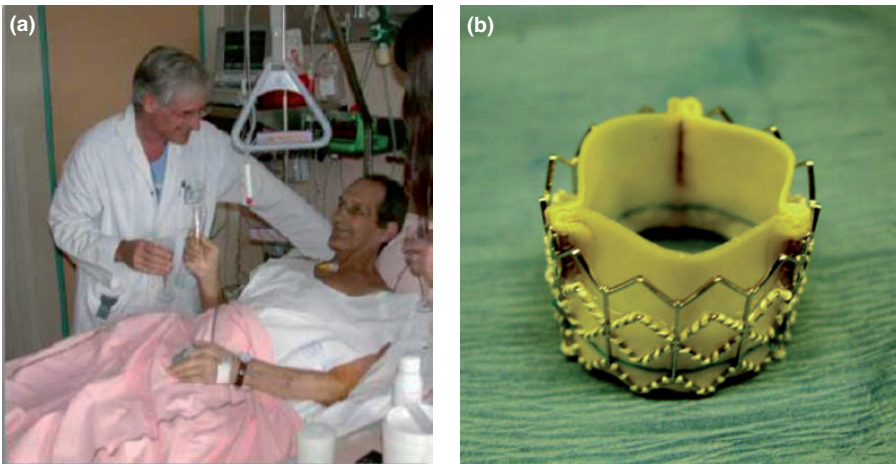


Fig. 14.1 (a) The first patient to undergo transcatheter aortic valve implantation (April 16, 2002) using the first generation balloon expandable valve (b) that housed trileaflet bovine pericardial leaflets. Image courtesy of the PCR-EAPCI Percutaneous Interventional Cardiovascular Medicine Textbook, 2012, Europa Publishing.

The challenging nature of antegrade transvenous transcatheter aortic valve implantation, and not infrequent hemodynamic instability encountered due to mitral valve tethering and injury, motivated the development of alternative implantation strategies. The retrograde approach via the femoral artery (transfemoral) and the antegrade approach via the apex of the left ventricle (transapical) were developed using the Edwards LifeSciences system (Irvine, CA) [19].

In July 2004, the CoreValve ReValving system (Paris, France) was first implanted (Fig. 14.2) [20]. Initially, these procedures were complex and time consuming, requiring general anesthesia, cardiopulmonary bypass, and surgical cutdown of the femoral artery. However, downsizing of the delivery catheter and increasing operator experience soon saw the majority of procedures being performed percutaneously, under conscious sedation and local anesthesia, without cardiopulmonary support [21].



Fig. 14.2 The first generation CoreValve ReValving System bioprosthesis housing trileaflet bovine pericardial leaflets. The current third generation Medtronic CoreValve bioprosthesis houses leaflets made of porcine pericardium.

A wealth of knowledge has been acquired with respect to patient selection, procedural techniques, and post-procedure care over the last 10 years. These refinements have improved patient safety and procedural outcomes.

PATIENT SELECTION

Transcatheter aortic valve replacement (TAVR) is currently indicated for high or prohibitive surgical risk patients with symptomatic calcific aortic stenosis (aortic valve area $<1.0 \text{ cm}^2$) requiring aortic valve replacement.

Clinical criteria

TAVR was developed to treat the high or prohibitive surgical risk patient. This risk is usually quantified using several cardiac surgical risk algorithms [22–34]. However, these risk models were developed using low to intermediate surgical risk patients and their reliability when applied to high or prohibitive surgical risk patients is unclear [35–38]. To date, the logistic EuroScore and the STS (Society of Thoracic Surgeons) Predicted Risk of Mortality score have directed enrolment of patients into TAVR trials [22,33]. A logistic EuroScore $\geq 15\%$ or STS score $\geq 10\%$ define the high surgical risk patient for trial inclusion [39,40]. The logistic EuroScore tends to overestimate the observed mortality risk of high-risk patients by a factor of 2–3 [35,36], and therefore the STS score may be more reliable [58]. Evidently, clinical judgment should always supersede surgical risk algorithms [41].

Anatomical criteria

Pre-procedure screening of the peripheral arterial vasculature and aortic valvular complex (left ventricular outflow tract, aortic annulus, sinus of Valsalva, sinotubular junction, ascending aorta) is required. This is achieved using a combination of transthoracic and transesophageal echocardiography (TTE, TEE), multislice computed tomography (MSCT), and fluoroscopy/angiography [42]. These data determine the most appropriate access route (i.e. transfemoral, subclavian, apical, or direct aortic) and the transcatheter valve size [43].

Assessment of the arterial vasculature

Peripheral contrast angiography is the most practical, readily available, and cost effective modality for assessing the peripheral vasculature. In contrast, MSCT is associated with a higher contrast load, higher radiation exposure, and is more expensive. However, MSCT provides greater appreciation of vessel size, tortuosity, and calcific burden (Fig. 14.3) [44,45]. Using contrast angiography, a SFAR ratio (i.e. outer sheath diameter to femoral artery minimal luminal diameter ratio) of ≥ 1.05 was identified as a predictor of Valvular Academic Research Consortium (VARC) major vascular complications and 30-day mortality [46,47]. This ratio increased to 1.10 in non-calcified vessels and decreased to 1.00 in the presence of calcium. The utility of the SFAR criteria in MSCT is unclear.

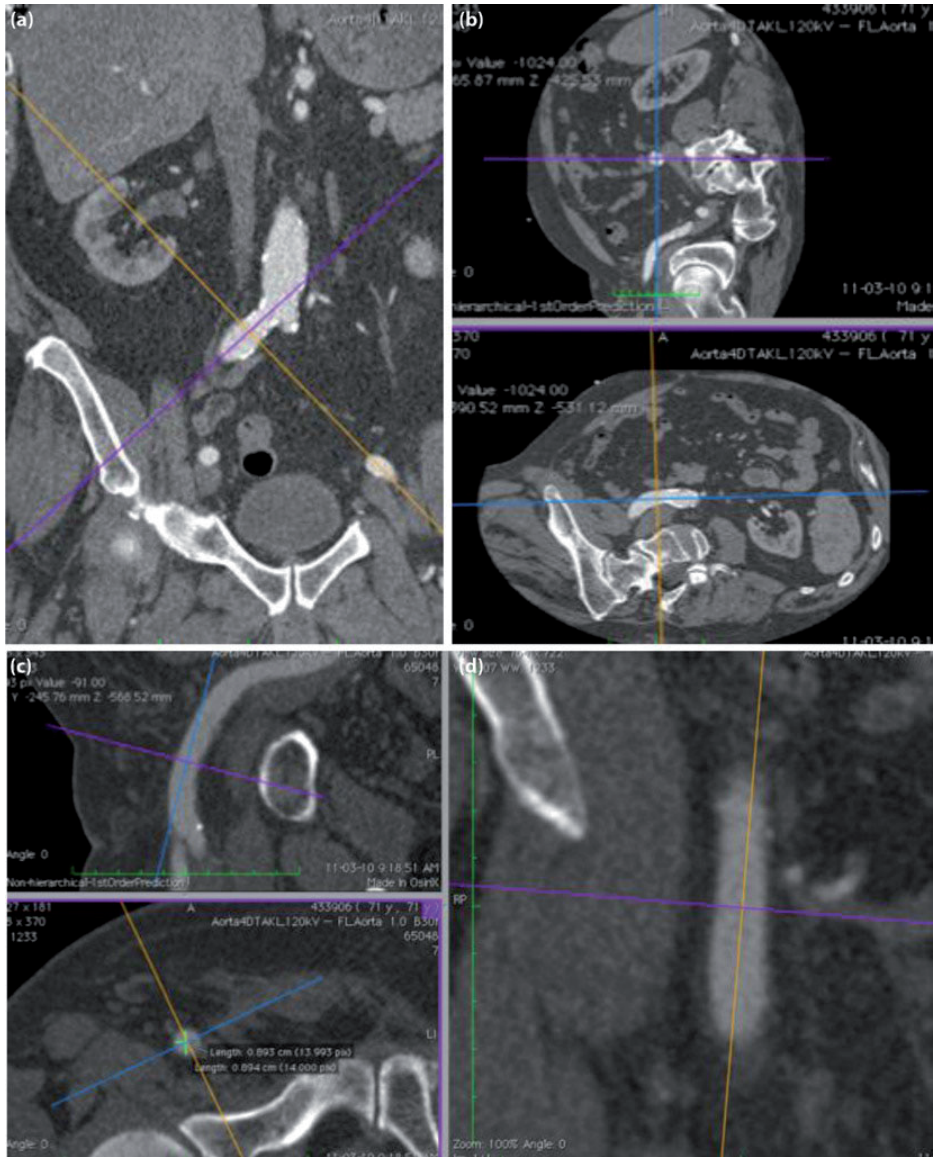


Fig. 14.3 MSCT scans provide the ability for 3D multiplanar reconstructions and therefore can provide superior information about minimum vessel diameter, tortuosity, and degree of calcification than a peripheral angiogram. (a, b) Cross-sectional measurements of the right common iliac artery. (c, d) Cross-sectional measurements of the right common femoral artery at the intended puncture site. Image courtesy of the PCR-EAPCI Percutaneous Interventional Cardiovascular Medicine Textbook, 2012, Europa Publishing.

Assessment of the aortic valve annulus

For the purposes of TAVR, the aortic valve annulus corresponds to a virtual ring formed by junction of the basal attachment points of the leaflets within the left ventricle (Fig. 14.4)

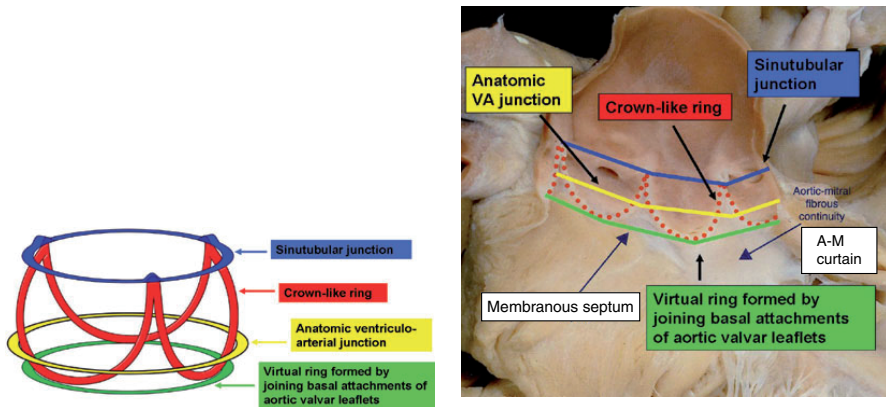


Fig. 14.4 The aortic root extends from the basal attachment points of the aortic valve leaflets (aortic annular plane) to their superior attachment points at the level of the sinutubular junction. There are three circular rings within the aortic root: (i) a virtual ring (i.e. without histologic demarcation) formed by joining the basal attachments of the aortic valvular leaflets; (ii) a ring at the anatomic ventriculo-arterial junction identified histologically as the transformation zone between aortic wall tissue and ventricular myocardium; and (iii) a ring at the sinutubular junction found at the apical attachment points of the aortic valvular leaflets. The “curtain-like” attachment line of the aortic valvular leaflets forms the crown-like ring. For purposes of transcatheter aortic valve sizing, it is the diameter of the virtual basal ring that is taken into consideration. Image courtesy of the PCR-EAPCI Percutaneous Interventional Cardiovascular Medicine Textbook, 2012, Europa Publishing.

[48]. This plane represents the transition from the left ventricular outflow tract into the aortic root. The non-circular shape of the aortic valve annulus has generated much debate about how best to measure its diameter for the purposes of transcatheter aortic valve size selection (Fig. 14.5) [49–51]. Currently, MSCT appears to be the most suitable method for assessment of aortic annulus dimensions. MSCT multiplanar reconstructions provide coronal, sagittal, and axial images of the aortic root [52,53]. On the axial view, the maximum and minimum diameter, perimeter, and area of the annulus can be measured. According to MSCT data, the mean difference between the maximum and minimum diameter of the non-circular aortic annulus is 6.5 mm (95% confidence interval, 5.7–7.2) [49,50]. Depending on the orientation, two-dimensional echocardiography appreciates only one view of the aortic annulus, and usually underestimates the annulus diameter with respect to MSCT. With this in mind, the use of two-dimensional measurements (TEE, TEE, contrast aortography) for transcatheter valve sizing is potentially problematic. Nevertheless, two-dimensional echocardiography remains the most commonly used method to assess the aortic valve annulus diameter, though a shift towards MSCT is emerging.

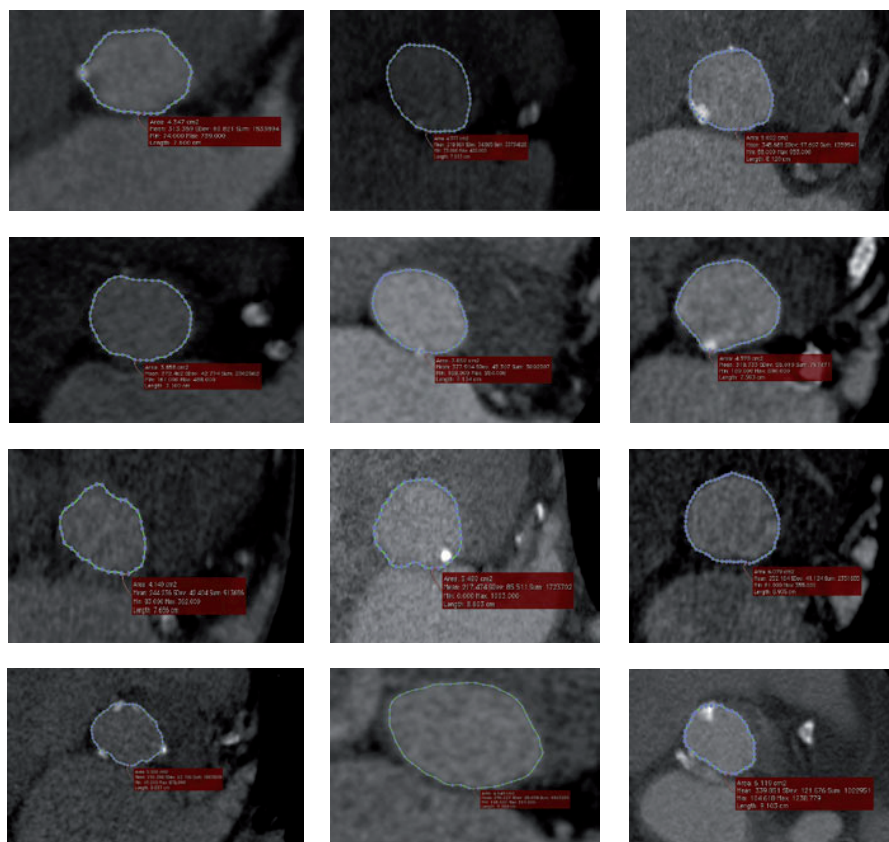


Fig. 14.5 MSCT axial cuts of the aortic annulus from 12 patients demonstrating that the aortic annulus is in fact non-circular. The difference between the maximum and minimum diameter measurements of the aortic annulus is on average 6.5 mm with a standard deviation of approximately 2 mm. The non-circularity of the aortic annulus limits applicability of two-dimensional imaging in estimating the annulus diameter for transcatheter valve sizing. Image courtesy of the PCR-EAPCI Percutaneous Interventional Cardiovascular Medicine Textbook, 2012, Europa Publishing.

APPROVED DEVICE DESCRIPTION

Current TAVR systems consist of three components: (i) the loading system; (ii) the delivery catheter; and (iii) the bioprosthetic aortic valve.

Edwards NovaFlex transfemoral system

The Edwards NovaFlex transfemoral system comprises the Edwards Sapien XT transcatheter heart valve (THV), the NovaFlex delivery system, the Edwards eSheath introducer sheath set, the Retroflex dilator kit, Retroflex balloon catheter, Crimper, and the Atrion inflation device (Fig. 14.6) [54,55].

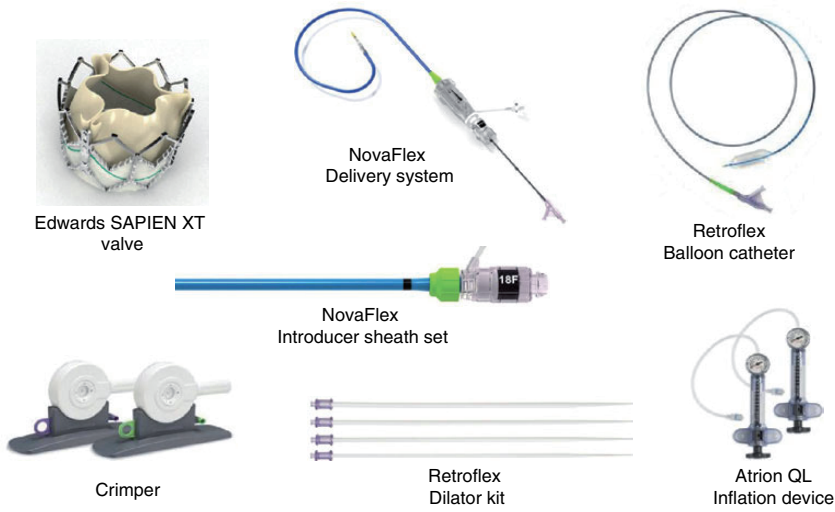


Fig. 14.6 Components of the transfemoral NovaFlex system.

The Edwards Sapien XT THV is a balloon-expandable valve consisting of a radiopaque cobalt-chromium frame, trileaflet bovine pericardial leaflets, and polyethylene terephthalate fabric skirt. The leaflets are manufactured according to *matching technology* and the Edwards Thermafix anticalcification process. The Edwards Sapien XT THV is currently available in four sizes (20, 23, 26, and 29mm) and can be implanted in native annuli with diameters of 16–27 mm (Fig. 14.7). Novel features of the delivery system include: (i) the deflectable NovaFlex delivery catheter, which has a tapered distal tip to facilitate crossing the native aortic valve; and (ii) the Edwards eSheath with dynamic expansion mechanism (DEM) that allows the sheath to transiently expand as the delivery system is advanced. The eSheath has an outer diameter of 6.6 mm (20 Fr) and 7.2 mm (21–22 Fr) for implantation of the 23 and 26 mm THVs, respectively.

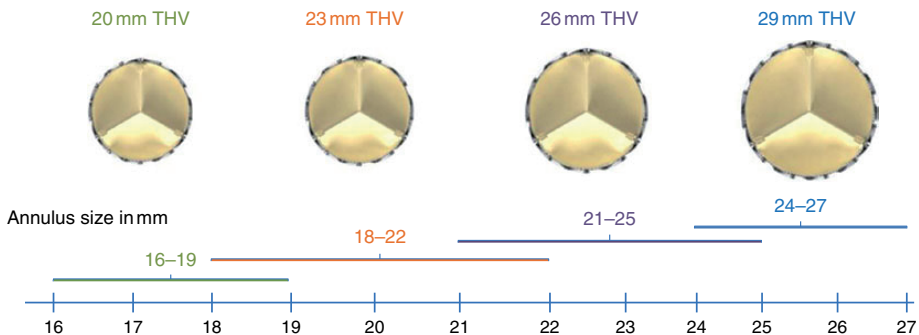


Fig. 14.7 The Edwards Sapien XT showing three of the available sizes.

Medtronic CoreValve system

The Medtronic CoreValve System comprises the CoreValve bioprosthesis, AccuTrak delivery catheter system, and a disposable loading system (Fig. 14.8).

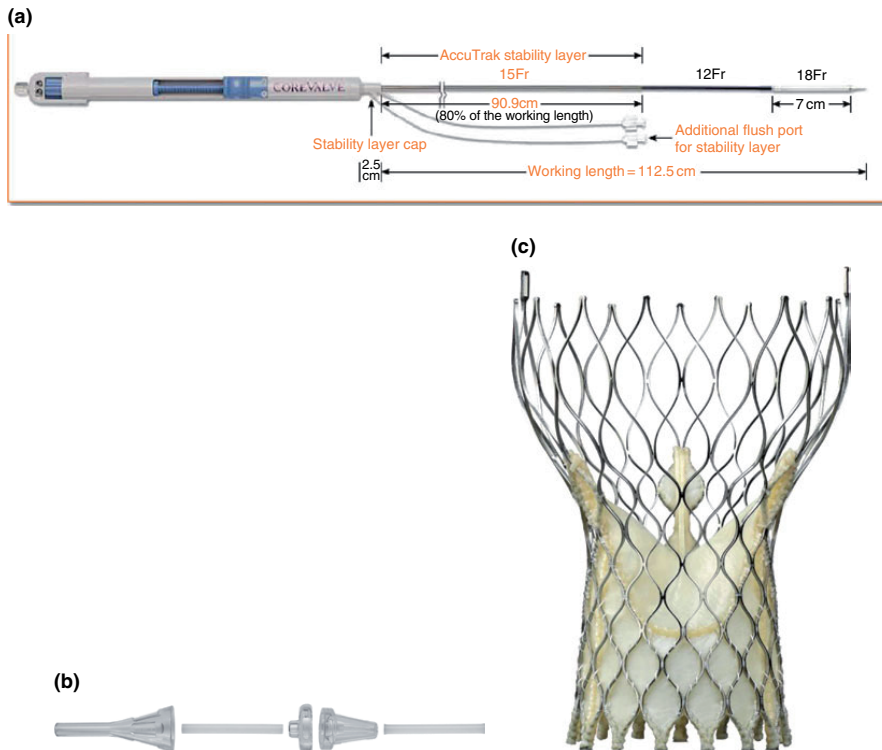


Fig. 14.8 The Medtronic CoreValve system comprises (a) the AccuTrak delivery catheter, (b) the five-piece disposable loading system, and (c) the bioprosthetic valve.

The current (third generation) Medtronic CoreValve bioprosthesis is a self-expandable valve manufactured from a radiopaque nitinol support frame, trileaflet porcine pericardial leaflets, and porcine pericardium fabric skirt. From 2012, the valve leaflets will undergo tissue treatment with alphaamino-oleic acid to reduce calcium deposition [56]. The nitinol support frame is a diamond cell pattern with various strut lengths and widths designed to expand to a non-uniform cylindrical “hour-glass” shape with three distinctive structure–function levels (Fig. 14.9). The inflow section has high radial force to anchor and seal against the native outflow tract and aortic valve to minimize paravalvular aortic regurgitation. The middle section houses the leaflets and has high hoop strength to minimize deformation and ensure optimal leaflet geometry. The outflow section sits in the ascending aorta, has low radial force, and functions to orient the prosthesis in the direction of blood flow.

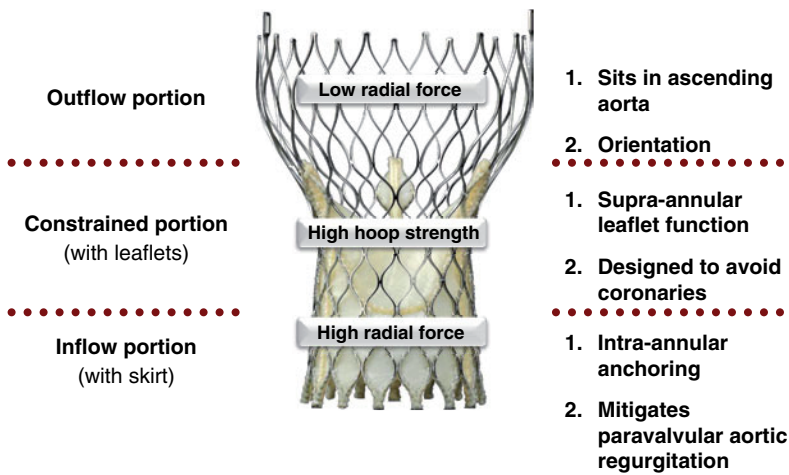


Fig. 14.9 The CoreValve bioprosthesis is characterized as a self-expanding multilevel frame with three distinct areas of form and function: (i) the inflow portion of the frame has high radial force and functions to anchor the prosthesis against the aortic annulus and aortic valve leaflets and together with the skirt creates a seal to mitigate paravalvular aortic regurgitation. (ii) The constrained portion of the frame houses the leaflets and has high hoop strength thereby resisting deformation and maintaining optimal leaflet geometry. Furthermore, this portion is constrained and was designed to avoid the coronary arteries. (iii) The outflow portion of the frame has low radial force and sits in the ascending aorta and was designed to orient the prosthesis in the direction of blood flow.

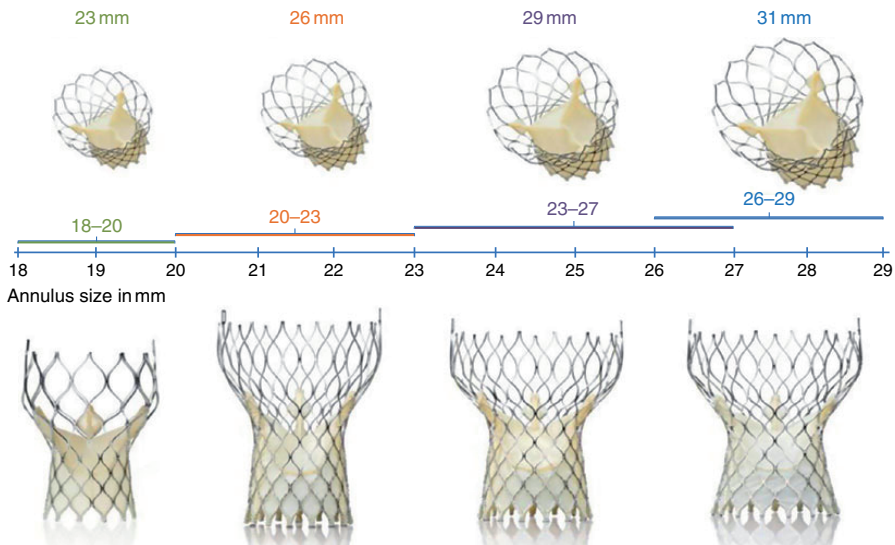


Fig. 14.10 The Medtronic CoreValve showing the four sizes currently available; in 2012.

The CoreValve is available in four sizes (23, 26, 29, and 31 mm) and can be implanted in native annuli with diameters ranging from 20 to 29 mm (Fig. 14.10). It can be implanted via the femoral artery, subclavian artery (57–59), and through a direct aortic access. The AccuTrak delivery catheter provides greater stability and precision during valve deployment than its predecessor and has an outer diameter of 18 Fr at its distal end (Fig. 14.11) [60].

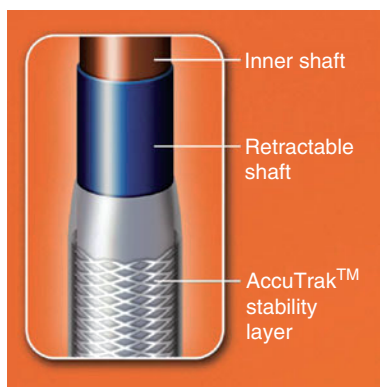


Fig. 14.11 The AccuTrak stability layer is an additional layer that isolates the retractable delivery sheath from the introducer and patient anatomy, thus providing a stable platform for deployment. The aim of the AccuTrak stability layer is to mitigate the forward motion (i.e. towards the ventricle) of the prosthesis during deployment which was characteristic of the predecessor generation of delivery catheter.

TRANSFEMORAL TAVR: PROCEDURAL STEPS

The generic steps involved in performing TAVR are outlined below [61,62].

1 Anesthesia: General or local anesthesia with mild sedation can be successfully used during TAVR [63–73].

2 Anticoagulation: Administer heparin to achieve and maintain an activated clotting time between 250 and 300 seconds. Typically, patients are loaded with 300 mg clopidogrel 24 hours prior to the procedure.

3 Antibiotic prophylaxis: Performed according to hospital protocol.

4 Preparation of the prosthesis: Both bioprostheses are gently agitated in sterile physiologic saline to remove the glutaraldehyde preservative. They are subsequently mounted and/or crimped onto the delivery system.

5 Temporary pacemaker implantation: A temporary pacemaker lead is placed into the right ventricle, and pacemaker function is assessed under rapid pacing, 160–180 beats/minute, such that systemic arterial pressure is reduced below 60 mmHg.

6 Supra-aortic angiogram: A pigtail catheter is placed in the non-coronary sinus to perform a supra-aortic angiogram. The C-arm is angulated to where the nadir of all three leaflets is in one plane, perpendicular to the viewing angle. This is typically located in a left anterior oblique (approximately 10°) with some cranial or caudal (0–15°) angulation. Several ancillary devices can be used to facilitate the optimal viewing angle for implantation [74–77].

7 Vascular access: Vascular access may be performed using a surgical arterial cutdown or percutaneously with aid of pre-closure vascular devices [78]. Vascular pre-closure of the femoral arterial access site can be accomplished with one 10 Fr Prostar XL percutaneous vascular surgical system (Abbott, Park, IL) or two 6 Fr Perclose ProGlide suture-mediated closure system (Abbott, Park, IL). A single puncture of the anterior wall of the common femoral artery is recommended to avoid pre-closure vascular device failure. Contralateral contrast injections and ultrasound-guided puncture can assist vascular puncture.

8 Vascular introducer sheath: Introduction and advancement of the large bore vascular introducer sheath should be performed under fluoroscopic guidance over a stiff guide wire (Amplatz Extra-stiff or Super-stiff). Any resistance encountered while advancing the sheath should be carefully evaluated in order to avoid vascular complications.

9 Crossing the native aortic valve: A variety of catheters can be used to cross the native aortic valve. The Amplatz left 2 is usually selected in patients with an enlarged or a horizontal aortic root whereas the Amplatz left 1 is preferred in those with a small or vertical aortic root. Straight-tipped guide wires should be used to cross the valve. Once crossed, the straight guide wire is exchanged for a pre-shaped long Extra-stiff Amplatz guide wire (Cook Medical, Bloomington, IN; for Edwards Sapien) or Super-stiff Amplatz guide wire (Cook Medical; for Medtronic CoreValve). Pre-shaping of the distal tip is mandatory to reduce the risk of cardiac perforation.

10 Pre-implant balloon aortic valvuloplasty: The Edwards Sapien system is equipped with a custom retroflex 20 or 23 mm × 4 cm balloon dilation kit for the 23 and 26 mm valve sizes, respectively. For the 26 and 29 mm Medtronic CoreValve devices, 22 mm × 4 cm and 25 mm × 4 cm balloons are recommended for pre-implant dilation, respectively.

11 Prosthesis positioning and deployment:

- *Edwards Sapien XT*. The NovaFlex delivery system is advanced through the introducer sheath until the prosthesis exits the sheath. Valve alignment is then performed in the descending aorta and the delivery system is advanced, using the Flex Wheel to traverse the aortic arch. The native aortic valve is crossed, the Flex Catheter retracted and the prosthesis positioned (50–60% ventricular). Under rapid pacing, to reduce the systolic aortic pressure <50 mmHg, the balloon is inflated, thus deploying the valve. After 4–5 seconds, the balloon is deflated and then the rapid pacing terminated. Finally, the delivery system is de-articulated and retracted across the aortic arch.
- *Medtronic CoreValve*. The CoreValve is advanced across the native aortic valve and is positioned such that its second horizontal radiopaque band lies at the level of the aortic annular plane. In this position, the valve lies approximately 4 mm below the annulus, the target implantation depth (Fig. 14.12). Once a baseline aortogram confirms the position of the prosthesis, the CoreValve is deployed in four steps (Fig. 14.13):
 - i. (i) The micro knob is turned clockwise, until the radiopaque ring reaches the second radiopaque band of the prosthesis (Fig. 14.13b). An aortogram is then performed to confirm the prosthesis target depth of 4 mm. At this stage, the prosthesis can be repositioned either more cranial or caudal.
 - ii. (ii) The micro knob is turned until the inflow portion of the valve is 40–50% away from contacting the opposite annular surface (Fig. 14.13c). An aortogram is again performed to re-confirm target depth. Again, the prosthesis can be repositioned cranially or caudally.
 - iii. (iii) The micro knob is slowly rotated until the inflow portion of the prosthesis comes into contact with the opposite annular surface and an aortogram repeated. Further micro knob rotation is performed until the valve is three-fourths deployed and again an aortogram is performed. At this stage, slight cranial (but *not* caudal) repositioning of the CoreValve can be performed.
 - iv. (iv) Further rotation of the micro knob is performed until complete deployment of the CoreValve is achieved.
- The stiff wire is withdrawn towards the tip of the nose cone and the delivery catheter is removed from the left ventricle. The macro knob is then used to recapture the nose cone in the descending aorta.

12 Verify valve position and performance, and rule out potential complications: After valve deployment and removal of the delivery catheters and guide wires, the cardiac rhythm and hemodynamic are carefully assessed. Severe bradycardia or high degrees of atrioventricular block will require immediate temporary pacing. A low aortic diastolic pressure (<35 mmHg), elevated left ventricular end-diastolic pressure, or near equalization of aortic diastolic and left ventricular end-diastolic pressures suggest significant prosthetic valve regurgitation. Valve performance should be assessed using contrast aortography and echocardiography. A supra-

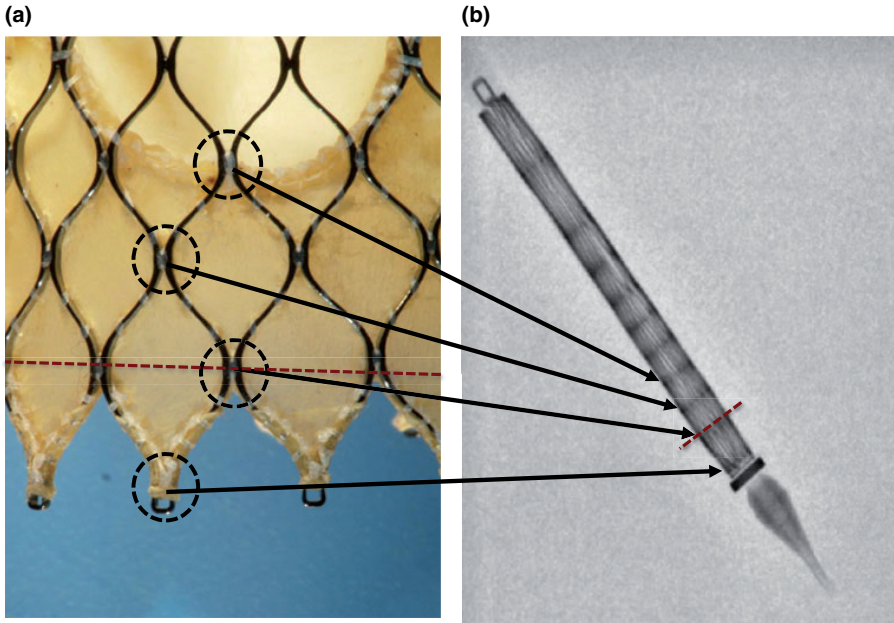


Fig. 14.12 The Medtronic CoreValve frame has a repeating diamond cell configuration. The junction between diamond cells, known as “nodes” (encircled in black in (a)); can be seen as horizontal radiopaque bands on the collapsed frame within the delivery catheter (b). The vertical distance between nodes at the inflow end is approximately 4 mm. The red dotted line represents an implantation depth of 4 mm (i.e. at the second horizontal radiopaque band). These horizontal radiopaque bands are used to guide positioning of the prosthesis during valve deployment.

aortic angiogram in the right anterior oblique (RAO) position is recommended to evaluate valve position, estimate the degree of aortic regurgitation, and confirm patency of the coronary arteries. The severity and origin of aortic regurgitation is optimally assessed with TEE.

13 Vessel closure and hemostasis: Prior to securing the pre-closure sutures, it is strongly recommended that a safety wire be placed from the contralateral femoral artery down the ipsilateral femoral artery beyond the bifurcation [79]. This enables immediate intervention of the ipsilateral femoral artery in case of vascular injury. A final contrast angiography of the peripheral vessels should be performed to confirm hemostasis and rule-out vascular injury.

14 Post-procedural care: All patients should be monitored in an intensive care setting for 24–48 hours after valve implantation. Particular attention should be given to the neurologic status, cardiopulmonary function, renal function, and vascular/ bleeding complications. Continuous telemetry monitoring is recommended for the duration of the hospital stay (4–10 days) [80,81].

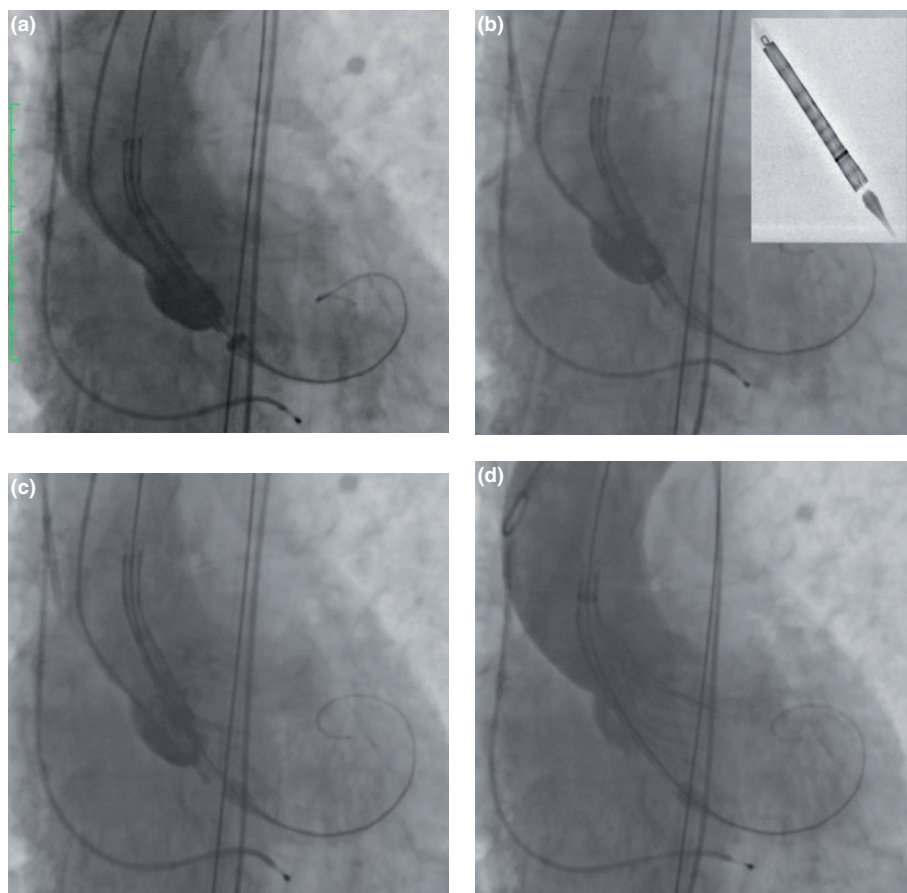


Fig. 14.13 Steps in deployment of the Medtronic CoreValve prosthesis. (a) The unsheathed prosthesis is positioned such that the second horizontal radiopaque band is at the level of the aortic annular plane. (b) Turn the micro knob until the radiopaque ring reaches the second radiopaque band of the prosthesis. (c) Slowly turn the micro knob until the inflow portion of the valve is 40–50% away from contacting the opposite annular surface. (d) Continue to slowly rotate the micro knob until the inflow portion of the prosthesis comes into contact with opposite annular surface. An aortogram may be repeated at this point; otherwise, continue to rotate the micro knob until the prosthesis is three-fourths deployed. Before retracting the delivery catheter verify that the loading hooks of the valve frame are detached from the delivery catheter; this is best appreciated in two orthogonal views. Image courtesy of the PCR-EAPCI Percutaneous Interventional Cardiovascular Medicine Textbook, 2012, Europa Publishing.

TAVR-RELATED COMPLICATIONS

Complications associated with TAVR are classified as cardiac or non-cardiac in origin (Box 14.1).

Box 14.1. Cardiac and non-cardiac complications of transcatheter aortic valve implantation

Cardiac

- Paravalvular aortic regurgitation
- Conduction abnormalities
- Atrial and ventricular arrhythmias
- Coronary obstruction
- Cardiac perforation
- Aortic root rupture
- Prosthetic valve dysfunction
- Embolization
- Transcatheter aortic valve thrombosis
- Transcatheter aortic valve endocarditis
- Mitral regurgitation and mitral valve injury

Non-cardiac

- Stroke
- Vascular injury
- Acute kidney injury

Cardiac complications

Paravalvular aortic regurgitation

A degree of post-implant aortic regurgitation (para-valvular or transvalvular) is observed in 70–90% of TAVR recipients, though less than 5% of cases have moderate to severe aortic regurgitation [82–88]. Mechanisms of aortic regurgitation include: (i) transcatheter valve undersizing [87,89]; (ii) malpositioning [90,91]; (iii) malapposition, under expansion or recoil of the transcatheter valve [92–94]; and (iv) malcoaptation or immobility of the valve leaflets [95–97]. Delayed severe aortic regurgitation has also been reported [98–100]. The mechanism of aortic regurgitation can usually be identified using TEE [85,101,102]. VARC recommends using an integrative echocardiographic approach when quantifying aortic regurgitation [101,102].

Management of significant aortic regurgitation depends on the underlying mechanism, though treatment may include post-implant dilation, implantation of a second valve, or repositioning of the frame using a snare (Fig. 14.14). Conversion to surgical aortic valve replacement is required in less than 1% of cases.

Conduction disturbance

The anatomic proximity of the aortic valvular complex and the conduction system explains the potential for conduction disturbances following TAVR (Fig. 14.15) [48]. Indeed, the average distance between the nadir of the non-coronary aortic valve leaflet and the left bundle branch is only 6.3 ± 2.4 mm (Fig. 14.15) [103]. New-onset left bundle branch block occurs in 30–65% of patients after Medtronic CoreValve implantation and in 7–18% [104–121] after Edwards Sapien implantation [122–124]. The long-term implications of new-onset left bundle branch block after TAVR are unclear however anecdotal evidence suggests that it has a negligible impact on 1-year survival. Approximately 15–47% [104–121] and 4–21% [122–124] of patients require a new permanent pacemaker after CoreValve and Edwards Sapien implantation, respectively.

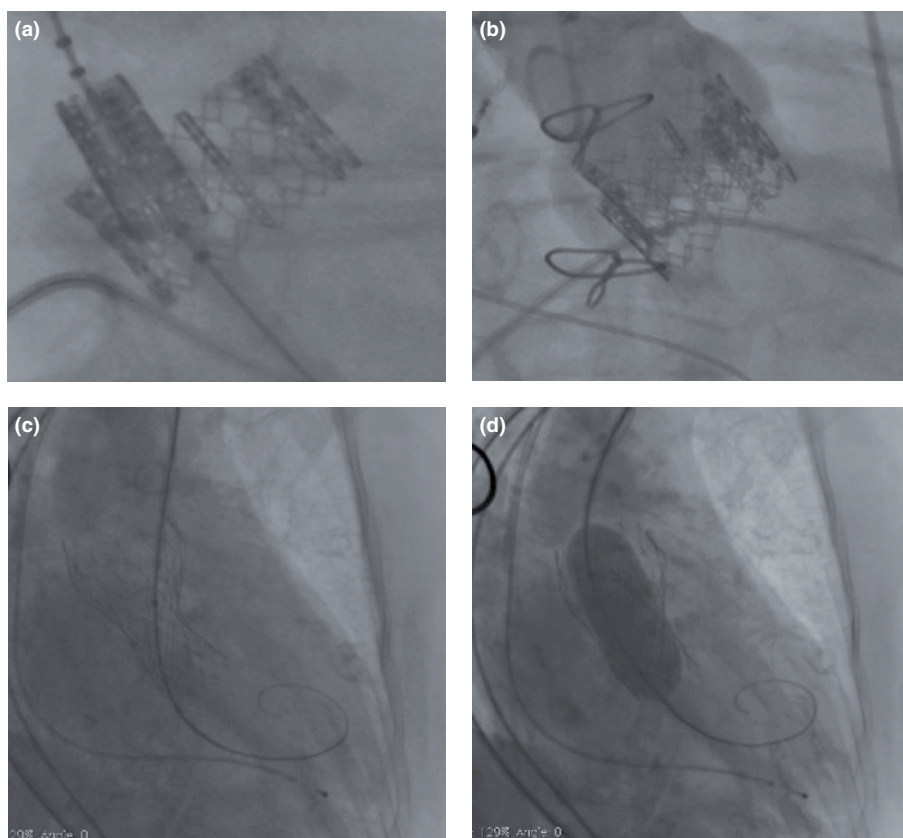


Fig. 14.14 (a) Severe paravalvular aortic regurgitation following low implantation of the Edwards Sapien prosthesis. (b) Transcatheter aortic valve-in-transcatheter aortic valve (TAV-in-TAV) implantation was successful in abolishing paravalvular aortic regurgitation. (c) Despite proper positioning, underexpansion of the CoreValve prosthesis due to severe bulky calcification led to severe paravalvular aortic regurgitation. (d) Post-implant dilation performed during rapid pacing was successful in abolishing the paravalvular aortic regurgitation. Image courtesy of the PCR-EAPCI Percutaneous Interventional Cardiovascular Medicine Textbook, 2012, Europa Publishing.

The most important predictors for new-onset conduction abnormalities after CoreValve implantation include a pre-existing right bundle branch block, baseline QRS duration (ms), and the depth of prosthesis implantation (mm) [104–111,113–115,117–119,121,125,126]. A CoreValve implantation depth of <6 mm has been found to mitigate conduction disturbances [117]. Most patients needing a new permanent pacemaker are identified immediately after valve implantation; however, a small percentage of patients may present with delayed conduction block. Therefore, temporary pacing should be maintained for 48–72 hours, especially after CoreValve implantation. Indications for permanent pacemaker implantation after TAVR are based upon the European Society of Cardiology guidelines [127,128].

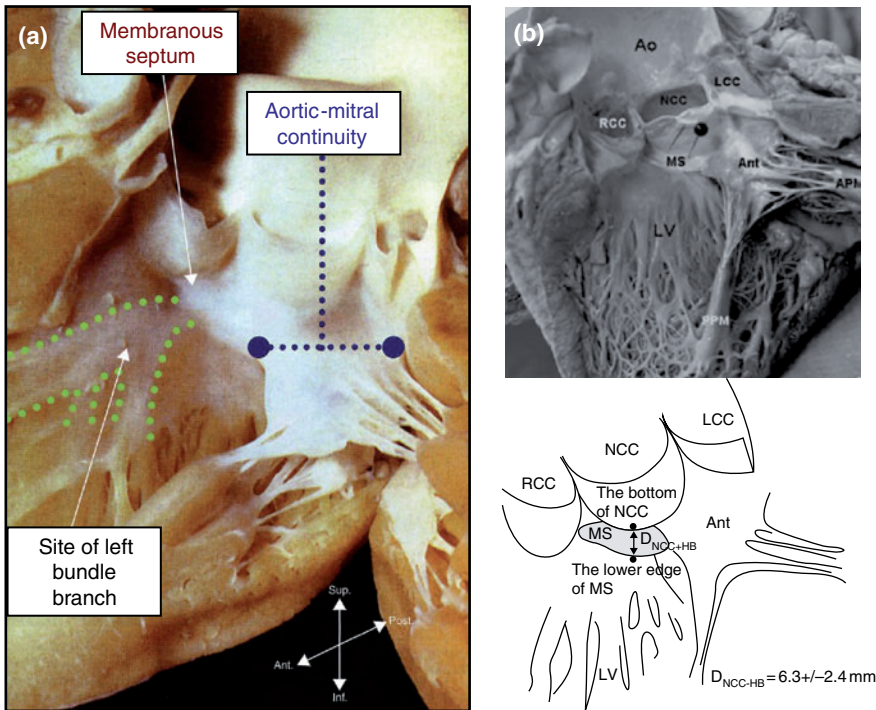


Fig. 14.15 (a) Human heart specimen of the left ventricular cavity, aortic valve, and ascending aorta. Note that the left bundle branch exits at the crest of the ventricular septum just beneath the membranous septum. (b) More specifically, the left bundle branch exits below the membranous septum approximately 6.3 ± 2.4 mm from the bottom of the non-coronary cusp of the aortic valve. Coincidentally, several investigators have noted that conduction abnormalities following CoreValve implantation can be mitigated by implanting the prosthesis ≤ 6 –8 mm from the aortic annular plane. Ant, anterior; Ao, aorta; LCC, left coronary cusp; LV, left ventricle; MS, membranous septum; NCC, non coronary cusp; PPM, posteromedial papillary muscle pacemaker; RCC, right coronary cusp. Green dotted line, site of left bundle branch block; blue dotted line, aortic mitral continuity. Image courtesy of the PCR-EAPCI Percutaneous Interventional Cardiovascular Medicine Textbook, 2012, Europa Publishing.

Cardiac arrhythmias

The reported rates of atrial fibrillation following TAVR vary considerably. A recent observational study found atrial fibrillation in 6% of patients following TAVR, as opposed to 33% in those undergoing surgical aortic valve replacement [129]. In contrast, another study found new-onset atrial fibrillation in 32% of patients undergoing TAVR. Importantly, new-onset atrial fibrillation is associated with higher rates of stroke/system embolism, though not with increased mortality [130].

Life-threatening ventricular arrhythmias (ventricular fibrillation/tachycardia) occur in up to 4% of TAVR patients [19,131]. Multiple ventricular ectopic beats can be induced by the left ventricular guide wire or delivery catheter, and can usually be terminated by repositioning. Defibrillator pads should be placed for the entirety of the procedure and maintained until the patient arrives in the intensive care unit.

Coronary obstruction

Occlusion of the left main coronary following TAVR occurs in less than 1% of cases [132–142]. Unsurprisingly, it frequently induces sudden hemodynamic compromise and death. The diagnosis is usually suspected on the basis of hemodynamics, electrocardiogram (ECG) pattern, and/or contrast aortography. Hemodynamic support and re-establishment of coronary perfusion is critical. The nature and severity of the coronary obstruction and hemodynamic status determines the mode of revascularization (percutaneous or surgical).

Possible mechanisms for coronary obstruction include: (i) impingement of the coronary ostia by the valve support structure; (ii) displacement of the native aortic valve leaflets towards the coronary ostia during valve deployment; and (iii) embolization from calcium, thrombus, air, and/or endocarditis. The width and height of the sinus of Valsalva, the height of the coronary ostia, and the bulkiness of the native leaflets play important roles in the pathogenesis of coronary occlusion following TAVR.

A contrast aortography during balloon aortic valvuloplasty may be performed to evaluate the potential for coronary obstruction. If the aortography suggests an increased risk for coronary obstruction, a safety coronary guide wire can be positioned into the coronary artery with the guiding catheter retracted into the ascending aorta during valve implantation.

Cardiac perforation

Cardiac perforation has been reported in 2–4% of patients undergoing TAVR [131,143,144]. Potential mechanisms include right or left ventricular injury due to the temporary pacemaker lead or stiff guide wire, respectively. Small hypertrophic left ventricular cavities (commonly seen in elderly females), or inadequate pre-shaping or positioning of the left ventricular support wire may increase the risk for this complication. Positioning of the left ventricular stiff guide wire should be performed in the right anterior oblique projection and reassessed throughout the procedure. Cardiac perforation and cardiac tamponade are usually suspected

on the basis of hypotension and/or a new pericardial effusion, and are diagnosed using TTE. Percutaneous pericardiocentesis and reversal of the anticoagulation are recommended.

Aortic annular rupture

Rupture of the annulus or aortic root is rare (<1%). This life-threatening complication is difficult to predict, but typically occurs during balloon inflation (pre-implant balloon aortic valvuloplasty or balloon-expandable valve implantation) (Fig. 14.16). A non-compliant aortic valvular complex, bulky calcification, and aggressive balloon/prosthesis oversizing are possible risk factors. Depending on its location, rupture may result in a ventricular septal defect, left ventricle-to-left atrial or left ventricle-to-right atrial shunt, or communication with the extracardiac space. Contrast aortography usually reveals contrast extravasation confirming the diagnosis. Emergent cardiopulmonary bypass support and surgical exploration is the management of choice.



Fig. 14.16 Extravasation of contrast into the pericardial space due to aortic annular rupture. The injury likely occurred immediately after aggressive balloon aortic valvuloplasty. Image courtesy of the PCR-EAPCI Percutaneous Interventional Cardiovascular Medicine Textbook, 2012, Europa Publishing.

Prosthetic valve dysfunction

Prosthetic valve dysfunction may manifest as symptoms and signs of valvular stenosis or regurgitation. Careful clinical history and examination coupled with echocardiography (TTE or TEE) are suggested to evaluate valve dysfunction [101,102]. Prosthetic valve dysfunction is graded as (i) normal, (ii) possible, or (iii) significant according to the VARC criteria [101,102]. To date, there are limited case reports describing degeneration of transcatheter valves [145,146].

Embolization

Transcatheter valve embolization usually occurs during valve implantation and appears to correlate with operator experience. Embolization may be caused by: (i) undersizing the prosthesis; (ii) malplacement of the prosthesis; (iii) improper rapid pacing during valve deployment or post-implant dilation; (iv) entanglement of a guide wire across the struts of the prosthesis during valve re-crossing; (v) entanglement of the nose cone with the inflow portion of the prosthesis upon retrieving the delivery catheter; and (vi) inadequate release of the loading hooks of the frame from the delivery catheter. Delayed embolization, presenting with unexpected hemodynamic compromise and severe aortic regurgitation, has also been described [98,99].

Thrombosis

Valve thrombosis is defined as any thrombus attached to or near an implanted valve that interrupts blood flow, interferes with valve function, or is sufficiently large to warrant treatment. Postmortem studies of patients implanted with the Edwards Sapien and CoreValve prostheses have observed thrombotic material attached to the frame and/or leaflets [147]. To date, transcatheter aortic valve thrombosis has been reported in only three individual case reports [148–150].

Currently, dual antiplatelet therapy (aspirin and clopidogrel) is recommended for 6 months following TAVR, with aspirin continued indefinitely [131,151]. However, a single-center randomized study observed no differences in clinical outcomes between groups who received dual antiplatelet therapy for 3 months versus aspirin alone [152].

Endocarditis

The diagnosis of prosthetic valve endocarditis can be made using the Duke criteria for endocarditis, during reoperation, or on autopsy [101,102]. Several case reports of bacterial or fungal transcatheter aortic valve endocarditis have been reported involving both the Edwards Sapien and Medtronic CoreValve systems [153–159]. These cases underline the importance of adequate dental care prior to TAVR, the importance of pre-procedural antibiotics, and sterile techniques during the procedure.

Mitral valve injury

Mitral valve injury associated with retrograde TAVR is rare. Resistance during the passage of the delivery catheter into the left ventricle or observation of new mitral regurgitation on TEE should raise the suspicion of catheter entanglement within the mitral valve apparatus. Pre-procedural mitral regurgitation can be identified in up to 75% of patients [160,161], and improves in approximately one-third of patients, and worsens in one-third following TAVR. Mitral annular calcification and deep implantation of the transcatheter valve into the left ventricular outflow tract have been associated with worsening mitral regurgitation [160–163].

Non-cardiac complications

Stroke

To date, observational series have reported 30-day stroke rates of 0–6% in patients undergoing TAVR [83,131,164–166]. In the randomized PARTNER Cohort A trial, the neurologic event rate (all strokes or transient ischemic attack) was nearly two-fold higher in the TAVR than in the surgical group at 30 days and 1-year follow-up (5.5% versus 2.4% at 30 days, 8.3% versus 4.3% at 1 year) [151]. Similarly, in the randomized PARTNER Cohort B trial, the neurologic event rate was higher in the TAVR than in the medical therapy group at 30 days and 1 year (6.7% versus 1.7% at 30 days, 10.6% versus 4.5% at 1 year). Interestingly, one-third to one-half

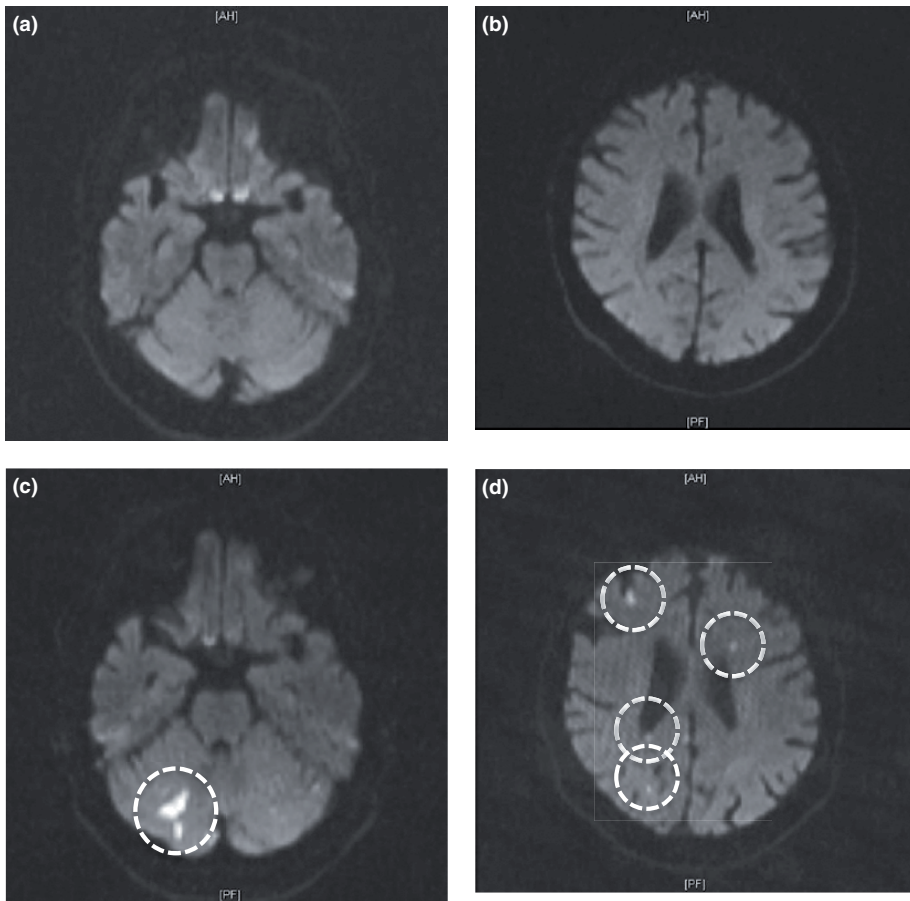


Fig. 14.17 (a, b) Diffusion-weighted MRI of the brain of a 79-year-old patient before undergoing TAVR. (c, d) corresponding diffusion-weighted MRI images of the same patient after a TAVR procedure showing multiple silent cerebral infarcts (encircled in white). Image courtesy of the PCR-EAPCI Percutaneous Interventional Cardiovascular Medicine Textbook, 2012, Europa Publishing.

of strokes occurred between 2 and 30 days after the index procedure [131,151,167]. A history of cerebrovascular disease is an independent predictor of neurologic injury after TAVR [168].

Post-TAVR magnetic resonance imaging (MRI) studies have observed new and multiple silent cerebral infarcts in 68–83% of cases (Fig. 14.17) [169–174]. This suggests that most strokes after TAVR are embolic in nature, a hypothesis corroborated by a recent study using intra-procedural transcranial Doppler which found cerebral microemboli in all patients undergoing transapical TAVR [175]. Cerebral embolic protection devices such as the Embrella (Edwards LifeSciences, Irvine, CA) and Montage System (Claret Medical, Santa Rosa, CA) have been developed to prevent cerebral embolization and have received a European CE mark (Fig. 14.18) [176,177]. These devices have the potential to reduce the incidence of clinical stroke in TAVR recipients [178].

Vascular injury

Vascular complications have been reported in 2–30% of patients undergoing TAVR, and are associated with increased short-term mortality [46,179–182]. Vascular injuries may include dissection, rupture, thrombosis, stenosis, artery avulsion during sheath retraction, failure of vascular pre-closure, arterial-venous fistula, and/or pseudoaneurysms. Femoral and iliac artery complications occur with near equal frequency, though dissections occur more frequently in the femoral artery, and ruptures more common in the iliac artery [46]. Failure of vascular closure devices is an important source of minor vascular complications [180]. Treatment is again cause specific, and includes external femoral artery compression, prolonged balloon inflation, implantation of bare/ covered stents, percutaneous endografts, or surgical repair. Guide wires are easily advanced from the contralateral femoral artery to delivery hemostatic occlusion balloons or stents when needed.

Serious vascular injuries can usually be avoided by: (i) careful vascular screening; (ii) low threshold for using non-femoral access; (iii) consideration for surgical cutdown; (iv) fluoroscopic guidance for advancing devices; and (v) never forcibly advancing materials. Ultrasound-guided femoral artery puncture may also reduce vascular injury [21].



Fig. 14.18 (a) The Embrella device is implanted via a radial artery approach and sits across the aortic arch. (b) SMT embolic deflection device (SMT Research and Development, Herzliya Pituach, Israel) is implanted via a femoral arterial approach and sits across the aortic arch. (c) Montage System (Claret Medical, Santa Rosa, CA) is implanted via a radial approach and each basket sits within a carotid artery.

Acute kidney injury

Chronic kidney failure is present in 10–25% of patients undergoing TAVR. Acute kidney injury (AKI) has been documented in 7–28% of patients following TAVR [80,183–187], and both baseline renal dysfunction and AKI have been associated with increased 30-day and 1-year mortality [183,185,186,188]. A variety of factors are predictive of AKI: history of hypertension, peripheral arterial disease, logistic EuroScore, pre-procedural creatinine level, and post-procedural aortic regurgitation >2+ [80,183–187]. Approximately 100–120 ml of contrast is used during a TAVR procedure, though the volume of contrast has not been linked to the development of AKI. The need for in-hospital renal replacement therapy has been reported in 1–10% of patients [183–187].

CLINICAL TRIAL OUTCOMES

Uniform definitions for clinical endpoints are of considerable importance when evaluating and summarizing current TAVR data.

Valvular Academic Research Consortium

The VARC was established to arrive at a consensus (i) on the most appropriate clinical endpoints reflecting device and patient effectiveness and safety, and (ii) to standardize the definition of endpoints for valve-related clinical trials [101,102,189].

Summary of TAVR clinical studies

Table 14.1 summarizes the clinical outcomes of selected TAVR studies [39,80,131,151,166,167,188,190–200].

PARTNER US Trial

The Placement of Aortic TraNscathetER Valve (PARTNER) US Trial was the first prospective, randomized-controlled trial for transcatheter heart valves. This trial consisted of two individually powered patient cohorts (Cohort A and B). In Cohort A, the Edwards Sapien prosthesis was compared with surgical aortic valve replacement in high-risk surgical patients with severe aortic stenosis [151]. In Cohort B, the Edwards Sapien THV was compared to best medical management in inoperable patients with severe aortic stenosis [167].

Cohort B results

In Cohort B, TAVR was superior to medical therapy and/or balloon aortic valvuloplasty for all-cause mortality at 1 year (31% versus 51%, $P < 0.001$, number needed to treat (NNT) = 5) and at 2 years (43% versus 68%, $P < 0.001$, NNT = 4) [167,201]. The observed rate of neurologic events (stroke and transient ischemic attack), were higher in the transcatheter group

Table 14.1 Summary of clinical outcomes with transcatheter aortic valve implantation.

Reference	Study sample size	Prosthesis type	Age (years)	Logistic EuroScore (%)	STS (%)	30-day mortality (%)	1-year mortality (%)	>1 year mortality (%) (as indicated)	Stroke (%)	MI and/or CO (%)	Vascular injury (%)	Bleeding (%)	Pacemaker implantation (%)	Acute renal injury/dialysis* (%)	Tamponade (%)	New-onset atrial fibrillation (%)	Conversion to surgery (%)
[193]	244	ES and MC	82.3 ± 7.3	25.6 ± 11.4	18.9 ± 12.8	12.7	-	-	3.6	1.2	7.3	-	11.8	-1.6*	2.1	-	-
[200]	697	ES and MC	81.4 ± 6.3	20.5 ± 13.2	-	12.4	-	-	2.8	0.4	19.5	-	39.3	-	1.8	-	-
[60]	646	MDT CV	81.0 ± 6.6	23.1 ± 13.8	9.6 ± 3.5	8	-	-	1.9	0.6	1.9	-	9.3	-	1.4	-	0.5
[199]	200	ES and MC	82.0 ± 6.5	24.6 ± 15.3	6.4 ± 4.9	7.5	-	-	4.5	0.5	13.5	35.5	22.5	19/-	1.1	-	-
[196]	70	ES	84.7 ± 7.6	31.7 ± 16.0	9.6 ± 3.5	-	-	38.6 (3-year)	8.6 (3-year)	8.6 (3-year)	-	7.1 (3-year)	7.1 (3-year)	-	-	-	1.4 (3-year)
[80]	150	MC	81 ± 7	12.3 (9.1-18.4)	6.1 (3.7-12.5)	11	-	-	8	1.1	16	26	19	18.0/-	-	-	0
[188]	663	MC	81.0 ± 7.3	23.0 ± 13.7	-	5.9	15	-	1.2	0	2	-	17.4	-	1.2	-	0.8
[151]	348	ES	83.6 ± 6.8	29.3 ± 16.5	11.8 ± 3.3	3.4	24.2	-	4.7	0	17	9.3	3.8	1.2/2.9*	-	8.6	2.5
[81,197]	1038	ES	81.2 ± 6.8	27.4 ± 15.1	-	8.5	23.9	-	2.5	0.6	12.8	-	7.1	-14.3*	-	-	-
[192]	328	ES and MC	83.1 ± 6.1	28.0 ± 16.0	-	11	-	-	5	-	-	-	13	-16*	-	-	-
[194]	136	MC	80.9	21.3	9.7	12.5	18.4	-	3.7	2.2	-	-	25	-	1.5	-	-
[190]	504	ES	81.2 ± 6.5	24 ± 16	11 ± 4	8.3	-	29 (2-year)	3.1	1.6	-	-	5.3	-	-	-	1.9
[195]	270	ES	83.3 ± 8.0	-	9.5	9.6	-	-	3.3	-	6.7	-	5.9	6.7/-	2.2	4.4	-
[167]	179	ES	83.1 ± 8.6	26.4 ± 17.2	11.2 ± 5.8	5	30.7	-	2.3	0	30.7	16.8	3.4	-11.1*	-	0.6	0

CO, coronary occlusion; ES, Edwards Sapien system; MC, Medtronic CoreValue system; MI, myocardial infarction; STS, Society of Thoracic Surgeons.

than in the medical group at 2-year follow-up (16% versus 6%, $P = 0.003$), though the need for hospitalization was 38% lower in the TAVR group compared with the medical group (35% versus 73%, $P < 0.001$). Quality of life, based on the Kansas City Cardiomyopathy Questionnaire (KCCQ) and SF-12 Health Survey, improved more in the transcatheter than standard therapy group at 30-days and 1-year follow-up [202]. At 12-month follow-up, total costs were significantly lower with TAVR compared with medical therapy: \$29,352 versus \$52,724 ($P < 0.001$) [203]. Incremental life expectancy of 1.9 years was noted with TAVR.

Cohort A results

In Cohort A, TAVR was non-inferior to surgical aortic valve replacement for all-cause mortality at 1 year (24% versus 27%, $P = 0.001$ for non-inferiority) [151]. The rate of neurologic events was higher in the transcatheter group than in the surgical group at 30 days (5.5% versus 2.4%, $P = 0.04$) and at 1 year (8.3% versus 4.3%, $P = 0.04$). The rates of a composite of death from any cause or major stroke were comparable between the transcatheter group and surgical group at 30 days (6.9 versus 8.2%, $P = 0.52$) and at 1 year (26.5 versus 28.0%, $P = 0.68$). Both surgical aortic valve replacement and TAVR improved disease-specific and generic health-related quality of life over 1-year follow-up [204]. For patients eligible for the transfemoral approach, TAVR resulted in substantial quality of life benefit over surgery at 1 month with similar benefits at 6-month and 1-year follow-up.

SPECIFIC PATIENT SUBGROUPS

Failing surgical bioprosthetic valves

Elective redo aortic valve surgery is associated with an operative mortality rate between 2% and 7%, though this increases to more than 30% in high-risk and non-elective patients [205–207]. In excess of 100 successful transcatheter aortic valve-in-surgical aortic valve (TAV-in-SAV) implantations have been reported with the Medtronic CoreValve and Edwards Sapien transcatheter heart valve for failing stented and stentless surgical bioprostheses [208].

Bicuspid valves

Congenital or acquired bicuspid aortic valve stenosis has been considered a contraindication to TAVR. However, several successful case reports have been documented [209–216]. Anecdotally, stenotic bicuspid aortic annuli are larger and more eccentric than stenotic tricuspid aortic valves, and thus MSCT is strongly recommended for transcatheter aortic valve sizing.

Lower surgical risk patients

Although TAVR was initially conceived for the treatment of high surgical risk or inoperable patients, a recent observational report observed a shift toward the selection of lower surgical

risk patients for TAVR [217]. This paradigm shift was associated with significantly better clinical outcomes in the lower (mean STS score 4%) than higher (mean STS score 7%) surgical risk patients undergoing TAVR at 30-day and 6-month follow-up [218]. As further evidence of this move towards lower surgical risk patients, the SURTAVI (SURgical aortic valve replacement versus Transcatheter Aortic Valve Implantation) and PARTNER II trials are expected to randomize intermediate surgical risk patients with an STS score of 4–8% to TAVR or surgical aortic valve replacement.

FUTURE TRANSCATHETER AORTIC VALVE PLATFORMS

Several novel transcatheter aortic valve designs are undergoing human trials. Table 14.2 summarizes these devices.

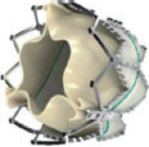
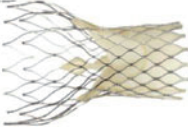


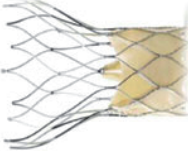




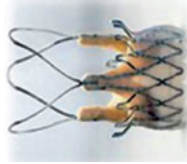
CONCLUSIONS

Transcatheter aortic valve implantation has developed into a relatively mature, safe, and effective therapy for high or prohibitive surgical risk patients with severe aortic stenosis. Device evolution and increasing operator experience have led to improved clinical outcomes. An ever-growing array of clinical studies has improved our understanding of the etiology of cardiac and non-cardiac complications. Meticulous patient selection, procedural techniques, and post-procedure care will further reduce these serious events. Compared with surgical aortic valve replacement, paravalvular aortic regurgitation, stroke, and conduction abnormalities are more common. A variety of novel transcatheter aortic valves are in development.

CONFLICT OF INTEREST STATEMENT

Nicolo Piazza is a consultant and proctor for Medtronic CoreValve.

Table 14.2 A summary of various transcatheter aortic valves and their characteristics.

<p>Manufacturer</p> <p>Access</p> <p>Deployment</p> <p>Support structure</p> <p>Leaflets</p> <p>Skirt</p> <p>Delivery catheter</p> <p>R³</p>					
	Edwards SAPIEN XT	Medtronic CoreValve	Direct Flow Medical	Boston Scientific Sadra Medical	St. Jude Medical Portico
	TF, TA, DAO	TF, SC, DAO	TF	TF	TF
	Balloon-expandable	Self-expandable	Inflatable	Self-expandable	Self-expandable
	Cobalt chromium	Nitinol	Inflatable	Nitinol	Nitinol
	Bovine pericardium	Porcine pericardium	Bovine pericardium	Bovine pericardium	Bovine pericardium
<p>Manufacturer</p> <p>Access</p> <p>Deployment</p> <p>Support structure</p> <p>Leaflets</p> <p>Skirt</p> <p>Delivery catheter</p> <p>R³</p>					
	Polyethylene terephthalate	Porcine pericardium	Polyester	Polyurethane	Porcine pericardium
	18F/19F	18F	18F	18F/20F	18F
	No	Partially	Yes	Yes	Yes
<p>Manufacturer</p> <p>Access</p> <p>Deployment</p> <p>Support structure</p> <p>Leaflets</p> <p>Skirt</p> <p>Delivery catheter</p> <p>R³</p>					
	Heart Leaflet Technology	Colibri Heart Valve	Medtronic Engager	Jena Valve Technology	Symetis Acurate System
	TF	TF	TA	TA	TA
	Self-expandable	Balloon-expandable	Self-expandable	Self-expandable	Self-expandable
	Nitinol	Stainless steel	Nitinol	Nitinol	Nitinol
	Porcine pericardium	Porcine pericardium	Bovine pericardium	Porcine aortic root	?
<p>Manufacturer</p> <p>Access</p> <p>Deployment</p> <p>Support structure</p> <p>Leaflets</p> <p>Skirt</p> <p>Delivery catheter</p> <p>R³</p>					
	Braided polyester	Porcine pericardium	Polyester	Polyurethane	?
	17F	14F/16F	26F	27F	?
	Yes	No	No	Partially	Yes

REFERENCES

1. Davies H. Catheter mounted valve for temporary relief of aortic insufficiency. *Lancet* 1965;1:250.
2. Mouloupoulos SD, Anthopoulos L, Stamatelopoulos S, et al. Catheter-mounted aortic valves. *Ann Thorac Surg* 1971;11:423–30.
3. Phillips SJ, Ciborski M, Freed PS, et al. A temporary catheter-tip aortic valve: hemodynamic effects on experimental acute aortic insufficiency. *Ann Thorac Surg* 1976;21:134–7.
4. Matsubara T, Yamazoe M, Tamura Y, et al. Balloon catheter with check valves for experimental relief of acute aortic regurgitation. *Am Heart J* 1992;124:1002–8.
5. Cribier A, Savin T, Saoudi N, et al. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? *Lancet* 1986;1:63–7.
6. Drobinski G, Lechat P, Metzger JP, et al. Results of percutaneous catheter valvuloplasty for calcified aortic stenosis in the elderly. *Eur Heart J* 1987;8:322–8.
7. Serruys PW, Luijten HE, Beatt KJ, et al. Percutaneous balloon valvuloplasty for calcific aortic stenosis. A treatment ‘sine cure’? *Eur Heart J* 1988;9:782–94.
8. Safian RD, Berman AD, Diver DJ, et al. Balloon aortic valvuloplasty in 170 consecutive patients. *N Engl J Med* 1988;319:125–30.
9. Block PC, Palacios IF. Clinical and hemodynamic follow-up after percutaneous aortic valvuloplasty in the elderly. *Am J Cardiol* 1988;62:760–3.
10. Berland J, Cribier A, Savin T, et al. Percutaneous balloon valvuloplasty in patients with severe aortic stenosis and low ejection fraction. Immediate results and 1-year follow-up. *Circulation* 1989;79:1189–96.
11. Letac B, Cribier A, Eltchaninoff H, et al. Evaluation of restenosis after balloon dilatation in adult aortic stenosis by repeat catheterization. *Am Heart J* 1991;122:55–60.
12. Otto CM, Mickel MC, Kennedy JW, et al. Three-year outcome after balloon aortic valvuloplasty. Insights into prognosis of valvular aortic stenosis. *Circulation* 1994;89:642–50.
13. Charlson E, Legedza AT, Hamel MB. Decision-making and outcomes in severe symptomatic aortic stenosis. *J Heart Valve Dis* 2006;15:312–21.
14. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005;111:3290–5.
15. Lung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J* 2005;26:2714–20.
16. Bouma BJ, van Den Brink RB, van Der Meulen JH, et al. To operate or not on elderly patients with aortic stenosis: the decision and its consequences. *Heart* 1999;82:143–8.
17. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 2002;106:3006–8.
18. Cribier A, Eltchaninoff H, Tron C, et al. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol* 2006;47:1214–23.
19. Webb JG, Chandavimol M, Thompson CR, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation* 2006;113:842–50.
20. Hijazi Z, Ruiz C, Bonhoeffer P, et al. *Transcatheter Valve Repair*, 1st edn. New York: Informa Healthcare, 2006.
21. de Jaegere P, van Dijk L, Laborde JC, et al. True percutaneous implantation of the CoreValve aortic valve prosthesis by the combined use of ultrasound guided vascular access, Prostar XL and the TandemHeart. *Eurointervention* 2007;2:500–5.

22. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2 – isolated valve surgery. *Ann Thorac Surg* 2009;88: S23–42.
23. Kuduvali M, Grayson AD, Au J, et al. A multi-centre additive and logistic risk model for in-hospital mortality following aortic valve replacement. *Eur J Cardiothorac Surg* 2007;31:607–13.
24. Hannan EL, Wu C, Bennett EV, et al. Risk index for predicting in-hospital mortality for cardiac valve surgery. *Ann Thorac Surg* 2007;83:921–9.
25. Rankin JS, Hammill BG, Ferguson TB, Jr, et al. Determinants of operative mortality in valvular heart surgery. *J Thorac Cardiovasc Surg* 2006;131:547–57.
26. Nilsson J, Algotsson L, Hoglund P, et al. Comparison of 19 pre-operative risk stratification models in open-heart surgery. *Eur Heart J* 2006;27:867–74.
27. Jin R, Grunkemeier GL, Starr A. Validation and refinement of mortality risk models for heart valve surgery. *Ann Thorac Surg* 2005;80:471–9.
28. Ambler G, Omar RZ, Royston P, et al. Generic, simple risk stratification model for heart valve surgery. *Circulation* 2005;112:224–31.
29. Nowicki ER, Birkmeyer NJ, Weintraub RW, et al. Multivariable prediction of in-hospital mortality associated with aortic and mitral valve surgery in northern New England. *Ann Thorac Surg* 2004;77: 1966–77.
30. Gardner SC, Grunwald GK, Rumsfeld JS, et al. Comparison of short-term mortality risk factors for valve replacement versus coronary artery bypass graft surgery. *Ann Thorac Surg* 2004;77:549–56.
31. Florath I, Rosendahl UP, Mortasawi A, et al. Current determinants of operative mortality in 1400 patients requiring aortic valve replacement. *Ann Thorac Surg* 2003;76:75–83.
32. Edwards FH, Peterson ED, Coombs LP, et al. Prediction of operative mortality after valve replacement surgery. *J Am Coll Cardiol* 2001;37:885–92.
33. Nashef SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16:9–13.
34. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation* 1989;79:13–12.
35. Osswald BR, Gegouskov V, Badowski-Zyla D, et al. Overestimation of aortic valve replacement risk by Euro-SCORE: implications for percutaneous valve replacement. *Eur Heart J* 2009;30:74–80.
36. Leontyev S, Walther T, Borger MA, et al. Aortic valve replacement in octogenarians: utility of risk stratification with EuroSCORE. *Ann Thorac Surg* 2009;87:1440–5.
37. Dewey TM, Brown D, Ryan WH, et al. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. *J Thorac Cardiovasc Surg* 2008;135:180–7.
38. Brown ML, Schaff HV, Sarano ME, et al. Is the European System for Cardiac Operative Risk Evaluation model valid for estimating the operative risk of patients considered for percutaneous aortic valve replacement? *J Thorac Cardiovasc Surg* 2008;136:566–71.
39. Lefevre T, Kappetein AP, Wolner E, et al. One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. *Eur Heart J* 2011;32:148–57.
40. Buellesfeld L, Gerckens U, Schuler G, et al. 2-year follow-up of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. *J Am Coll Cardiol* 2011;57:1650–7.
41. Piazza N, Wenaweser P, van Gameren M, et al. Relationship between the logistic EuroSCORE and the Society of Thoracic Surgeons Predicted Risk of Mortality score in patients implanted with the CoreValve ReValving system – a Bern-Rotterdam Study. *Am Heart J* 2010;159:323–9.
42. Delgado V, Ewe SH, Ng AC, et al. Multimodality imaging in transcatheter aortic valve implantation: key steps to assess procedural feasibility. *Eurointervention* 2010;6: 643–52.

43. Piazza N, de Jaegere P, Manoharan G, et al. Patient selection for the CoreValve ReValving System. In: Serruys P, Piazza N, Cribier A, Webb J, Laborde JC, de Jaegere P (eds) *Transcatheter Aortic Valve Implantation: tips and tricks to avoid failure*. New York: Informa Healthcare, 2011, p. 82.
44. Nietlispach F, Leipsic J, Al-Bugami S, et al. CT of the ilio-femoral arteries using direct aortic contrast injection: proof of feasibility in patients screened towards percutaneous aortic valve replacement. *Swiss Med Wkly* 2009;139:458–62.
45. Eltchaninoff H, Kerkeni M, Zajarias A, et al. Aorto-iliac angiography as a screening tool in selecting patients for transfemoral aortic valve implantation with the Edwards SAPIEN bioprosthesis. *Eurointervention* 2009;5:438–42.
46. Hayashida K, Lefevre T, Chevalier B, et al. Transfemoral aortic valve implantation new criteria to predict vascular complications. *JACC Cardiovasc Interv* 2011;4:851–8.
47. Piazza N, Serruys PW, Lange R. Getting safely in and out of a transcatheter aortic valve implantation procedure vascular complications according to the valvular academic research consortium criteria. *JACC Cardiovasc Interv* 2011;4:859–60.
48. Piazza N, de Jaegere P, Schultz C, et al. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. *Circ Cardiovasc Intervent* 2008;1:74–81.
49. Schultz CJ, Moelker A, Piazza N, et al. Three dimensional evaluation of the aortic annulus using multislice computer tomography: are manufacturer's guidelines for sizing for percutaneous aortic valve replacement helpful? *Eur Heart J* 2010;31:849–56.
50. Tops LF, Wood DA, Delgado V, et al. Noninvasive evaluation of the aortic root with multislice computed tomography implications for transcatheter aortic valve replacement. *JACC Cardiovasc Imaging* 2008;1:321–30.
51. Ng AC, Yiu KH, Ewe SH, et al. Influence of left ventricular geometry and function on aortic annular dimensions as assessed with multi-detector row computed tomography: implications for transcatheter aortic valve implantation. *Eur Heart J* 2011;32:2806–13.
52. Schultz C, Moelker A, Tzikas A, et al. The use of MSCT for the evaluation of the aortic root before transcatheter aortic valve implantation: the Rotterdam approach. *Eurointervention* 2010;6:505–11.
53. Schultz CJ, Moelker AD, Tzikas A, et al. Cardiac CT: necessary for precise sizing for transcatheter aortic implantation. *Eurointervention* 2010;6(Suppl G):G6–13.
54. Nietlispach F, Wijesinghe N, Wood D, et al. Current balloon-expandable transcatheter heart valve and delivery systems. *Catheter Cardiovasc Interv* 2010;75:295–300.
55. Rodes-Cabau J, Delarochelliere R, Dumont E. First-in-man transcatheter aortic valve implantation of a 20-mm edwards SAPIEN XT valve: one step forward for the treatment of patients with severe aortic stenosis and small aortic annulus. *Catheter Cardiovasc Interv* 2012;79:789–93.
56. Chen W, Schoen FJ, Levy RJ. Mechanism of efficacy of 2-amino oleic acid for inhibition of calcification of glutaraldehyde-pretreated porcine bioprosthetic heart valves. *Circulation* 1994;90:323–9.
57. Vavuranakis M, Vrachatis DA, Toutouzas K, et al. Successful percutaneous aortic valve implantation via a stenotic left subclavian artery access. *Heart Vessels* 2010;25:359–62.
58. Munoz-Garcia AJ, Alonso-Briaes JH, Such-Martinez M, et al. Left subclavian artery approach to CoreValve aortic prosthesis implantation. *Rev Esp Cardiol* 2010;63:121–2.
59. Ruge H, Lange R, Bleiziffer S, et al. First successful aortic valve implantation with the CoreValve ReValving System via right subclavian artery access: a case report. *Heart Surg Forum* 2008;11:E323–4.
60. Sarkar K, Ussia GP, Tamburino C. Transcatheter aortic valve implantation for severe aortic regurgitation in a stentless bioprosthetic valve with the core valve revalving system – technical tips and role of the Accutrak system. *Catheter Cardiovasc Interv* 2011;78:485–90.

61. de Jaegere P, Piazza N, Tzikas A, et al. Implantation of the CoreValve ReValving System. In: Serruys P, Piazza N, Cribier A, Webb J, Laborde J, de Jaegere P (eds) *Transcatheter Aortic Valve : tips and tricks to avoid failure*, 1st edn. New York: Informa Healthcare, 2011, pp. 183–97.
62. Nietlispach F, Webb J. Implantation of the Edwards SAPIEN valve. In: Serruys P, Piazza N, Cribier A, Webb J, Laborde J, de Jaegere P (eds) *Transcatheter Aortic Valve Implantation*, 1st edn. New York: Informa Healthcare, 2011, pp. 198–206.
63. Hutchinson N. Sedation vs general anaesthesia for the 'high-risk' patient – what can TAVI teach us? *Anaesthesia* 2011;66:965–8.
64. Motloch LJ, Rottlaender D, Reda S, et al. Local versus general anesthesia for transfemoral aortic valve implantation. *Clin Res Cardiol* 2012;101:45–53.
65. Dehedin B, Guinot PG, Ibrahim H, et al. Anesthesia and perioperative management of patients who undergo transfemoral transcatheter aortic valve implantation: an observational study of general versus local/regional anesthesia in 125 consecutive patients. *J Cardiothorac Vasc Anesth* 2011;25:1036–43.
66. Covello RD, Landoni G, Zangrillo A. Anesthetic management of transcatheter aortic valve implantation. *Curr Opin Anaesthesiol* 2011;24:417–25.
67. Guinot PG, Depoix JP, Tini L, et al. [Transcatheter aortic valve implantation: anesthetic and perioperative management]. *Ann Fr Anesth Reanim* 2011;30:734–42.
68. Vavuranakis M, Voudris V, Vrachatis DA, et al. Transcatheter aortic valve implantation, patient selection process and procedure: two centres' experience of the intervention without general anaesthesia. *Hellenic J Cardiol* 2010;51:492–500.
69. Guinot PG, Depoix JP, Etchegoyen L, et al. Anesthesia and perioperative management of patients undergoing transcatheter aortic valve implantation: analysis of 90 consecutive patients with focus on perioperative complications. *J Cardiothorac Vasc Anesth* 2010;24:752–61.
70. Covello RD, Ruggeri L, Landoni G, et al. Transcatheter implantation of an aortic valve: anesthesiological management. *Minerva Anesthesiol* 2010;76:100–8.
71. Behan M, Haworth P, Hutchinson N, et al. Percutaneous aortic valve implants under sedation: our initial experience. *Catheter Cardiovasc Interv* 2008;72:1012–15.
72. Bergmann L, Kahlert P, Eggebrecht H, et al. Transfemoral aortic valve implantation under sedation and monitored anaesthetic care – a feasibility study. *Anaesthesia* 2011;66:977–82.
73. Fassl J, Walther T, Groesdonk HV, et al. Anesthesia management for transapical transcatheter aortic valve implantation: a case series. *J Cardiothorac Vasc Anesth* 2009;23:286–91.
74. Wood DA, Tops LE, Mayo JR, et al. Role of multislice computed tomography in transcatheter aortic valve replacement. *Am J Cardiol* 2009;103:1295–301.
75. Tzikas A, Schultz C, Van Mieghem NM, et al. Optimal projection estimation for transcatheter aortic valve implantation based on contrast-aortography: validation of a Prototype Software. *Catheter Cardiovasc Interv* 2010;76:602–7.
76. Dvir D, Kornowski R. Percutaneous aortic valve implantation using novel imaging guidance. *Catheter Cardiovasc Interv* 2010;76:450–4.
77. Kurra V, Kapadia SR, Tuzcu EM, et al. Pre-procedural imaging of aortic root orientation and dimensions: comparison between X-ray angiographic planar imaging and 3-dimensional multidetector row computed tomography. *JACC Cardiovasc Interv* 2010;3:105–13.
78. Cockburn J, de Belder A, Brooks M, et al. Large calibre arterial access device closure for percutaneous aortic valve interventions: use of the prostar system in 118 cases. *Catheter Cardiovasc Interv* 2012;79:143–9.
79. Sharp AS, Michev I, Maisano F, et al. A new technique for vascular access management in transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2010; 75:784–93.

80. Nuis RJ, Piazza N, Van Mieghem NM, et al. In-hospital complications after transcatheter aortic valve implantation revisited according to the valve academic research consortium definitions. *Catheter Cardiovasc Interv* 2011;78:457–67.
81. Conradi L, Seiffert M, Treede H, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement: a propensity score analysis in patients at high surgical risk. *J Thorac Cardiovasc Surg* 2012;143:64–71.
82. Clavel MA, Webb JG, Pibarot P, et al. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. *J Am Coll Cardiol* 2009;53:1883–91.
83. Himbert D, Descoutures F, Al-Attar N, et al. Results of transfemoral or transapical aortic valve implantation following a uniform assessment in high-risk patients with aortic stenosis. *J Am Coll Cardiol* 2009;54:303–11.
84. Jilaihawi H, Chin D, Spy T, et al. Prosthesis-patient mismatch after transcatheter aortic valve implantation with the Medtronic-Corevalve bioprosthesis. *Eur Heart J* 2010;31:857–64.
85. Moss RR, Ivens E, Pasupati S, et al. Role of echocardiography in percutaneous aortic valve implantation. *JACC Cardiovasc Imaging* 2008;1:15–24.
86. Jabbour A, Ismail TF, Moat N, et al. Multimodality imaging in transcatheter aortic valve implantation and post-procedural aortic regurgitation: comparison among cardiovascular magnetic resonance, cardiac computed tomography, and echocardiography. *J Am Coll Cardiol* 2011;58:2165–73.
87. Detaint D, Lepage L, Himbert D, et al. Determinants of significant paravalvular regurgitation after transcatheter aortic valve: implantation impact of device and annulus incongruence. *JACC Cardiovasc Interv* 2009;2:821–7.
88. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol* 2011;58:2130–8.
89. Schultz C, Rossi A, van Mieghem N, et al. Aortic annulus dimensions and leaflet calcification from contrast MSCT predict the need for balloon post-dilatation after TAVI with the Medtronic CoreValve prosthesis. *Eurointervention* 2011;7:564–72.
90. Ong SH, Mueller R, Gerckens U. Sequential CoreValve implantation for a mal-positioned prosthesis during transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2011;77:1071–5.
91. Zahn R, Schiele R, Kilkowski C, et al. Correction of aortic regurgitation after transcatheter aortic valve implantation of the Medtronic CoreValve™ prosthesis due to a too-low implantation, using transcatheter repositioning. *J Heart Valve Dis* 2011;20:64–9.
92. Litzler PY, Cribier A, Zajarias A, et al. Surgical aortic valve replacement after percutaneous aortic valve implantation: what have we learned? *J Thorac Cardiovasc Surg* 2008;136:697–701.
93. Al-Attar N, Ghodbane W, Himbert D, et al. Unexpected complications of transapical aortic valve implantation. *Ann Thorac Surg* 2009;88:90–4.
94. Takagi K, Latib A, Al-Lamee R, et al. Predictors of moderate-to-severe paravalvular aortic regurgitation immediately after CoreValve implantation and the impact of postdilatation. *Catheter Cardiovasc Interv* 2011;78:432–43.
95. Al-Attar N, Himbert D, Vahanian A, et al. Severe intra-prosthetic regurgitation by immobile leaflet after transcatheter aortic valve implantation. *Eur J Cardiothorac Surg* 2011;39:591–2.
96. Zahn R, Schiele R, Kilkowski C, et al. Severe aortic regurgitation after percutaneous transcatheter aortic valve implantation: on the importance to clarify the underlying pathophysiology. *Clin Res Cardiol* 2010;99:193–7.

97. Miranda-Balbuena N, Araj OA, Gutierrez-Martin MA, et al. Management of aortic valve dysfunction after transapical approach using the technique “valve after valve”. *Ann Thorac Surg* 2011;92:1102–4.
98. Clavel MA, Dumont E, Pibarot P, et al. Severe valvular regurgitation and late prosthesis embolization after percutaneous aortic valve implantation. *Ann Thorac Surg* 2009;87:618–21.
99. Baumbach H, Hill S, Hansen M, et al. Severe aortic insufficiency after transapical aortic valve implantation. *Ann Thorac Surg* 2011;92:728–9.
100. Pagnotta P, Ferrante G, Presbitero P. Rescue “valve in valve” implantation after late onset corevalve cusp rupture leading to acute massive aortic insufficiency. *Catheter Cardiovasc Interv* 2014;83:E283–6.
101. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *Eur Heart J* 2011;32:205–17.
102. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol* 2011;57:253–69.
103. Igawa O, Adachi M, Yano A, et al. Anatomical information for catheter ablation concerning the relationship between the aortic non-coronary cusp and the His-bundle. *Circ J* 2009;257:73.
104. Aktug O, Dohmen G, Brehmer K, et al. Incidence and predictors of left bundle branch block after transcatheter aortic valve implantation. *Int J Cardiol* 2011;160:26–30.
105. Baan J, Jr, Yong ZY, Koch KT, et al. Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis. *Am Heart J* 2010;159:497–503.
106. Bleiziffer S, Ruge H, Horer J, et al. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2010;3:524–30.
107. Calvi V, Puzzangara E, Pruiti GP, et al. Early conduction disorders following percutaneous aortic valve replacement. *Pacing Clin Electrophysiol* 2009;32(Suppl 1):S126–30.
108. Erkapic D, Kim WK, Weber M, et al. Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. *Europace* 2010;12:1188–90.
109. Ferreira ND, Caeiro D, Adao L, et al. Incidence and predictors of permanent pacemaker requirement after transcatheter aortic valve implantation with a self-expanding bioprosthesis. *Pacing Clin Electrophysiol* 2010;33:1364–72.
110. Fraccaro C, Buja G, Tarantini G, et al. Incidence, predictors, and outcome of conduction disorders after transcatheter self-expandable aortic valve implantation. *Am J Cardiol* 2011;107:747–54.
111. Guetta V, Goldenberg G, Segev A, et al. Predictors and course of high-degree atrioventricular block after transcatheter aortic valve implantation using the CoreValve Revalving system. *Am J Cardiol* 2011;108:1600–5.
112. Haworth P, Behan M, Khawaja M, et al. Predictors for permanent pacing after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2010;76:751–6.
113. Khawaja MZ, Rajani R, Cook A, et al. Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). *Circulation* 2011;123:951–60.
114. Koos R, Mahnken AH, Aktug O, et al. Electrocardiographic and imaging predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. *J Heart Valve Dis* 2011;20:83–90.
115. Latsios G, Gerckens U, Buellesfeld L, et al. “Device landing zone” calcification, assessed by MSCT, as a predictive factor for pacemaker implantation after TAVI. *Catheter Cardiovasc Interv* 2010;76:431–9.

116. Nuis RJ, Van Mieghem NM, Schultz CJ, et al. Timing and potential mechanisms of new conduction abnormalities during the implantation of the Medtronic CoreValve System in patients with aortic stenosis. *Eur Heart J* 2011;32:2067–74.
117. Piazza N, Nuis RJ, Tzikas A, et al. Persistent conduction abnormalities and requirements for pacemaking six months after transcatheter aortic valve implantation. *Eurointervention* 2010;6:475–84.
118. Piazza N, Onuma Y, Jesserun E, et al. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. *J Am Coll Cardiol Interv* 2008;1:310–16.
119. Roten L, Wenaweser P, Delacretaz E, et al. Incidence and predictors of atrioventricular conduction impairment after transcatheter aortic valve implantation. *Am J Cardiol* 2010;106:1473–80.
120. Rubin JM, Avanzas P, del Valle R, et al. Atrioventricular conduction disturbance characterization in transcatheter aortic valve implantation with the CoreValve prosthesis. *Circ Cardiovasc Interv* 2011;4:280–6.
121. Jilaihawi H, Chin D, Vasa-Nicotera M, et al. Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. *Am Heart J* 2009;157:860–6.
122. Godin M, Eltchaninoff H, Furuta A, et al. Frequency of conduction disturbances after transcatheter implantation of an Edwards Sapien aortic valve prosthesis. *Am J Cardiol* 2010;106:707–12.
123. Gutierrez M, Rodes-Cabau J, Bagur R, et al. Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. *Am Heart J* 2009;158:302–8.
124. Sinhal A, Altwegg A, Pasupati S, et al. Atrioventricular block after transcatheter balloon expandable aortic valve implantation. *J Am Coll Cardiol Interv* 2008;1: 305–309.
125. Koektuerk B, Schaefer U, Bergmann M, et al. Acquired conduction disturbances after percutaneous aortic valve replacement. *Circulation* 2009;120:S307.
126. Saia F, Lemos PA, Bordoni B, et al. Transcatheter aortic valve implantation with a self-expanding nitinol bioprosthesis: prediction of the need for permanent pacemaker using simple baseline and procedural characteristics. *Catheter Cardiovasc Interv* 2011;79:712–19.
127. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/ AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/ NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;51:e1–62.
128. Vardas PE, Auricchio A, Blanc JJ, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Europace* 2007;9:959–98.
129. Motloch LJ, Reda S, Rottlaender D, et al. Postprocedural atrial fibrillation after transcatheter aortic valve implantation versus surgical aortic valve replacement. *Ann Thorac Surg* 2012;93(1):124–31.
130. Amat-Santos JJ, Rodes-Cabau J, Urena M, et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. *J Am Coll Cardiol* 2012; 59(2):178–88.
131. Piazza N, Grube E, Gerckens U, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 F) CoreValve ReValving System – results from the Multicenter, Expanded Evaluation Registry 1-year following CE mark approval. *Eurointervention* 2008; 4:242–9.

132. Fiorina C, Curello S, Maffeo D, et al. Management of acute left main obstruction after transcatheter aortic valve replacement: the "tunnel technique." *Cardiovasc Revasc Med* 2012;13(2):142 e5–9.
133. Gurvitch R, Cheung A, Bedogni F, et al. Coronary obstruction following transcatheter aortic valve-in-valve implantation for failed surgical bioprostheses. *Catheter Cardiovasc Interv* 2011;77:439–44.
134. Kapadia SR, Svensson L, Tuzcu EM. Successful percutaneous management of left main trunk occlusion during percutaneous aortic valve replacement. *Catheter Cardiovasc Interv* 2009;73:966–72.
135. Kukucka M, Pasic M, Dreyse S, et al. Delayed subtotal coronary obstruction after transapical aortic valve implantation. *Interact Cardiovasc Thorac Surg* 2011;12:57–60.
136. Webb JG. Coronary obstruction due to transcatheter valve implantation. *Catheter Cardiovasc Interv* 2009;73:973.
137. Gogas BD, Zacharoulis AA, Antoniadis AG. Acute coronary occlusion following TAVI. *Catheter Cardiovasc Interv* 2011;77:435–8.
138. Saia F, Marrozzini C, Marzocchi A. Displacement of calcium nodules of the native valve as a possible cause of left main occlusion following transcatheter aortic valve implantation. *J Invasive Cardiol* 2011;23:E106–9.
139. Gerckens U, Latsios G, Mueller R, et al. Left main PCI after trans-subclavian CoreValve implantation. Successful outcome of a combined procedure for management of a rare complication. *Clin Res Cardiol* 2009;98:687–90.
140. Bagur R, Dumont E, Doyle D, et al. Coronary ostia stenosis after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2010;3:253–5.
141. Bartorelli AL, Andreini D, Sisillo E, et al. Left main coronary artery occlusion after percutaneous aortic valve implantation. *Ann Thorac Surg* 2010;89:953–5.
142. Stabile E, Sorropago G, Cioppa A, et al. Acute left main obstructions following TAVI. *Eurointervention* 2010;6:100–5.
143. Lange R, Bleiziffer S, Piazza N, et al. Incidence and treatment of procedural cardiovascular complications associated with trans-arterial and trans-apical interventional aortic valve implantation in 412 consecutive patients. *Eur J Cardiothorac Surg* 2011;40:1105–13.
144. Webb JG, Pasupati S, Humphries K, et al. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. *Circulation* 2007;116:755–63.
145. Ong SH, Mueller R, Iversen S. Early calcific degeneration of a CoreValve transcatheter aortic bioprosthesis. *Eur Heart J* 2012;33(5):586.
146. Hammerstingl C, Nickenig G, Grube E. Treatment of a degenerative stenosed CoreValve(®) aortic bioprosthesis by transcatheter valve-in-valve insertion. *Catheter Cardiovasc Interv* 2012;79(5):748–55.
147. Virmani R, Bonan R, Nakazawa G, et al. Accumulation of worldwide experience with postmortem studies of transcatheter aortic valve implantation – what should we be avoiding? In: Serruys P, Piazza N, Cribier A, Webb J, Laborde J (eds) *Transcatheter Aortic Valve Implantation: tips and tricks to avoid failure*. New York: Informa Healthcare, 2011, pp. 18–39.
148. Tay EL, Gurvitch R, Wijeyesinghe N, et al. Valve thrombosis after transcatheter heart valve implantation. *Eurointervention* 2011;7:170–1.
149. Kefer J, Astarci P, Renkin J, et al. Images and case reports in interventional cardiology. Thrombotic aortic restenosis after transapical Sapien valve implantation. *Circ Cardiovasc Interv* 2010;3:289–92.
150. Trepels T, Martens S, Doss M, et al. Images in cardiovascular medicine. Thrombotic restenosis after minimally invasive implantation of aortic valve stent. *Circulation* 2009;120:e23–4.
151. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–98.

152. Ussia GP, Scarabelli M, Mule M, et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol* 2011;108:1772–6.
153. Head SJ, Dewey TM, Mack MJ. Fungal endocarditis after transfemoral aortic valve implantation. *Catheter Cardiovasc Interv* 2011;78:1017–19.
154. Carnero-Alcazar M, Maroto Castellanos LC, Carnicer JC, et al. Transapical aortic valve prosthetic endocarditis. *Interact Cardiovasc Thorac Surg* 2010;11:252–3.
155. Gotzmann M, Mugge A. Fatal prosthetic valve endocarditis of the CoreValve ReValving System. *Clin Res Cardiol* 2011;100:715–17.
156. Santos M, Thiene G, Sievers HH, et al. Candida endocarditis complicating transapical aortic valve implantation. *Eur Heart J* 2011;32:2265.
157. Comoglio C, Boffini M, El Qarra S, et al. Aortic valve replacement and mitral valve repair as treatment of complications after percutaneous core valve implantation. *J Thorac Cardiovasc Surg* 2009;138:1025–7.
158. Wong DR, Boone RH, Thompson CR, et al. Mitral valve injury late after transcatheter aortic valve implantation. *J Thorac Cardiovasc Surg* 2009;137:1547–9.
159. Rafiq I, Parthasarathy H, Tremlett C, et al. Infective endocarditis caused by *Moraxella nonliquefaciens* in a percutaneous aortic valve replacement. *Cardiovasc Revasc Med* 2011;12:184–6.
160. Tzikas A, Piazza N, van Dalen BM, et al. Changes in mitral regurgitation after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2010; 75:43–9.
161. De Chiara B, Moreo A, De Marco F, et al. Influence of CoreValve ReValving System implantation on mitral valve function: an echocardiographic study in selected patients. *Catheter Cardiovasc Interv* 2011; 78:638–44.
162. Durst R, Avelar E, McCarty D, et al. Outcome and improvement predictors of mitral regurgitation after transcatheter aortic valve implantation. *J Heart Valve Dis* 2011;20:272–81.
163. Hekimian G, Detaint D, Messika-Zeitoun D, et al. Mitral regurgitation in patients referred for transcatheter aortic valve implantation using the Edwards Sapien prosthesis: mechanisms and early postprocedural changes. *J Am Soc Echocardiogr* 2012;25(2):160–5.
164. Webb JG, Altwegg L, Boone RH, et al. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. *Circulation* 2009;119:3009–16.
165. Rodes-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol* 2010;55:1080–90.
166. Thomas M, Schymik G, Walther T, et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2011;124:425–33.
167. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607.
168. Tay EL, Gurvitch R, Wijesinghe N, et al. A high-risk period for cerebrovascular events exists after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2011;4:1290–7.
169. Astarci P, Glineur D, Kefer J, et al. Magnetic resonance imaging evaluation of cerebral embolization during percutaneous aortic valve implantation: comparison of transfemoral and trans-apical approaches using Edwards Sapiens valve. *Eur J Cardiothorac Surg* 2011;40:475–9.
170. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation* 2010; 121:870–8.

171. Ghanem A, Muller A, Nahle CP, et al. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. *J Am Coll Cardiol* 2010;55:1427–32.
172. Rodes-Cabau J, Dumont E, Boone RH, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. *J Am Coll Cardiol* 2011;57:18–28.
173. Arnold M, Schulz-Heise S, Achenbach S, et al. Embolic cerebral insults after transapical aortic valve implantation detected by magnetic resonance imaging. *JACC Cardiovasc Interv* 2010;3:1126–32.
174. Fairbairn TA, Mather AN, Bijsterveld P, et al. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. *Heart* 2012; 98(1):18–23.
175. Drews T, Pasic M, Buz S, et al. Transcranial Doppler sound detection of cerebral microembolism during transapical aortic valve implantation. *Thorac Cardiovasc Surg* 2011;59:237–42.
176. Etienne PY, Papadatos S, Pieters D, et al. Embol-x intraaortic filter and transaortic approach for improved cerebral protection in transcatheter aortic valve implantation. *Ann Thorac Surg* 2011;92:e95–6.
177. Nietlispach F, Wijesinghe N, Gurvitch R, et al. An embolic deflection device for aortic valve interventions. *JACC Cardiovasc Interv* 2010;3:1133–8.
178. Macdonald S. New embolic protection devices: a review. *J Cardiovasc Surg (Torino)* 2011;52:821–7.
179. Tchetché D, Dumonteil N, Sauguet A, et al. Thirty-day outcome and vascular complications after transarterial aortic valve implantation using both Edwards Sapien and Medtronic CoreValve bioprostheses in a mixed population. *Eurointervention* 2010;5:659–65.
180. Van Mieghem NM, Nuis RJ, Piazza N, et al. Vascular complications with transcatheter aortic valve implantation using the 18 Fr Medtronic CoreValve System: the Rotterdam experience. *Eurointervention* 2010;5:673–9.
181. Ducrocq G, Francis F, Serfaty JM, et al. Vascular complications of transfemoral aortic valve implantation with the Edwards SAPIEN prosthesis: incidence and impact on outcome. *Eurointervention* 2010;5:666–72.
182. Kahlert P, Al-Rashid F, Weber M, et al. Vascular access site complications after percutaneous transfemoral aortic valve implantation. *Herz* 2009;34:398–408.
183. Elhmidi Y, Bleiziffer S, Piazza N, et al. Incidence and predictors of acute kidney injury in patients undergoing transcatheter aortic valve implantation. *Am Heart J* 2011;161:735–9.
184. Bagur R, Webb JG, Nietlispach F, et al. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. *Eur Heart J* 2010;31:865–74.
185. Nuis RJ, Van Mieghem NM, Tzikas A, et al. Frequency, determinants, and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2011;77:881–9.
186. Sinning JM, Ghanem A, Steinhäuser H, et al. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2010;3:1141–9.
187. Aregger F, Wenaweser P, Hellige GJ, et al. Risk of acute kidney injury in patients with severe aortic valve stenosis undergoing transcatheter valve replacement. *Nephrol Dial Transplant* 2009;24:2175–9.
188. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation* 2011;123:299–308.
189. Piazza N, Cutlip DE, Onuma Y, et al. Clinical endpoints in transcatheter aortic valve implantation: a call to ARC for standardised definitions. *Eurointervention* 2009;5:29–31.

190. Kempfert J, Rastan A, Holzhey D, et al. Transapical aortic valve implantation: analysis of risk factors and learning experience in 299 patients. *Circulation* 2011; 124:S124–9.
191. D'Onofrio A, Rubino P, Fusari M, et al. Clinical and hemodynamic outcomes of “all-comers” undergoing transapical aortic valve implantation: results from the Italian Registry of Trans-Apical Aortic Valve Implantation (I-TA). *J Thorac Cardiovasc Surg* 2011;142:768–75.
192. Bosmans JM, Kefer J, De Bruyne B, et al. Procedural, 30-day and one year outcome following CoreValve or Edwards transcatheter aortic valve implantation: results of the Belgian national registry. *Interact Cardiovasc Thorac Surg* 2011;12:762–7.
193. Eltchaninoff H, Prat A, Gilard M, et al. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. *Eur Heart J* 2011;32:191–7.
194. Grube E, Buellesfeld L, Mueller R, et al. Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving System. *Circ Cardiovasc Interv* 2008; 1:167–75.
195. Gurvitch R, Tay EL, Wijesinghe N, et al. Transcatheter aortic valve implantation: lessons from the learning curve of the first 270 high-risk patients. *Catheter Cardiovasc Interv* 2011;78:977–84.
196. Gurvitch R, Wood DA, Tay EL, et al. Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. *Circulation* 2010;122:1319–27.
197. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2010;122:62–9.
198. Walther T, Kempfert J, Rastan A, et al. Transapical aortic valve implantation at 3 years. *J Thorac Cardiovasc Surg* 2012;143(2):326–31.
199. Wenaweser P, Pilgrim T, Roth N, et al. Clinical outcome and predictors for adverse events after transcatheter aortic valve implantation with the use of different devices and access routes. *Am Heart J* 2011; 161:1114–24.
200. Zahn R, Gerckens U, Grube E, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *Eur Heart J* 2011;32:198–204.
201. Makkar RR
. Two-Year Outcomes of Transcatheter Aortic Valve Replacement (TAVR) in “Inoperable” Patients With Severe Aortic Stenosis: The PARTNER Trial. San Francisco: Transcatheter Cardiovascular Therapeutics (TCT), 2011.
202. Reynolds MR, Magnuson EA, Lei Y, et al. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. *Circulation* 2011;124:1964–72.
203. Reynolds M.
Lifetime Cost Effectiveness of Implantation Compared with Standard Care in Inoperable Patients: Results from the PARTNER Trial (Cohort B). New Orleans: American Heart Association, 2011.
204. Cohen D.
Health-Related Quality of Life After Transcatheter vs. Surgical Aortic Valve Replacement in High-Risk Patients with Severe Aortic Stenosis – Results from the PARTNER Trial (Cohort A). San Francisco: Transcatheter Cardiovascular Therapeutics (TCT), 2011.
205. Jamieson WR, Burr LH, Miyagishima RT, et al. Re-operation for bioprosthetic aortic structural failure – risk assessment. *Eur J Cardiothorac Surg* 2003;24:873–8.
206. Vogt PR, Brunner-LaRocca H, Sidler P, et al. Reoperative surgery for degenerated aortic bioprostheses: predictors for emergency surgery and reoperative mortality. *Eur J Cardiothorac Surg* 2000;17:134–9.
207. Christiansen S, Schmid M, Autschbach R. Perioperative risk of redo aortic valve replacement. *Ann Thorac Cardiovasc Surg* 2009;15:105–10.

208. Piazza N, Bleiziffer S, Brockmann G, et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthesis: from concept to clinical application and evaluation (part 2). *JACC Cardiovasc Interv* 2011;4:733–42.
209. Kochman J, Huczek Z, Koltowski L, et al. Transcatheter implantation of an aortic valve prosthesis in a female patient with severe bicuspid aortic stenosis. *Eur Heart J* 2012;33(1):112.
210. Wijesinghe N, Ye J, Rodes-Cabau J, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. *JACC Cardiovasc Interv* 2010;3: 1122–5.
211. Ferrari E, Locca D, Sulzer C, et al. Successful transapical aortic valve implantation in a congenital bicuspid aortic valve. *Ann Thorac Surg* 2010;90:630–2.
212. Chiam PT, Chao VT, Tan SY, et al. Percutaneous transcatheter heart valve implantation in a bicuspid aortic valve. *JACC Cardiovasc Interv* 2010;3:559–61.
213. Unsworth B, Malik I, Mikhail GW. Recognising bicuspid aortic stenosis in patients referred for transcatheter aortic valve implantation: routine screening with three-dimensional transoesophageal echocardiography. *Heart* 2010;96:645.
214. Delgado V, Tops LF, Schuijf JD, et al. Successful deployment of a transcatheter aortic valve in bicuspid aortic stenosis: role of imaging with multislice computed tomography. *Circ Cardiovasc Imaging* 2009;2: e12–3.
215. Jilaihawi H, Asgar A, Bonan R. Good outcome and valve function despite Medtronic-corevalve under-expansion. *Catheter Cardiovasc Interv* 2010;76:1022–5.
216. Raja Y, Holloway B, Doshi SN. Symmetrical expansion of an Edwards Sapien valve in a congenitally bicuspid aortic valve. *Heart* 2011;97:1113.
217. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2012;59:280–7.
218. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients a glimpse into the future. *J Am Coll Cardiol* 2011;157(5):860–6.

**ERRONEOUS MEASUREMENT
OF THE AORTIC ANNULAR
DIAMETER USING 2-DIMENSIONAL
ECHOCARDIOGRAPHY RESULTING
IN INAPPROPRIATE COREVALVE
SIZE SELECTION: A RETROSPECTIVE
COMPARISON WITH MULTISLICE
COMPUTED TOMOGRAPHY**

Erroneous measurement of the aortic annular diameter using 2-dimensional echocardiography resulting in inappropriate CoreValve size selection: a retrospective comparison with multislice computed tomography
Mylotte D, Dorfmeister M, Elhmidi Y, Mazzitelli D, Bleiziffer S, Wagner A, Noterdaeme T, Lange R, Piazza N.
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ABSTRACT

Objectives

This study sought to assess the differential adherence to transcatheter heart valve (THV)-oversizing principles between transesophageal echocardiography (TEE) and multislice computed tomography (CT) and its impact on the incidence of paravalvular leak (PVL).

Background

CT has emerged as an alternative to 2-dimensional TEE for THV sizing.

Methods

In our early experience, TEE-derived aortic annular diameters determined THV size selection. CT datasets originally obtained for vascular screening were retrospectively interrogated to determine CT-derived annular diameters. Annular dimensions and expected THV oversizing were compared between TEE and CT. The incidence of PVL was correlated to TEE- and CT-based oversizing calculations.

Results

Using TEE-derived annulus measurements, 157 patients underwent CoreValve implantation (23 mm: n = 66; 29 mm: n = 91). The estimated THV oversizing on the basis of TEE was $20.1 \pm 8.2\%$. Retrospective CT analysis yielded larger annular diameters than TEE ($p < 0.0001$). When these CT diameters were used to recalculate the percentage of oversizing achieved with the TEE-selected CoreValve, the actual THV oversizing was only $10.4 \pm 7.8\%$. Consequently, CT analysis suggested that up to 50% of patients received an inappropriate CoreValve size. When CT-based sizing criteria were satisfied, the incidence of PVL was 21% lower than that with echocardiography (14% vs. 35%; $p = 0.003$). Adherence to CT-based oversizing was independently associated with a reduced incidence of PVL (odds ratio 0.36; 95% confidence interval: 0.14 to 0.90; $p = 0.029$); adherence to TEE-based sizing was not.

Conclusions

Retrospective CT-based annular analysis revealed that CoreValve size selection by TEE was incorrect in 50% of patients. The percentage of oversizing with CT was one-half of that calculated with TEE resulting in the majority of patients receiving a THV that was too small.

Keywords: aortic stenosis, computed tomography, transcatheter aortic valve replacement, transcatheter heart valve, transesophageal echocardiography

Appropriate valve sizing is of critical importance to optimize outcomes in patients undergoing transcatheter aortic valve replacement (TAVR). Oversizing the transcatheter heart valve (THV) relative to the aortic annulus is required to generate interference between the prosthesis and the annulus and thus to provide adequate anchoring and sealing. Insufficient THV oversizing (i.e., selecting a valve that is too small) can be problematic and may result in intraprocedural valve embolization, or more commonly paravalvular leak (PVL), an independent predictor of poor long-term prognosis (1,2). However, excessive THV oversizing has been associated with annular rupture (balloon-expandable TAVR) and/or prosthesis dysfunction (3).

Historically, 2-dimensional (D) echocardiography was the imaging modality of choice for TAVR sizing. More recently, multislice computed tomography (CT) has emerged as an alternative and perhaps superior technique (4). CT provides a more reliable and detailed anatomical assessment of the aortic valvular complex and yields larger aortic annular diameters than echocardiography (5–11). Consequently, echocardiographic-based TAVR sizing may be inaccurate and may fail to provide the expected THV oversizing. Supporting this hypothesis is the observation that the rates of both PVL and mortality decline with CT-based sizing (5–11). Although it is axiomatic that the superiority of CT-based sizing is achieved through more accurate adherence to manufacturer THV-oversizing principles, this hypothesis has not been corroborated.

We sought to assess the differential adherence to THV-oversizing principles between 2D-echocardiography and multislice CT and to further correlate this difference with rates of PVL in a large series of patients undergoing TAVR.

METHODS

Patients

Between January 6, 2009 and June 6, 2010, 165 consecutive high-risk patients with severe aortic stenosis underwent vascular access screening with CT prior to TAVR at the German Heart Centre, Munich. Patients with symptomatic severe aortic stenosis (valve area ≤ 1.0 cm²) were considered candidates for TAVR if surgery was deemed to be of high or excessive risk. The decision to proceed with TAVR was discussed by a dedicated Heart Team. Procedures were performed according to standard protocol as previously described (12). In this case series, all patients were treated with the self-expanding CoreValve system (Medtronic, S.a.r.l, Luxembourg).

TAVR sizing

Early in our experience, CT was routinely performed to evaluate the iliofemoral vasculature with the intention of proceeding to transfemoral TAVR. In all 165 cases, TAVR sizing was determined solely using transesophageal echocardiography (TEE)-derived aortic annular

diameters and standard sizing criteria: annulus diameters of 20 to 23 mm and 23 to 27 mm for the 26- and 29-mm CoreValves, respectively. These sizing criteria yield THV oversizing of 13% to 30% for the 26-mm CoreValve and 7% to 26% for the 29-mm CoreValve (prosthesis diameter – annulus diameter / annulus diameter \times 100). Appropriate valve sizing was defined as adherence to these criteria. The diameters of the sinuses of Valsalva and the ascending aorta, the extent of sinotubular and aortic root calcification, and the height of the coronary ostia were also considered when choosing the size of the THV. Only the 26- and 29-mm CoreValves were commercially available during study enrollment; however, the 31- and 23-mm CoreValves have more recently received Conformité Européenne–mark approval. We retrospectively assessed patient eligibility for these newer prostheses: annular diameter range of 18 to 20 mm and 26 to 29 mm for the 23- and 31-mm CoreValves, respectively.

Echocardiography

Pre-procedural 2D-TEE was performed in all subjects using a commercially available TEE transducer and ultrasound system (X7-2t Live 3D-TEE transducer, iE33, Philips Medical System, Andover, Massachusetts) according to standard techniques (13). All images were digitally stored for off-line analysis. The aortic root dimensions were measured during early systole in the 3-chamber long-axis view at approximately 120° angulation (14). In each patient, these measurements were used to calculate the percentage of THV oversizing and to select the appropriate valve size for implantation.

CT acquisition protocol

All examinations were performed using a Somatom Definition Flash CT scanner (Siemens Medical, Siemens, Munich, Germany). All CT were performed using the flash technique. Standard technical parameters were used: gantry rotation time 0.28 ms; axial coverage 0.75 mm (128 \times 0.6 mm); 80 kV to 120 kV tube voltage according to body weight; milliamperere intensity with Care Dose 4D modulation; and temporal resolution of 70 ms. Retrospective electrocardiographic gating was performed. Contrast enhancement was achieved with 60 to 100 ml of iomeprol 350 mg/ml (Iomeron, Bracco Imaging SpA, Milan, Italy). To achieve optimal synchronization, a bolus tracking method was used in the ascending aorta. Additional beta-blockade was not administered. The thickness of reconstructed images was 0.5 mm (increment 0.8 mm).

CT reconstruction and aortic annular measurements

Among 165 patients with a screening CT, 159 CT datasets were of sufficient quality for analysis and were retrospectively reconstructed using software from 3mensio Valves (version 4.1.sp1, Medical Imaging BV, Bilthoven, the Netherlands), as previously described (4). The aortic annulus dimensions were carefully assessed, including the major and orthogonal minor diameters, the area, and the perimeter. The CT_{mean} diameter was calculated as the mean of the

major and minor diameters. The CT_{area} -derived diameter was calculated using the following equation: $2 \times \sqrt{[\text{area (mm}^2) / \pi]}$. The $CT_{\text{perimeter}}$ -derived diameter was determined as: perimeter (mm) / π . These diameters were retrospectively calculated for each patient and were applied to the TEE-based CoreValve size in order to recalculate the CT-derived THV oversizing and adherence to recommended oversizing principles. The annular ellipticity index was calculated as the ratio of the major and minor diameters.

Calcification of the aortic root specifically associated with the valve leaflets was evaluated with the automated 3mensio software. Aortic valvular calcification was assessed between the sinotubular junction and 10 mm below the aortic annulus plane in the left ventricular outflow tract; calcification above and below the aortic leaflets was only included if it was continuous with that on the aortic leaflets. We selected an appropriate threshold value (Hounsfield units) to highlight and segment only calcified tissue from the aortic root. This threshold varied among patients due to differences in image acquisition, and therefore, multiple values were evaluated for each patient. Appropriate highlighting of the calcification (e.g., excluding opacified blood but not obvious calcification) was visually inspected in each case to determine the optimal threshold value. For each cusp, the calcification volumes were divided into quartiles and given a corresponding score of 1 to 4. Calcification volumes were then summed for each patient and classified as trivial (= 1), mild (= 2), moderate (= 3), or severe (= 4).

Depth of CoreValve implantation

The depth of CoreValve implantation was calculated using fluoroscopic imaging. The height of the CoreValve frame was assessed in the angiographic view with the least foreshortening for calibration so that the absolute depth could be measured. The distance from the bottom of each aortic sinus was measured as well as the total visible length of the device from inflow to outflow. The total length of the device was then compared to the known implanted device height and this ratio was used to calibrate the depth measurements. Length measurements were recorded in pixels and then converted to millimeters on the basis of the device length. The right- and left-sided depths were averaged to provide a single depth of implant. Suitable angiographic imaging was available in 135 patients.

Endpoints

For the purposes of this study, PVL was the primary outcome and was defined as post-procedural paravalvular aortic regurgitation grade ≥ 2 or the requirement for post-implantation balloon dilation despite appropriate CoreValve position. PVL was assessed using echocardiography during the index procedure and prior to discharge, and it was classified as mild, moderate, or severe according to the updated Valve Academic Research Consortium criteria (15). Post-implantation balloon dilation was performed with a 22- to 25-mm balloon for the 26-mm CoreValve and a 25- to 28-mm balloon for the 29-mm CoreValve. PVL cases resulting from THV malposition, defined as an implantation depth >9 mm, were excluded from the

analyses. Clinical outcomes including vascular complications, bleeding, stroke, myocardial infarction, acute kidney injury, requirement for new pacemaker, and 30-day and 6-month mortality were assessed according to the updated Valve Academic Research Consortium criteria.

Statistical analysis

Continuous variables are presented as mean \pm SD, or median and range, according to distribution. Categorical variables are presented as frequencies and percentages. Continuous variables were compared with either the Student *t* test or Mann-Whitney test. Multiple comparisons of the aortic annular diameters were analyzed using analysis of variance with Bonferroni correction or with the Kruskal-Wallis test. Categorical variables were compared using the chi-square or Fisher exact test, or McNemar test for related variables. Univariable and multivariable logistic regression analyses were performed to assess predictors of PVL. All variables that could plausibly be associated with PVL with a *p* value of <0.1 in the univariate analysis were entered into the multivariate model. Separate models were constructed for each sizing modality (if $p < 0.1$) due to multicollinearity of these variables. Receiver-operating characteristic (ROC) curves were developed and the areas under the curve (AUC) were calculated to compare the discriminatory power of TEE and CT to predict PVL. Comparisons of correlated AUC from the ROC analysis were compared with the method of DeLong. The nominal level of significance was 5%. Analyses were performed using SPSS (version 20.0, IBM Corp, Armonk, New York).

RESULTS

Patients, procedures, and outcomes

Among the 159 patients with CT datasets of suitable quality, 2 were excluded due to THV malposition (depth >9 mm). The baseline characteristics of the remaining 157 patients are presented in Table 1. Sixty-six patients (42%) received a 26-mm CoreValve and 91 (58%) received a 29-mm CoreValve.

TEE-derived diameters were significantly smaller than CT-based measurements ($p < 0.0001$) (Fig. 1A). Compared with CT_{area}, CT_{mean}, and CT_{perimeter}-derived diameters, TEE diameters were 1.3 mm (95% confidence interval [CI]: 0.7 to 2.0 mm), 1.5 mm (95% CI: 0.9 to 2.2 mm), and 2.0 mm (95% CI: 1.4 to 2.7 mm) smaller, respectively. Comparing the CT measurements, there was no significant difference between CT_{perimeter} and CT_{mean} ($p = 0.32$), though CT_{perimeter} was marginally larger than CT_{area} ($p = 0.05$). According to CT, aortic root calcification was classified as trivial in 26%, mild in 25%, moderate in 24%, and severe in 25% of patients.

Table 1 Study Population: Baseline and Procedural Characteristics (N = 157)

Baseline characteristics	
Age, years	79.7 ± 6.8
Male	56 (35.6)
Body mass index, kg/m ²	26.3 ± 4.6
Aortic valve indices	
Aortic valve area, mm ²	0.7 ± 0.2
Aortic valve peak gradient, mm Hg	76.7 ± 26.8
Aortic valve mean gradient, mm Hg	46.4 ± 17.1
Aortic regurgitation grade ≥2	21 (13.4)
Left ventricular EF ≤30%	30 (19.1)
NYHA functional class III/IV	156 (99.4)
Coronary artery disease	86 (54.8)
Prior aortocoronary bypass surgery	17 (10.8)
Peripheral vascular disease	23 (14.7)
Prior stroke	21 (13.4)
Diabetes mellitus	61 (38.8)
Chronic obstructive pulmonary disease	31 (19.8)
Pulmonary hypertension, PAP >60 mm Hg	33 (21.0)
Logistic EuroSCORE	17.8 ± 21.1
STS predicted mortality risk score	5.3 ± 3.4
Procedural characteristics	
26-mm CoreValve	66 (42.0)
29-mm CoreValve	91 (58.0)
Vascular access	
Femoral	131 (83.5)
Subclavian	22 (14.0)
Direct aortic	4 (2.5)

Values are mean ± SD or n (%).

EF = ejection fraction; EuroSCORE = European System for Cardiac Operative Risk Evaluation score; NYHA = New York Heart Association; PAP = pulmonary artery pressure; STS = Society of Thoracic Surgeons.

Suitability for available CoreValve sizes

We subsequently analyzed the number of patients whose annular dimensions fell within the range of the manufacturer's recommended sizing guidelines for the 23-, 26-, 29-, and 31-mm CoreValves using TEE and CT (Fig. 2). Some patients were eligible for treatment with 2 THV sizes due to overlap in the sizing criteria: for example, a 20-mm annulus can be treated with either a 23- or 26-mm CoreValve. According to TEE measurements, 95.5% of patients were suitable for either a 26-mm (35%) or 29-mm (60.5%) CoreValve; 10.8% were suitable for the 23-mm valve and 10.8% for the 31-mm CoreValve. In contrast, 18% fewer patients (78.3%)

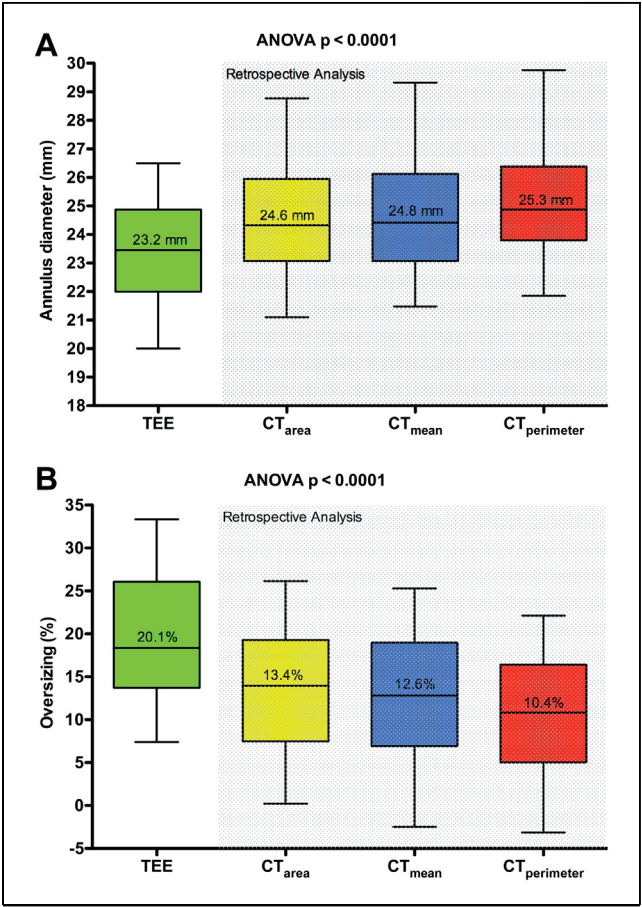


Figure 1 Annulus Diameter and Percentage Oversizing (A) Mean aortic annulus diameters measured using transesophageal echocardiography (TEE) and computed tomography (CT). (B) Estimated THV oversizing according to TEE- and CT-derived annular diameters. Data are means and 95% confidence intervals. Shaded region represents retrospective CT analysis. ANOVA = analysis of variance.

were suitable for a 26- or 29-mm CoreValve, 11% more (21.7%) were suitable for a 31-mm device and 8.9% had annuli too large for currently available valve sizes using CT_{perimeter}. Furthermore, no patients were eligible for the 23-mm CoreValve using CT_{perimeter}.

Adherence to THV-oversizing criteria

The expected THV oversizing was calculated by relating the annular diameters measured with TEE and CT to the implanted CoreValve size (determined by TEE) (Fig. 1B). With TEE, the average THV-oversizing was $20.1 \pm 8.2\%$. When CT data were applied retrospectively, the expected THV oversizing decreased considerably ($p < 0.0001$ for trend). Specifically, THV

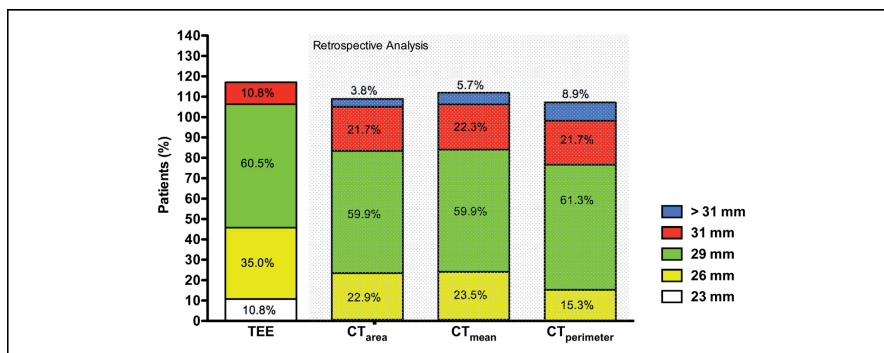


Figure 2 Suitability for CoreValve Sizes According to Imaging Modality

The proportion of patients suitable for currently available CoreValve sizes according to aortic annular measurements with TEE and CT. Note, some patients were eligible for treatment with 2 transcatheter heart valve sizes due to overlap in the sizing criteria. Shaded region represents retrospective CT analysis. Abbreviations as in Figure 1.

oversizing with CT_{area}, CT_{mean}, and CT_{perimeter} was $13.4 \pm 8.2\%$, $12.6 \pm 8\%$, and $10.4 \pm 7.8\%$, respectively. This meant that the absolute and relative difference in expected THV oversizing was 9.7% and 48.3% less using CT_{perimeter} than when using TEE.

Using the TEE-derived annular measurements, 80.9% of patients realized the recommended THV oversizing and hence were deemed to have received the appropriate CoreValve size (Fig. 3); 19.1% did not achieve the recommended THV oversizing (12.7% excessive and 6.4% insufficient oversizing) and thus received an inappropriate valve size.

When CT data were applied retrospectively to the TEE-selected CoreValve size, the proportion of patients that satisfied the recommended THV-oversizing criteria decreased significantly ($p < 0.0001$ for trend). Using CT_{area} and CT_{mean}, 60.5% of cases achieved recommended THV-oversizing. Applying CT_{perimeter} data, only 51% of patients achieved recommended THV oversizing, and thus 49% received an inappropriate CoreValve size. With CT_{perimeter}, 30.6% had annuli too large for the available CoreValve sizes at that time.

THV oversizing and PVL

Following CoreValve implantation, approximately one-quarter of patients ($n = 38$) met the criteria for significant PVL (paravalvular aortic regurgitation grade ≥ 2 in 16.1% or need for post-implantation dilation in 8.1%) (Table 2): 14 of 66 (21.2%) 26-mm and 24 of 91 (26.4%) 29-mm CoreValve ($p = 0.57$). With TEE, the proportion of patients with PVL was similar among those that satisfied THV-oversizing criteria and those that did not meet these criteria (23.6% vs. 26.7%; $p = 0.81$) (Fig. 4). According to CT_{perimeter} data, however, the proportion of patients with PVL was 21% lower in those who satisfied THV-oversizing criteria than those who did not (13.8% vs. 35.1%; $p = 0.003$).

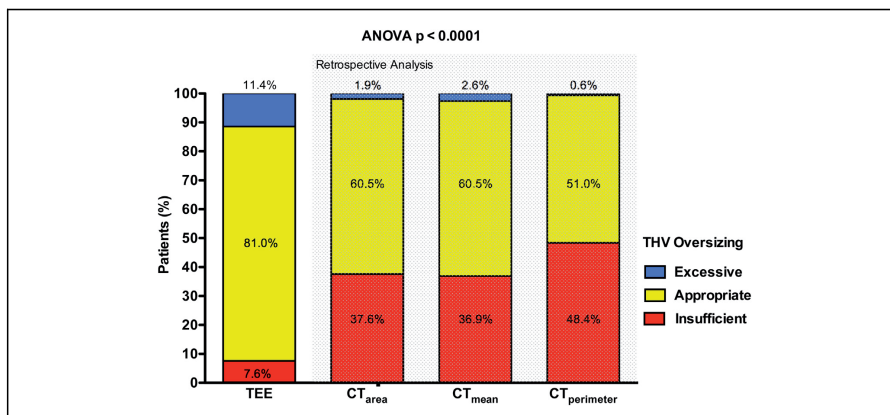


Figure 3 Excessive, Insufficient, or Appropriate THV Oversizing

The proportion of patients with excessive, insufficient, or appropriate transcatheter heart valve (THV) oversizing according to the manufacturer's sizing recommendations on the basis of TEE and CT. Shaded region represents retrospective CT analysis. Abbreviations as in Figure 1.

Table 2 Procedural and Clinical Outcomes (N = 157)

TAVR performance	
Aortic regurgitation grade ≥ 2 or post-implantation dilation	38 (17.8)
Aortic valve peak gradient, mm Hg	21.7 \pm 7.3
Aortic valve mean gradient, mm Hg	11.3 \pm 4.1
Vascular complications	
VARC major	14 (8.9)
VARC minor	18 (11.5)
Bleeding	
VARC life-threatening	4 (2.6)
VARC major	2 (1.3)
VARC minor	8 (5.1)
Stroke	4 (2.6)
Periprocedural myocardial infarction	1 (0.6)
Acute kidney injury, modified RIFLE criteria stage 2 or 3*	11 (19.3)
Pacemaker	39 (24.8)
30-day combined safety endpoint	32 (20.4)
30-day mortality	10 (6.4)
VARC cardiovascular	10 (6.4)
VARC noncardiovascular	0 (0.0)
6-month mortality	25 (15.9)

Values are n (%) or mean \pm SD.

* Modified RIFLE criteria. RIFLE = Risk, Injury, Failure, Loss, and End-stage Kidney; TAVR = transcatheter aortic valve replacement; VARC = Valve Academic Research Consortium.

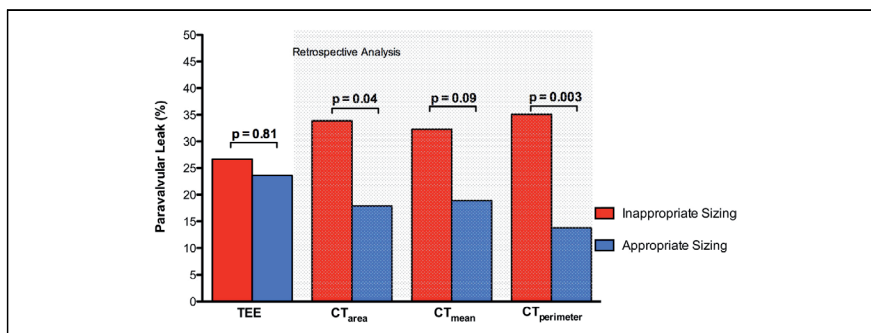


Figure 4 Appropriateness of THV Oversizing and PVL According to Imaging Modality

The proportion of patients with significant paravalvular leak (PVL) that achieved (blue) or did not achieve (red) appropriate THV oversizing according to TEE- and CT-based sizing. Shaded region represents retrospective CT analysis. Abbreviations as in Figures 1 and 3.

Using TEE, there was no difference in THV oversizing between patients with and without PVL ($19.0 \pm 8.6\%$ vs. $20.5 \pm 8.1\%$; $p = 0.32$) (Fig. 5). According to CT data, there was significantly less THV oversizing in those with PVL than those without PVL (CT_{area}: $9.0 \pm 7.1\%$ vs. $14.9 \pm 8.0\%$, $p < 0.0001$; CT_{mean}: $9.0 \pm 7.2\%$ vs. $13.7 \pm 8.0\%$, $p < 0.001$; and CT_{perimeter}: $6.2 \pm 7.1\%$ vs. $11.7 \pm 7.5\%$, $p = 0.0001$).

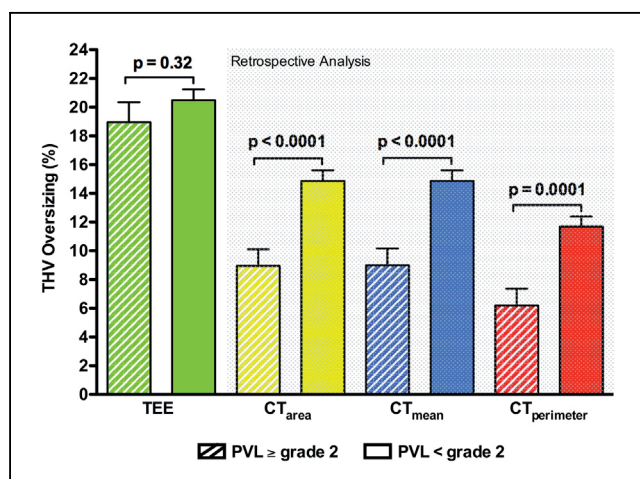


Figure 5 THV Oversizing and PVL According to Imaging Modality

Estimated percentage of THV oversizing according to TEE- and CT-based aortic annular diameters in patients with (diagonal lines) or without (solid) significant paravalvular leak. Shaded region represents retrospective CT analysis. Abbreviations as in Figures 1, 3, and 4.

Predictors of PVL

In the univariable analysis, several factors were associated with PVL (Table 3). Interestingly, increasing aortic annular diameter measured with CT, but not with TEE, was associated with a higher incidence of PVL. Similarly, adherence to CT-based rather than TEE-based THV-oversizing principles was associated with a reduction in PVL. In the multivariable analysis (Model 1), adherence to $CT_{\text{perimeter}}$ -based TVH oversizing was independently associated with a reduction in the incidence of PVL (odds ratio [OR]: 0.36; 95% CI: 0.14 to 0.90; $p = 0.029$), whereas increasing depth of CoreValve implantation (OR: 1.19; 95% CI: 1.04 to 1.35; $p = 0.009$) and severe aortic root calcification (OR: 2.97; 95% CI: 1.2 to 7.38; $p = 0.019$) were both predictors of increased PVL.

Receiver-operating characteristic curves

ROC curves were used to compare the precision of TEE and CT to predict PVL (Fig. 6). TEE appeared to be the least efficacious imaging modality, with an intercept parallel to the line of equality (AUC: 0.51). The AUC for $CT_{\text{perimeter}}$ (0.65) was significantly greater than that of TEE ($p = 0.05$), but it was not significantly different from that calculated for CT_{area} (0.60) or CT_{mean} (0.59). Adhering to THV-oversizing criteria with $CT_{\text{perimeter}}$ gave a sensitivity, specificity, positive predictive value, and negative predictive value of predicting PVL of 71.1%, 58%, 35.1%, and 86.3%, respectively.

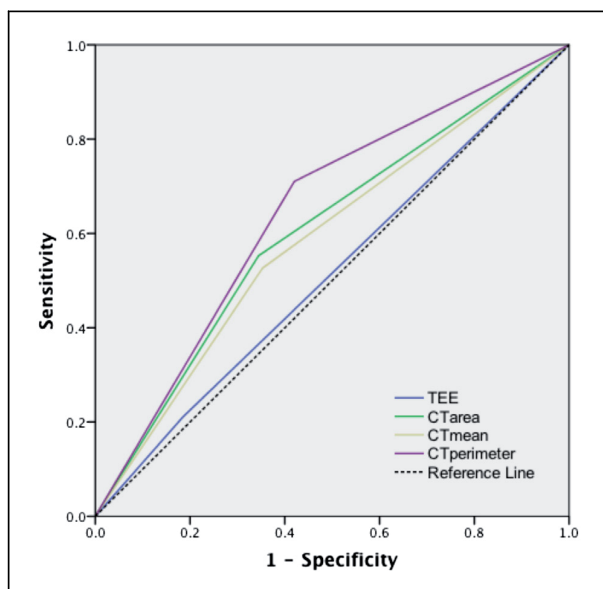


Figure 6 ROC Curves for Predicting PVL According to Adherence to Oversizing Criteria With TEE and CT. The receiver-operating characteristic (ROC) curves suggest that adherence to oversizing principles with $CT_{\text{perimeter}}$, CT_{mean} , and CT_{area} results in more accurate prediction of PVL than using TEE does. TEE = trans-esophageal echocardiography; other abbreviations as in Figures 1 and 4.

Table 3 Predictors of PVL

	Odds Ratio	95% CI	p Value
Univariable model			
Age, yrs	0.98	0.93–1.03	0.353
Male	1.44	0.68–3.03	0.343
BMI	0.76	0.13–4.57	0.765
Transfemoral TAVR	1.41	0.49–4.05	0.518
CoreValve size	1.10	0.87–1.41	0.457
Left ventricular EF	1.45	0.93–2.25	0.103
Aortic valve area	0.31	0.05–1.89	0.204
Aortic valve mean gradient	1.03	0.98–1.05	0.320
Logistic EuroSCORE	1.99	0.98–1.04	0.739
STS predicted mortality risk score	1.03	0.92–1.14	0.641
Depth of implant*	1.21	1.07–1.36	0.002
CT ellipticity	0.67	0.26–17.08	0.810
Severe aortic root calcification*	3.04	1.38–6.68	0.006
Annulus diameter			
TEE	1.14	0.94–1.37	0.175
CT _{area} *	1.32	1.12–1.16	0.001
CT _{mean} *	1.26	1.07–1.48	0.005
CT _{perimeter} *	1.30	1.11–1.53	0.001
Appropriate THV oversizing			
TEE	0.85	0.34–2.2	0.726
CT _{area} *	0.43	0.20–8.9	0.024
CT _{mean} *	0.49	0.23–1.03	0.059
CT _{perimeter} *	0.23	0.10–0.52	<0.0001
Multivariable model 1: CT_{perimeter}			
Depth of implant	1.19	1.04–1.35	0.009
Severe aortic root calcification	2.97	1.20–7.38	0.019
CT _{perimeter}	0.36	0.14–0.90	0.029
Multivariable model 2: CT_{area}			
Depth of implant	1.19	1.05–1.35	0.006
Severe aortic root calcification	3.31	1.35–8.10	0.009
CT _{area}	0.60	0.25–1.45	0.258
Multivariable model 3: CT_{mean}			
Depth of implant	1.19	1.05–1.35	0.006
Severe aortic root calcification	3.40	1.39–8.29	0.007
CT _{mean}	0.68	0.28–1.63	0.385

Univariate and multivariate predictors of PVL (grade ≥ 2 or post-implantation dilation). Separate multivariable analysis due to multicollinearity of CT variables.

* Variables associated with PVL in univariate analysis.

Further analysis of the $CT_{\text{perimeter}}$ data with sensitivity-specificity curves identified minimal oversizing thresholds of 9% for the 26-mm CoreValve and 9.6% for the 29-mm CoreValve that best predicted PVL (Fig. 7). Using this cut point, the sensitivity, specificity, positive predictive value, and negative predictive value for the 26-mm Core-Valve were 100%, 4.8%, 33%, and 100%. The corresponding values for the 29-mm CoreValve were 84.2%, 42.4%, 45.7%, and 82.4%. These $CT_{\text{perimeter}}$ thresholds predicted a higher incidence of PVL for both the 26 (33.3% vs. 11.1%; $p = 0.037$) and 29-mm CoreValves (42.1% vs. 15.1%; $p = 0.007$).

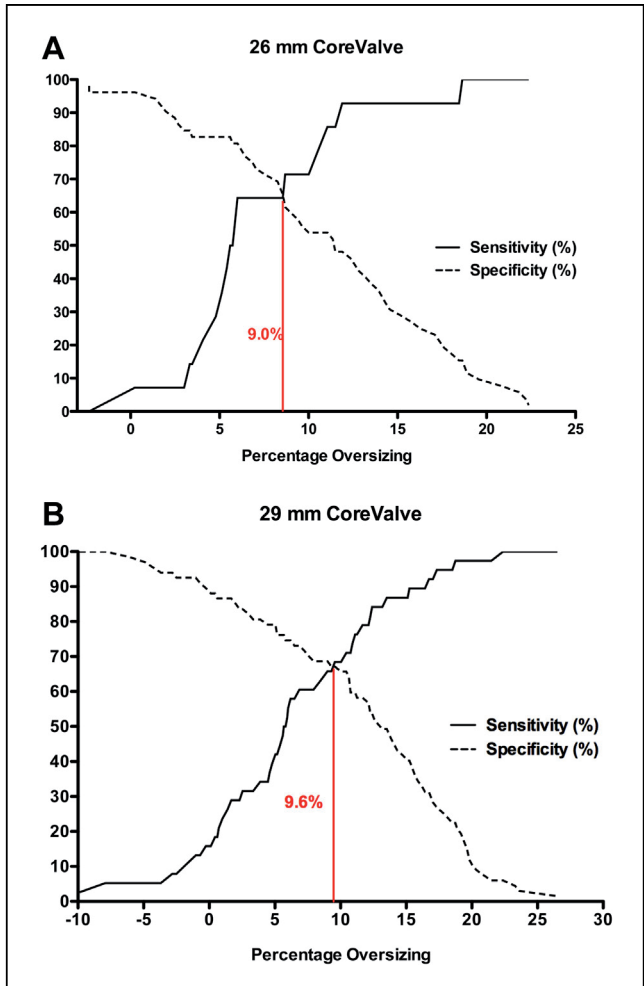


Figure 7 Sensitivity and Specificity Curves for $CT_{\text{perimeter}}$
 The sensitivity and specificity curves identified $CT_{\text{perimeter}}$ -derived oversizing thresholds of 9.0% (A) and 9.6% (B) for the 26-mm and 29-mm CoreValves to be predictive of PVL. Abbreviations as in Figures 1 and 4.

DISCUSSION

The current study confirms previous observations that CT-based aortic annular diameters are significantly larger than those obtained by 2D echocardiography. When these CT diameters were used to recalculate the oversizing relative to the TEE-selected CoreValve, the actual THV oversizing was reduced by 48%. Accordingly, the retrospective CT analysis suggested that up to 50% of patients did not achieve the manufacturer's recommended THV-oversizing criteria and therefore received an inappropriate CoreValve size. CT data also suggested that one-third of patients had annuli too large for available CoreValve sizes during the time of enrollment. Adherence to CT-based but not TEE-based oversizing was a predictor of reduced PVL. According to CT, significantly lower PVL rates were observed in those patients who received a correct CoreValve size than in those who did not. Finally, we identified a lower limit threshold for CT_{perimeter}-based THV oversizing associated with a reduced incidence of PVL: 9% and 9.6% for the 26-mm and 29-mm prostheses, respectively.

Transcatheter heart valve sizing

Pre-procedural anatomical screening is of considerable importance for TAVR. In particular, appropriate THV sizing is recognized to be a key factor for optimizing patient outcomes: PVL is an independent risk factor for mortality and has been reported in 9% to 21% of CoreValve and 6% to 13.9% of Edwards Sapien (Edwards Lifesciences Inc., Irvine, California) recipients (1,2,16). Appropriate THV sizing involves achieving a predefined amount of prosthesis oversizing relative to the aortic annulus. Previous studies have demonstrated that failing to achieve a 1:1 ratio of the THV relative to the aortic annulus (cover index: $[\text{TAVR area}/\text{annular area} - 1] \times 100$) is associated with PVL (6,8,9,17). Evidently, accurate measurement of the dimensions of the aortic annulus is fundamental for accurate THV sizing.

Although there is no consensus as to the gold-standard technique for measuring the aortic annulus, CT provides more accurate annular measurements than TEE does, and the use of CT for THV sizing has been associated with improved clinical outcomes (4–10). CT multiplanar reformatting allows accurate 3D reconstruction of the aortic annulus in its true plane. The superiority of this technique over 2D TEE is explained by the oval shape and variable orientation of the aortic annulus and the likelihood that 2D echocardiographic imaging will measure a short-axis tangent across the annulus. Herein, we confirm previous observations that CT provides larger annular diameters than TEE does (4–10): CT_{perimeter}-derived diameters were on average 2.0 mm larger than TEE measurements.

The smaller diameters measured with TEE compared with CT have a significant impact on the amount of THV oversizing achieved. In 2007, the oversizing recommendations suggested by the manufacturer were based on the assumption that echocardiography was an accurate method of assessing the annular dimensions. This led us to believe that we were achieving approximately 20% THV oversizing among CoreValve recipients. When we retrospectively

applied CT-based sizing to the TEE-based valve size, however, we were surprised to realize that the mean THV oversizing was only 10%. This translates into a 48% relative overestimation of THV oversizing with TEE versus CT. Obviously, this information would have had a substantial impact on THV size selection: up to one-half of all patients were deemed to have received the incorrect CoreValve size and approximately 30% would have been deemed ineligible for the available CoreValve prostheses at that time. The results of recent publications demonstrating enhanced clinical outcomes with CT-based THV sizing suggest that the initial THV-oversizing recommendations were appropriate, but the imaging modality (2D-echocardiography) was not (5–11).

BMI = body mass index; CI = confidence interval; CT = computed tomography; PVL = paravalvular leak; TEE = transesophageal echocardiography; THV = transcatheter heart valve; other abbreviations as in Tables 1 and 2.

In the present study, achieving TEE-based oversizing recommendations was insensitive for predicting PVL. In contrast, when $CT_{\text{perimeter}}$ data were retrospectively applied, the proportion of patients with PVL was significantly lower in those that achieved THV-oversizing criteria than in those that did not (13.8% vs. 35.1%; $p = 0.0026$). In those with significant PVL, oversizing was 3× more with TEE (19%) than with $CT_{\text{perimeter}}$ (6.2%). This reinforces the message that TEE led us to select valves that were too small for patients' anatomy, especially in those with significant PVL. Our ROC analysis further reinforces the hypothesis that TEE-based sizing was a poor predictor of PVL when compared with CT measures.

Moderate to severe PVL has been reported in 9% to 21% of CoreValve and 6% to 13.9% of Edwards Sapien valve recipients (17). We can speculate that this historical incidence of PVL with TAVR may reflect inaccurate TEE-based sizing in a considerable proportion of patients. Our data would appear to support previous observations that CT-sizing can reduce the incidence of significant PVL considerably (23.6% to 13.8%) (8). It is important to note, however, that appropriate THV sizing is not a panacea for eliminating PVL. Severe aortic root calcification and increasing depth of CoreValve implantation were also independent predictors of PVL, emphasizing the key role of pre-procedural CT for optimizing patient selection and the continued importance of refining procedural techniques.

Which CT diameter to choose?

Compared with CT_{area} and CT_{mean} , $CT_{\text{perimeter}}$ was found to yield larger annular diameters, affect TAVR sizing more frequently, and be a predictor of PVL in the multivariable analyses. Furthermore, $CT_{\text{perimeter}}$ had the greatest discrimination for PVL in the ROC analysis. Greater annular dimensions require THV of larger diameter, which increases the risk of annular rupture or coronary occlusion. Annular rupture, however, has not been reported with a self-expanding prosthesis, and coronary occlusion remains rare, particularly if guidelines regarding sinus of Valsalva width are respected (3,10). Previous investigators have suggested that CT_{area} or CT_{mean} are the most useful determinants of PVL in patients undergoing balloon-expandable TAVR

(6,8,9,11). The mechanistic differences in the structure and function between the Core-Valve and the Edwards Sapien valve may explain supremacy of CT_{perimeter} in this analysis of CoreValve patients. Finally, CT_{perimeter}-oversizing thresholds of 9% and 9.6% for the 26-mm and 29-mm CoreValves were predictive of PVL. When CoreValve oversizing was less than these threshold values, we observed a 3-fold increase in the rate of PVL.

Study limitations

Post-implantation PVL may be caused by malposition, underexpansion, or undersizing of the THV. Differentiating between THV undersizing and underexpansion remains challenging. Thus, although we excluded THV-malposition from the analysis, our definition of PVL included cases where THV post-dilation was performed, and thus potentially included patients with THV-underexpansion rather than THV-undersizing. As underexpansion is more likely to occur with severe aortic root calcification, we performed detailed CT analysis of the aortic root to identify patients with heavy calcification. Significantly, after adjusting for both aortic root calcification and the depth of THV implantation, achieving CT-based oversizing criteria remained an independent predictor of reduced PVL. As the CT scans were obtained early in our TAVI experience, different acquisition protocols were used. A standardized acquisition protocol would have further optimized the CT analysis. Fluoroscopic assessment of THV malposition was only possible in 135 of 157 patients.

Although the results of this study suggest that CT-based annular measurements would result in larger valves being implanted in a large proportion of patients and, compared with 2D echocardiography, has the potential to reduce PVL, these strategies were not directly compared in a prospective manner. Therefore, the retrospective design and observational nature of the data imply that the conclusions should be viewed as hypothesis-generating. Furthermore, we did not use 3D TEE, which correlates more closely with CT-derived annular measurements, and could mitigate the inaccuracy associated with 2D TEE (18). Finally, this consecutive series of patients were treated with the Medtronic CoreValve and therefore the findings should not be extrapolated to other TAVR systems.

CONCLUSIONS

Aortic annular measurements are significantly larger when measured with CT than with TEE. Retrospective application of these CT-derived measurements to recalculate the oversizing of the TEE-selected CoreValve size revealed that the expected THV oversizing was overestimated 2-fold. Consequently, the TEE-selected CoreValve size was incorrect in one-half of all patients. CT_{perimeter} appears to be the most sensitive CT-based measure for predicting PVL and is recommended for THV sizing in all patients undergoing CoreValve implantation.

ABBREVIATIONS AND ACRONYMS

AUC	= area under the curve
CI	= confidence interval
CT	= computed tomography
D	= dimensional
OR	= odds ratio
PVL	= paravalvular leak
ROC	= receiver-operating characteristic
TAVR	= transcatheter aortic valve replacement
TEE	= transesophageal echocardiography
THV	= transcatheter heart valve

REFERENCES

1. Gilard M, Eltchaninoff H, Iung B, et al., for the FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012;366:1705–15.
2. Kodali SK, Williams MR, Smith CR, et al., for the PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686–95.
3. Barbanti M, Yang TH, Rodès Cabau J, et al. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. *Circulation* 2013; 128: 244–53.
4. de Vaan J, Verstraeten L, de Jaegere P, Schultz C. The 3mensio Valves multimodality workstation. *EuroIntervention* 2012;7:1464–9.
5. Jabbour A, Ismail TF, Moat N, et al. Multimodality imaging in transcatheter aortic valve implantation and post-procedural aortic regurgitation: comparison among cardiovascular magnetic resonance, cardiac computed tomography, and echocardiography. *J Am Coll Cardiol* 2011;58:2165–73.
6. Jilaihawi H, Kashif M, Fontana G, et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. *J Am Coll Cardiol* 2012;59:1275–86.
7. Kempfert J, Van Linden A, Lehmkuhl L, et al. Aortic annulus sizing: echocardiographic versus computed tomography derived measurements in comparison with direct surgical sizing. *Eur J Cardiothorac Surg* 2012; 42:627–33.
8. Hayashida K, Bouvier E, Lefevre T, et al. Impact of CT-guided valve sizing on post-procedural aortic regurgitation in transcatheter aortic valve implantation. *EuroIntervention* 2012;8:546–55.
9. Willson AB, Webb JG, Labounty TM, et al. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. *J Am Coll Cardiol* 2012;59:1287–94.
10. Schultz CJ, Tzikas A, Moelker A, et al. Correlates on MSCT of paravalvular aortic regurgitation after transcatheter aortic valve implantation using the Medtronic CoreValve prosthesis. *Catheter Cardiovasc Interv* 2011;78:446–55.
11. Gurvitch R, Webb JG, Yuan R, et al. Aortic annulus diameter determination by multidetector computed tomography: reproducibility, applicability, and implications for transcatheter aortic valve implantation. *J Am Coll Cardiol Intv* 2011;4:1235–45.
12. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2011;59:280–7.
13. Nishimura RA, Miller FA Jr, Callahan MJ, Benassi RC, Seward JB, Tajik AJ. Doppler echocardiography: theory, instrumentation, technique, and application. *Mayo Clin Proc* 1985;60:321–43.
14. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;22:1–23.
15. Kapteina AP, Head SJ, G  n  reux P, et al., for the Valve Academic Research Consortium-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *EuroIntervention* 2012;8:782–95.
16. G  n  reux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. *J Am Coll Cardiol* 2013;61:1125–36.
17. Pontone G, Andreini D, Bartorelli AL, et al. Aortic annulus area assessment by multidetector computed tomography for predicting paravalvular regurgitation in patients undergoing balloon-expandable transcatheter aortic valve implantation: a comparison with transthoracic and transesophageal echocardiography. *Am Heart J* 2012;164:576–84.

18. Khalique OK, Kodali S, Paradis JM, et al. Aortic annular sizing using a novel 3-dimensional echocardiographic method: utility and comparison to cardiac computed tomography. *Circ Cardiovasc Imaging* 2014;7: 155–63.

TAVI CANDIDATES AND TECHNOLOGY ADOPTION

II

- Chapter 6 Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study**
Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP.
J Am Coll Cardiol. 2013;62:1002-12.
- Chapter 7 Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization**
Mylotte D, Osnabrugge RL, Windecker S, Lefèvre T, de Jaegere P, Jeger R, Wenaweser P, Maisano F, Moat N, Søndergaard L, Bosmans J, Teles RC, Martucci G, Manoharan G, Garcia E, Van Mieghem NM, Kappetein AP, Serruys PW, Lange R, Piazza N.
J Am Coll Cardiol. 2013;62:210-9.
- Chapter 8 Considerations and Recommendations for the Introduction of Objective Performance Criteria for Transcatheter Aortic Heart Valve Device Approval**
Head SJ, Mylotte D, Mack MJ, Piazza N, van Mieghem N, Leon MB, Kappetein AP, Holmes Jr DR.
Circulation 2016;133:2086-93.

**AORTIC STENOSIS IN THE ELDERLY:
DISEASE PREVALENCE AND
NUMBER OF CANDIDATES FOR
TRANSCATHETER AORTIC VALVE
REPLACEMENT: A META-ANALYSIS
AND MODELING STUDY**

Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study

Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. J Am Coll Cardiol. 2013;62:1002-12.

ABSTRACT

Objectives

The purpose of this study was to evaluate the prevalence of aortic stenosis (AS) in the elderly and to estimate the current and future number of candidates for transcatheter aortic valve replacement (TAVR).

Background

Severe AS is a major cause of morbidity and mortality in the elderly. A proportion of these patients is at high or prohibitive risk for surgical aortic valve replacement, and is now considered for TAVR.

Methods

A systematic search was conducted in multiple databases, and prevalence rates of patients (>75 years) were pooled. A model was based on a second systematic literature search of studies on decision making in AS. Monte Carlo simulations were performed to estimate the number of TAVR candidates in 19 European countries and North America.

Results

Data from 7 studies (n = 9,723 subjects) were used. The pooled prevalence of all AS in the elderly was 12.4% (95% confidence interval [CI]: 6.6% to 18.2%), and the prevalence of severe AS was 3.4% (95% CI: 1.1% to 5.7%). Among elderly patients with severe AS, 75.6% (95% CI: 65.8% to 85.4%) were symptomatic, and 40.5% (95% CI: 35.8% to 45.1%) of these patients were not treated surgically. Of those, 40.3% (95% CI: 33.8% to 46.7%) received TAVR. Of the high-risk patients, 5.2% were TAVR candidates. Projections showed that there are approximately 189,836 (95% CI: 80,281 to 347,372) TAVR candidates in the European countries and 102,558 (95% CI: 43,612 to 187,002) in North America. Annually, there are 17,712 (95% CI: 7,590 to 32,691) new TAVR candidates in the European countries and 9,189 (95% CI: 3,898 to 16,682) in North America.

Conclusions

With a pooled prevalence of 3.4%, the burden of disease among the elderly due to severe AS is substantial. Under the current indications, approximately 290,000 elderly patients with severe AS are TAVR candidates. Nearly 27,000 patients become eligible for TAVR annually.

Keywords: aortic stenosis, prevalence, transcatheter aortic valve replacement

Aortic stenosis (AS) is the most common valvular heart disease in developed countries, and its impact on public health and health care resources is expected to increase due to aging Western populations (1,2). Each year, approximately 67,500 surgical aortic valve replacements (SAVR) are performed in the United States (3). Studies describing the prevalence of AS are scarce and report disparate results (3% to 23%) (4,5), and currently there is no systematic overview of population-based studies that have assessed the prevalence of AS. The emergence of transcatheter aortic valve replacement (TAVR) has renewed interest in the epidemiology of AS.

In particular, these data may be important to predict the number of TAVR candidates, service development, financial planning, and physician training. In addition, estimates of potential TAVR candidates at intermediate and low surgical risk are not available. Several factors must be considered when estimating the number of TAVR candidates: the percentage of patients with severe AS who are symptomatic; the proportion of patients with symptomatic severe AS who do not undergo SAVR and could thus be considered TAVR candidates; and the percentage of those patients referred for TAVR who actually receive a transcatheter valve.

Therefore, we sought to assess the prevalence of AS in the general elderly population (age ≥ 75 years) through a systematic review and meta-analysis of population-based studies. The second objective was to systematically estimate the number of elderly patients who are TAVR candidates in both the European countries and North America.

METHODS

Studies were identified through a systematic search of MEDLINE and EMBASE in February 2012. Keywords included “valvular heart disease,” “heart valve disease,” “aortic stenosis,” “aortic valve stenosis,” “epidemiology,” “incidence,” “prevalence,” and “survey.” No time restrictions were applied. Reference lists of selected studies and (systematic) reviews were examined, and the related article feature in PubMed was used to maximize relevant study identification.

All titles and abstracts were screened independently by 2 investigators using the following criteria: 1) the publication was an original full-length manuscript in a peer-reviewed journal; 2) the publication reported numbers of AS cases and sample size or the prevalence of AS in the general elderly population (≥ 75 years of age); and 3) AS and AS severity was diagnosed with echocardiography (6,7). The definition of AS used in each study was extracted, as was other relevant information including study location, inclusion period, and patient characteristics. After excluding manuscripts on the basis of title and abstract, the remaining full-text manuscripts were carefully assessed and were evaluated according to the criteria. If overlap between studies existed, only the publication with the largest population was included. Disagreement on study inclusion was solved by consensus.

For each included study, the prevalence rate of AS and its 95% binomial confidence interval (CI) was calculated based on the numbers of subjects in the sample and the number of patients with AS. These rates were subsequently combined to produce a pooled prevalence rate of both AS and severe AS. Both fixed- and random-effects models were used, and results of the appropriate model are presented as Forest plots. The fixed-effects model was performed using the inverse variance method and the random-effects model with the DerSimonian and Laird method. Heterogeneity was assessed by the Cochran Q test and I^2 statistics, derived from the inverse variance fixed-effects model (8). All analyses were performed with Stata SE version 12.0 (StataCorp, College Station, Texas).

Estimation of TAVR candidates

To estimate the number of elderly patients who could potentially be treated with TAVR under current indications, we performed a second literature search on clinical decision making in patients with severe AS. Specifically, we searched for studies that reported: 1) the percentage of patients with severe AS who experienced symptoms; 2) the percentage of patients with symptomatic severe AS who did not undergo SAVR and could thus be considered potential TAVR candidates; and/or 3) the percentage of those patients referred for TAVR who actually received a transcatheter valve. As TAVR is an approved therapy for patients at high operative risk, we also determined the proportion of elderly high-risk patients (The Society of Thoracic Surgery-Predicted Risk Of Mortality [STS-PROM] score $\geq 10\%$) undergoing SAVR (9), and the percentage of patients who would be considered TAVR-eligible. In anticipation of current and potential future trials in lower risk groups, estimates of the proportion of intermediate-and low-risk patients were also derived. For all studies, the point estimate and 95% binomial CI were calculated.

These data were combined to produce a pooled percentage estimate for each individual search. In each case, a fixed- or random-effects model was used and heterogeneity was assessed. To calculate national estimates of the number of patients with AS and TAVR candidates, we obtained population demographic data focusing on the elderly (≥ 75 years of age) for the following nations: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, the Republic of Ireland, Luxembourg, Norway, Poland, Portugal, Spain, Sweden, Switzerland, the Netherlands, the United Kingdom, Canada, and the United States (10–12). The annual number of new TAVR candidates was calculated using the number of people ages 75 years old in 2011 in the individual countries.

A flowchart was built in TreeAge Pro 2011 (TreeAge Software, Williamstown, MA). The probabilities in the flowchart were based on the pooled estimates from the systematic literature searches. Beta distributions were used and 10,000 Monte Carlo simulations were performed to estimate the number of elderly patients who are eligible to undergo TAVR, along with its 95% percentile CI.

To account for the heterogeneous nature of the studies, sensitivity analyses were performed. In particular, the proportion of patients receiving TAVR after referral for TAVR

assessment was determined using European studies alone and then by combining European and U.S. studies. This analysis was performed to account for the different adoption of TAVR in the United States, where until recently TAVR was only used in the context of clinical trials. In a second sensitivity analysis, we varied the percentage of high-risk SAVR-eligible patients who undergo TAVR.

RESULTS

The systematic literature search yielded 1,523 studies. After the title and abstract were screened, 1,408 studies were excluded because they did not focus on the epidemiology of disease. After assessing full-text articles, another 109 studies were excluded because they were not performed in the general elderly population, AS was not assessed, or because it was not an original publication. After the inclusion of an additional study through cross-referencing, our final analysis consisted of 7 studies, with a total of 9,723 elderly patients (Fig. 1) (1,4,5,13–16). The characteristics of these studies are outlined in Table 1. The 7 studies reported the prevalence of AS in 9 study populations on 3 continents. The study periods ranged from 1989 to 2009. All studies had a cross-sectional character, and most were part of larger population-based cohort studies. In all 7 studies, echocardiography was used to diagnose AS, although definitions of AS and its severity were variable (Table 1).

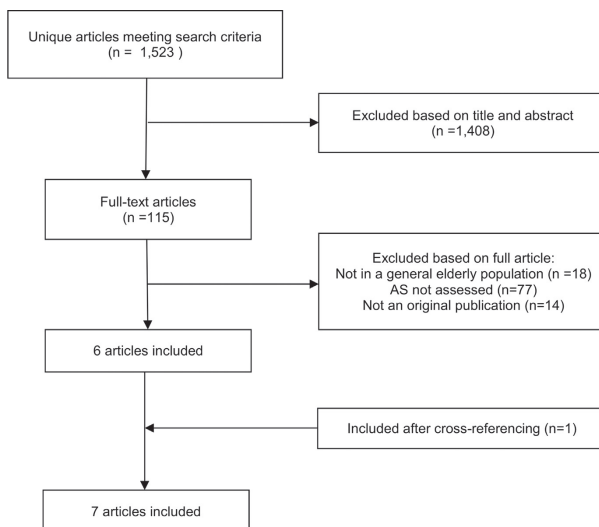


Figure 1 Flowchart of Study Selection

AS = aortic stenosis.

The combined prevalence of AS in the elderly was reported in 6 studies and ranged from 2.6% to 22.8% (Fig. 2A) (4,5,13,15,16). The pooled prevalence was 12.4% (95% CI: 6.6% to

Table 1 Main Study Characteristics of the Included Studies

First Author (Year), Study, Country	Study Design, Study Period, Population, % Men	Age (yrs) Category in meta-Analysis	Recruitment Method, Examination Period	Response Rate (%), Reasons for Exclusion	Diagnostic Method, AS Definition
Lorz (1993), Switzerland	Cross-sectional study, 70–96 yrs (n = 129), 43% men	70–96, mean 80 ± 6.6 (n = 129)	Random selection within community and nursing homes. 1990	51%; death, unable to contact, and “other reasons”	Doppler echo; all AS: thickening of cusps, V_{\max} >1.7 m/s level, or systolic separation of cusps <15 mm
Lindroos (1993), Helsinki Ageing Study, Finland	Cross-sectional substudy of larger population-based study, >55 yrs (n = 552), 28% men	75–86 (n = 476)	Random selection in population register. 1990–1991	From complete cohort 84 (9.3%) persons had died, 21 (2.3%) could not be contacted, and 144 (16%) refused; 77% agreed with substudy.	Doppler echo; moderate AS: $VR \leq 0.35$ and AVA 1.0–1.2 cm ² ; severe AS: $VR \leq 0.35$ and AVA ≤ 1.0 cm ² ; critical AS: $VR \leq 0.35$ and AVA ≤ 0.8 cm ²
Stewart (1997), Cardiovascular Health Study, USA	Cross-sectional substudy of larger population-based study, >65 yrs (n = 5,201), 43% men	>75 (n = 1,736)	Random selection from 4 communities of Medicare-eligible patients. 1989–1990	57%; reasons not stated. Also, subjects with AVR (n = 23), MVS/MVR/both (n = 37), BAV (n = 4), AVE (n = 2), or inadequate echo data (n = 25) were excluded.	Doppler echo; all AS: thickened leaflets with reduced systolic opening and V_{\max} >2.5 m/s
Lin (2005), Taiwan	Cross-sectional analysis, 20–97 yrs (n = 3,030), 59% of 2,850 group were men	>80 (n = 82)	Persons undergoing routine physical checkups; those with severe health conditions were excluded. Examination period NR.	NR	Doppler echo; all AS: leaflet thickening with reduced systolic opening, gradient ≥ 20 mm Hg; severe AS: gradient >50 mm Hg

Table 1 Main Study Characteristics of the Included Studies (continued)

First Author (Year), Study, Country	Study Design, Study Period, Population, % Men	Age (yrs) Category in meta-Analysis	Recruitment Method, Examination Period	Response Rate (%), Reasons for Exclusion	Diagnostic Method, AS Definition
Nkomo (2006),* Olmsted County Cohort, USA	Cross-sectional substudy of larger community study; >18 yrs (n = 16,501), 49% men	>75 (n = 6,663)	Patients who underwent echocardiography in affiliated hospital. 1990–2000	90% of population received care at affiliated hospital.	Doppler echo; Mild AS: V_{\max} 2.5–3 m/s and AVA 1.5–2 cm ² ; Moderate AS: V_{\max} 3–4 m/s and AVA 1–1.5 cm ² ; Severe AS: V_{\max} >4 m/s and AVA <1.0 cm ²
Van Bommel (2010), Leiden 85-Plus Study, the Netherlands	Cross-sectional substudy of larger population-based study; >90 yrs (n = 18), 33% men	>90 (n = 81)	All inhabitants of Leiden >85 yrs were invited. At 90 yrs participants were invited for echo examination. 1997–1999	13% of total participants (n = 705) refused to participate; 71% of 277 participants eligible for echo were not able to visit study center.	Doppler echo; mild AS: gradient <25 mm Hg; moderate AS: gradient 25–40 mm Hg; Severe AS: Gradient >40 mm Hg
Vaes (2012), BELFRAIL (BF _{C80+}), Belgium	Cross-sectional analysis of population-based study; >80 yrs (n = 556) 37% men	>80 (n = 556)	29 general practitioners in 3 regions included >80 yr olds. 2008–2009	Severe dementia and medical emergency patients were excluded.	Doppler echo; mild AS: AVA >1.5 cm ² ; moderate AS: AVA 1.0 cm ² –1.5 cm ² ; severe AS: AVA <1 cm ²

* Only the Olmsted County community study was included in this analysis. Of the 3 pooled population-based studies in this publication, only the Cardiovascular Health Study was eligible and is included in this systematic review (Stewart et al. 1997). The other 2 studies did not meet the selection criteria because the population studied was too young.

AS = aortic stenosis; AVA = aortic valve area; AVE = aortic valve endocarditis; AVR = aortic valve replacement; echo = echocardiography; MVS = mitral valve stenosis; MVR = mitral valve replacement; NR = not reported; VR = velocity ratio; V_{\max} = peak velocity.

18.2%) using a random-effects model ($I^2 = 98.5\%$; $Q = 337.70$, $p < 0.001$). The prevalence of severe AS in the elderly was reported separately in 5 studies and ranged from 1.2% to 6.1% (Fig. 2B) (1,4,13,14,16). The pooled prevalence of severe AS was 3.4% (95% CI: 1.1% to 5.7%) using a random-effects model ($I^2 = 85.7\%$; $Q = 27.99$, $p < 0.001$).

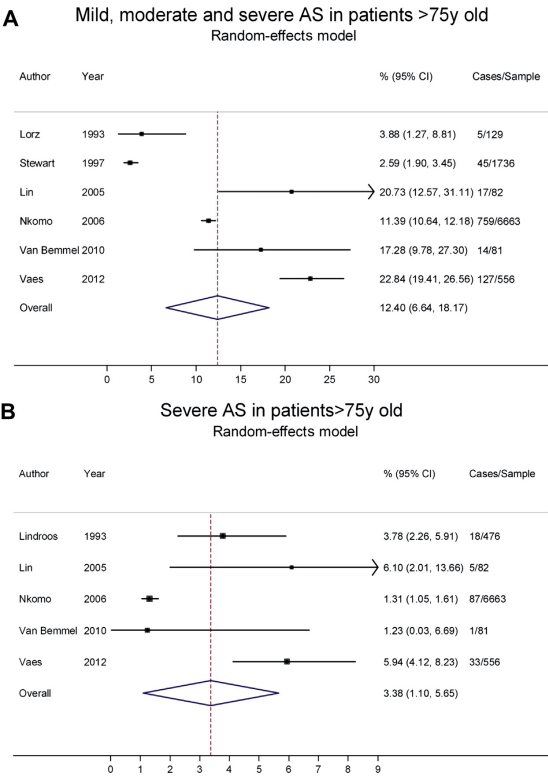


Figure 2 Forest Plots on the Prevalence of AS (A) Mild, moderate, and severe aortic stenosis (AS) in the elderly, using a random-effects model. $I^2 = 97.1\%$, $Q = 140.25$, $p < 0.001$. (B) Severe AS in the elderly, using a random-effects model. $I^2 = 85.7\%$, $Q = 27.99$, $p < 0.001$. CI = confidence interval.

These estimates of the prevalence of AS in patients ≥ 75 years old correspond to approximately 4.9 million elderly patients with AS in the European countries and 2.7 million in North America. If only symptomatic severe AS is considered, this translates to 1.0 million elderly patients in the European countries and 540,000 in North America. In 2011, 8.5% of the population in the 19 European countries was ≥ 75 years of age, and this number is expected to increase to 10.7% in 2025 and 16.6% in 2050 (11). In North America, similar increases in the population demographics of the elderly are expected (2025, 8.3%, and 2050, 11.8%) (10,12). These numbers correspond to approximately 1.3 million and 2.1 million patients with symptomatic severe AS in the 19

European countries in 2025 and 2050, respectively. In North America, there will be an estimated 0.8 million and 1.4 million patients with symptomatic severe AS in 2025 and 2050, respectively.

Estimates of TAVR candidates

The number of elderly patients who could potentially benefit from TAVR was estimated using the model outlined in Figure 3, with inputs from the systematic search and meta-analyses (Fig. 4). Seven studies reported the percentage of patients with severe AS who were symptomatic, resulting in a pooled estimate of severe symptomatic AS of 75.6% (95% CI: 65.8% to 85.4%) (Fig. 4A, Online Table 1). Of these patients with symptomatic severe AS, 40.5% (95% CI: 35.8% to 45.1%) did not undergo SAVR and thus could be considered candidates for TAVR (Fig. 4B, Online Table 2). Nine studies reported the percentage of patients referred for TAVR who actually received a transcatheter valve (Online Table 3). Three of these studies were performed in Europe, and 6 in the United States. The pooled percentage including both European and U.S. studies was 28.7% (95% CI: 22.8% to 34.6%) (Figs. 4C and 4D, respectively). The European pooled percentage was 40.3% (95% CI: 33.8% to 46.7%), whereas the U.S. pooled percentage was 24.4% (95% CI: 18.9% to 29.8%). In total, 12.3% of patients with symptomatic severe AS at prohibitive surgical risk are TAVR candidates.

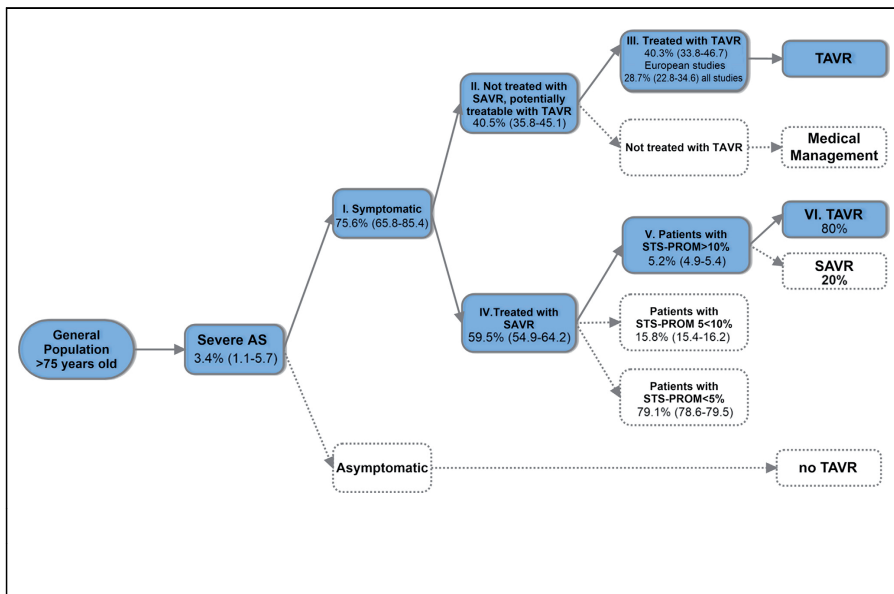


Figure 3 Model for the Estimation of TAVR Candidates Among the Elderly

AS = aortic stenosis; SAVR = surgical aortic valve replacement; STS-PROM = The Society of Thoracic Surgery Predicted Risk of Mortality; TAVR = transcatheter aortic valve replacement.

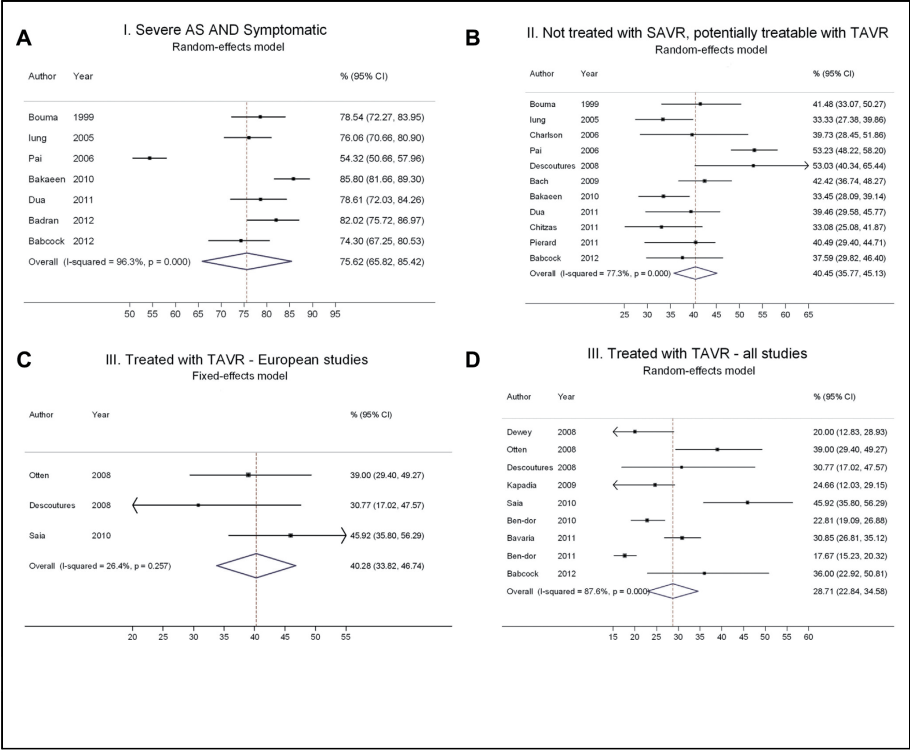


Figure 4 Forest Plots of the Different Steps in Estimation Model

(A) Severe aortic stenosis (AS) and symptomatic; (B) not treated with surgical aortic valve replacement (SAVR), potentially treatable with transcatheter aortic valve replacement (TAVR); (C) treated with TAVR, European studies; and (D) treated with TAVR, all studies. CI = confidence interval.

To assess the proportion of elderly SAVR patients who was deemed to be at high surgical risk, we used a study that reported on all elderly SAVR patients in the United States between 1999 and 2007 (17). Among elderly patients undergoing isolated SAVR, 5.2% (95% CI: 4.9% to 5.4%) were at high risk (STS-PROM $\geq 10\%$), 15.8% (95% CI: 15.4% to 16.2%) at intermediate risk (STS-PROM 5% to 10%), and 79.1% (95% CI: 78.6% to 79.5%) at low risk (STS-PROM $< 5\%$). A recent study showed that in a group of operable patients with a EuroSCORE (European System for Cardiac Operative Risk Evaluation) ≥ 15 , approximately 80% were treated with TAVR (18).

In 2011, there were 39,316,978 people ≥ 75 years of age in the European countries and 21,182,683 in North America (10–12). Combining these figures with the Monte Carlo simulations in the model (Fig. 3), we estimated that a total of 292,000 high- or prohibitive-risk elderly patients with symptomatic severe AS are candidates for TAVR. Specifically, there are 189,836 (95% CI: 80,281 to 347,372) TAVR candidates in the European countries and 102,558 (95% CI: 43,612 to 187,002) in North America. Annually there are 17,712 (95% CI: 7,590 to 32,691)

new TAVR candidates in the European countries and 9,189 (95% CI: 3,898 to 16,682) in North America. The total and annual number of TAVR candidates in the individual countries is presented in Figures 5 and 6, respectively.

The intermediate surgical risk group comprises approximately 145,000 elderly patients with symptomatic severe AS. Specifically, there are 94,730 (95% CI: 40,574 to 171,896) patients at intermediate risk in the European countries and 50,733 (95% CI: 22,148 to 90,451) in North America. The low surgical risk group includes approximately 730,000 patients with symptomatic severe AS. Specifically, there are 477,314 (95% CI: 206,798 to 862,958) patients at low-risk in the European countries and 255,727 (95% CI: 108,549 to 460,026) in North America.

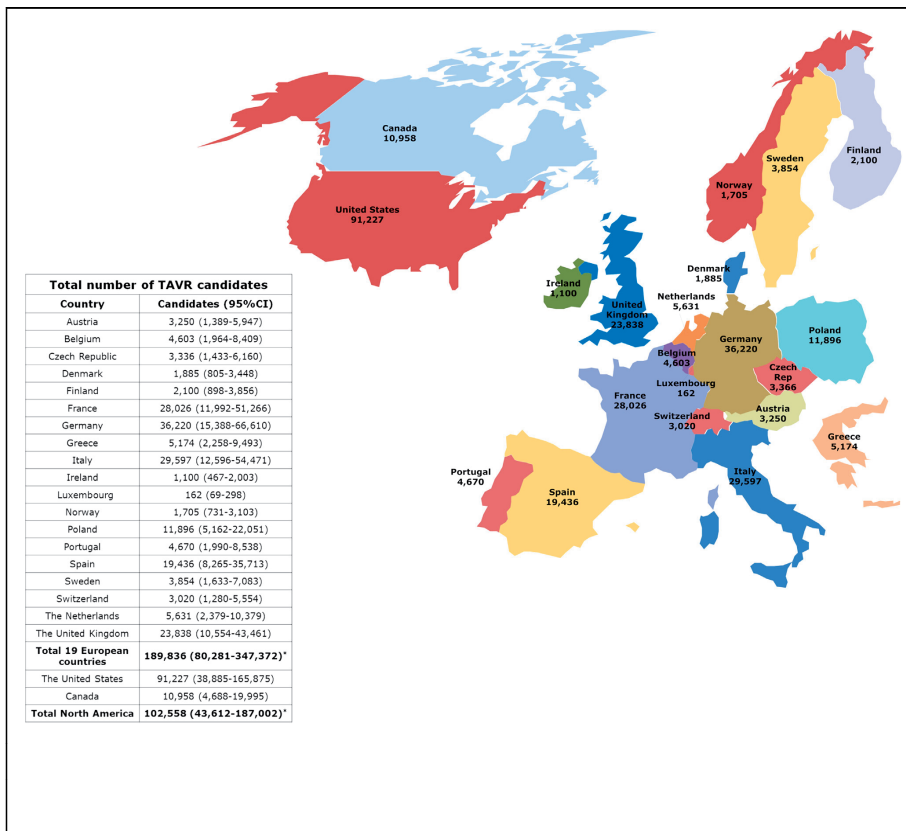


Figure 5 Total of TAVR Candidates in Different Countries Under Current Treatment Indications

*Due to the simulation process, the totals are not exactly the same as the sum of the individual countries. CI = confidence interval; TAVR = transcatheter aortic valve replacement.

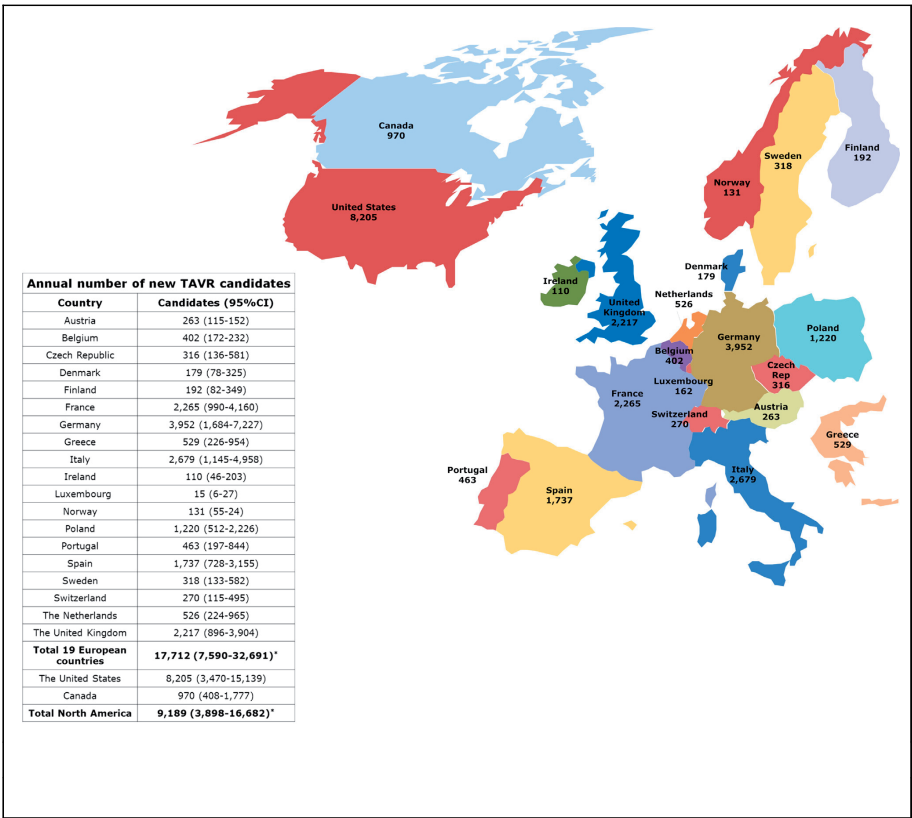


Figure 6 Annual Number of TAVR Candidates in Different Countries Under Current Treatment Indications
*Due to the simulation process, the totals are not exactly the same as the sum of the individual countries. CI = confidence interval; TAVR = transcatheter aortic valve replacement.

Sensitivity analyses

In the pre-specified sensitivity analysis that varied the proportion of patients receiving TAVR after referral for TAVR assessment according to study location (28.7%, 95% CI: 22.8% to 34.6% in Europe and the United States combined), we estimated that approximately 220,000 patients are TAVR candidates. Of these, 142,658 (95% CI: 61,065 to 263,795) candidates lived in the European countries and 76,962 (95% CI: 32,805 to 140,673) in North America.

In the sensitivity analysis varying the percentage of high-risk operable patients who would undergo TAVR, the total number of TAVR candidates was 277,570 (95% CI: 119,406 to 512,707) assuming that 50% would undergo TAVR whereas there were 302,865 (95% CI: 129,433 to 550,562) candidates if all the high-risk patients would undergo TAVR. Finally, we estimated that the total number of patients with symptomatic severe AS in the intermediate-risk category was 145,936 (95% CI: 62,802 to 263,340), and 733,861 (95% CI: 310,623 to 1,302,586) in the low-risk category.

DISCUSSION

The current study found that the prevalence of AS in the elderly (≥ 75 years of age) is 12.4%, and severe AS is present in 3.4%. Among elderly patients with severe AS, 75.6% are symptomatic, and 40.5% of these patients are not treated surgically. From those, 40.3% are potentially treated with TAVR. In total, 12.3% of the prohibitive risk group are TAVR candidates. Among patients undergoing SAVR for severe symptomatic AS, 5.2% are high risk and 80% of those are potential TAVR candidates. Based on these data, we estimated that there are currently approximately 190,000 and 100,000 TAVR candidates in the European countries and North America, respectively. Each year, approximately 18,000 new TAVR candidates emerge in the European countries and 9,000 in North America.

The prevalence of AS

Our estimates of the prevalence demonstrate that the overall burden of disease due to AS in the general elderly population is substantial. Population demographics clearly show that Western populations are aging, thereby further increasing the impact of AS. No effective medical therapy is available for patients with AS, and if not treated by intervention, the estimated 5-year survival of severe AS is only 15% to 50% (7). These data suggest that the treatment of AS in the elderly will have an increasing impact on public health and health care resource consumption in the future.

Based on echocardiographic diagnosis, we found that severe AS occurs in 12.4% of the general elderly (≥ 75 years of age) population. Previous autopsy series and a study based on aortic valve diagnoses in Medicare claims have reported AS prevalence estimates of 9.2% and 16%, respectively (19,20). Our pooled prevalence of AS (12.4%) is lower than the estimates from Medicare claims, but covered a lower age group and did not include diagnoses of aortic regurgitation. The methodological differences between studies are likely to account for the variability in AS estimates.

We explored heterogeneity by assessing the individual study characteristics, but the limited number of studies prevented separate analyses. The heterogeneity is reflective of different diagnostic definitions for AS, dissimilar recruitment methods, and varying study periods (Table 1). Study participation was only 50% to 60% in 2 studies, making their results vulnerable for selection bias (5,15). In 1 study, AS was diagnosed using clinically indicated echocardiography (1). That might have caused a lower prevalence rate of AS. Moreover, improvements of echocardiographic techniques and interobserver variability might have had an influence on the prevalence rates and heterogeneity.

The number TAVR candidates

Nearly 40.5% of all patients with symptomatic severe AS did not undergo SAVR (Fig. 4B). Possible explanations for the lower than expected rates of SAVR include excessive operative

risk, advanced age, comorbidities, and patient preference (21,22). TAVR is a safe, effective, and less invasive treatment strategy for a highly selected proportion of the patients who do not undergo SAVR (23), represented by the 40.3% of patients who underwent TAVR (Fig. 4C). The treatment decisions reflect heart team discussions, in which (interventional) cardiologists and cardiac surgeons combine risk models with additional factors such as frailty, porcelain aorta, and vessel tortuosity (24).

The estimated large number of TAVR candidates has clinical, economic, and social implications. If the index admission costs (US \$72,000) of the PARTNER (Placement of Aortic Transcatheter Valves) trial are applied (25), treating all TAVR candidates would represent a budget impact of \$13.7 billion in the European countries and \$7.2 in North America. At a price of \$30,000, the total device turnover would be approximately \$8.7 billion. Although TAVR is cost effective in the United States for patients at high and prohibitive risk (25,26), data from other countries show that, for intermediate-risk patients, the costs of TAVR at 1 year are considerably higher than the costs of SAVR (27). Importantly, cost is not the only factor that determines the adoption of novel technologies such as TAVR (28). Reimbursement strategies, physician training, and health care culture may be related to the dissemination of this costly technology.

Despite budgetary concerns, current clinical trials are evaluating TAVR for patients at intermediate surgical risk (NCT01314313 and NCT01586910) (9,29). If TAVR proves to be noninferior to SAVR in this population, we estimate that a further 145,000 patients would become TAVR eligible. Indeed, there is some evidence that suggests that TAVR is already being performed in these intermediate-risk patients (18,30). Thus, our estimates of the impact of positive outcomes in the ongoing trials are likely to be conservative. In the future, TAVR may even compete with SAVR in patients at low surgical risk (30,31), a group that comprises 730,000 severe AS patients in the European countries and North America combined.

TAVR learning curve analyses show increasing proficiency with evidence of plateau after the first 30 cases (32). In addition, governmental bodies mandate that each TAVR center performs at least 20 to 50 TAVR procedures per year (33–35). These requirements, combined with the figures from this study, are useful to estimate the number of TAVR centers and physicians who need to be trained in TAVR in the individual countries. For example, the 526 (95% CI: 224 to 965) new TAVR candidates per year in the Netherlands justify approximately 10 certified centers, assuming that each center performs 50 cases annually. Similarly, the 8,205 (95% CI: 3,470 to 15,139) new TAVR candidates per year in the United States suggest a requirement of approximately 165 certified TAVR centers.

The divergent standards of medical evidence required to introduce new therapies in Europe and the United States are likely to account for the difference in TAVR dissemination between the continents (36). Although the Edwards Sapien valve (Edwards Lifesciences, Inc., Irvine, California) and Medtronic CoreValve (Medtronic, Inc., Minneapolis, Minnesota) both received the Conformité Européenne (CE) mark in 2007, the U.S. Food and Drug Administra-

tion used trial data to approve the Edwards Sapien valve for patients at prohibitive and high surgical risk only in November 2011 and October 2012, respectively. Consequently, TAVR has been performed with greater frequency and for a wider range of indications in Europe than in the United States. The studies on decision making in patients with AS reflect the commercial use of TAVR in Europe, whereas the U.S. studies display decision making in a time when TAVR use was restricted to clinical trials. These differences in practice are likely to disappear after the commercialization of TAVR in the United States and were taken into account in our sensitivity analyses.

Study limitations

Although we systematically searched the literature, relatively few reports on the prevalence of AS in the general population were identified. Additional population-based studies that use a unified echocardiographic definition of AS are warranted. The current study, however, reflects all of the currently available evidence on the prevalence of AS.

The estimation of TAVR candidates is as accurate as the currently available inputs and assumptions from the literature. However, we used sensitivity analyses to assess the influence of uncertain parameters. In addition, we included measures of uncertainty in each step of the model to calculate confidence intervals, representing the likelihood of the final estimates.

CONCLUSIONS

This systematic review and meta-analysis of population-based studies found that the prevalence of AS and severe AS among the elderly is 12.4%, and 3.4%, respectively. The overall burden of disease due to severe AS in the general elderly population is substantial. Our model showed that under the current indications approximately 290,000 elderly patients at high or prohibitive surgical risk could potentially be treated with TAVR in Europe and North America, and that each year there are approximately 27,000 new TAVR candidates. These estimates have considerable clinical, economic, and social implications.

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ABBREVIATIONS AND ACRONYMS

AS	= aortic stenosis
CI	= confidence interval
SAVR	= surgical aortic valve replacement
STS-PROM	= The Society of Thoracic Surgery Predicted Risk Of Mortality
TAVR	= transcatheter aortic valve replacement

APPENDIX

For supplementary tables and references, please see the online version of this article.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005–11.
2. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol* 2011;8:162–72.
3. Clark MA, Duhay FG, Thompson AK, et al. Clinical and economic outcomes after surgical aortic valve replacement in Medicare patients. *Risk Manag Healthc Policy* 2012;5:117–26.
4. Vaes B, Rezzoug N, Pasquet A, et al. The prevalence of cardiac dysfunction and the correlation with poor functioning among the very elderly. *Int J Cardiol* 2012;155:134–43.
5. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. *J Am Coll Cardiol* 1997;29:630–4.
6. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol* 2008;52:e1–142.
7. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;42:S1–44.
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
9. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;60:1438–54.
10. Statistics Canada. 2012. Available at: <http://www.statcan.gc.ca/start-debut-eng.html>. Accessed November 16, 2012.
11. EUROSTAT. 2012. Available at: <http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database>. Accessed November 16, 2012.
12. United States Census Bureau 2011. Available at: <http://www.census.gov/popest/data/national/asrh/2011/index.html>. Accessed November 16, 2012.
13. Lin SL, Liu CP, Young ST, Lin M, Chiou CW. Age-related changes in aortic valve with emphasis on the relation between pressure loading and thickened leaflets of the aortic valves. *Int J Cardiol* 2005;103:272–9.
14. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikkilä J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. *Eur Heart J* 1994;15:865–70.
15. Lorz W, Cottier C, Gyr N. The prevalence of aortic stenosis in an elderly population: an echocardiographic study in a small Swiss community. *Cardiol Elderly* 1993;1:511–5.
16. van Bommel T, Delgado V, Bax JJ, et al. Impact of valvular heart disease on activities of daily living of nonagenarians: the Leiden 85-Plus Study, a population based study. *BMC Geriatr* 2010;10:17.
17. Brennan JM, Edwards FH, Zhao Y, et al. Long-term survival after aortic valve replacement among high-risk elderly patients in the united states: insights from The Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007. *Circulation* 2012;126:1621–9.
18. Wenaweser P, Pilgrim T, Kadner A, et al. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. *J Am Coll Cardiol* 2011;58:2151–62.

19. Bach DS, Radeva JI, Birnbaum HG, Fournier AA, Tuttle EG. Prevalence, referral patterns, testing, and surgery in aortic valve disease: leaving women and elderly patients behind? *J Heart Valve Dis* 2007;16:362–9.
20. Sugiura M, Matsushita S, Ueda K. A clinicopathological study on valvular diseases in 3,000 consecutive autopsies of the aged. *Jpn Circ J* 1982;46:337–45.
21. Freed BH, Sugeng L, Furlong K, et al. Reasons for nonadherence to guidelines for aortic valve replacement in patients with severe aortic stenosis and potential solutions. *Am J Cardiol* 2010;105:1339–42.
22. Jung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J* 2005;26:2714–20.
23. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607.
24. Osnabrugge RL, Head SJ, Bogers AJ, Kappetein AP. Towards excellence in revascularization for left main coronary artery disease. *Curr Opin Cardiol* 2012;27:604–10.
25. Reynolds MR, Magnuson EA, Lei Y, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (cohort A). *J Am Coll Cardiol* 2012;60:2683–92.
26. Reynolds MR, Magnuson EA, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (cohort B). *Circulation* 2012;125:1102–9.
27. Osnabrugge RL, Head SJ, Genders TS, et al. Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. *Ann Thorac Surg* 2012;94:1954–60.
28. Mylotte D, Osnabrugge RL, Windecker S, et al. Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. *J Am Coll Cardiol* 2013;62:210–9.
29. Osnabrugge RL, Head SJ, Bogers AJ, Kappetein P. Patient selection for transcatheter aortic valve replacement: what does the future hold? *Expert Rev Cardiovasc Ther* 2012;10:679–81.
30. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2012;59: 280–7.
31. Webb JG. Mid-term follow-up after transcatheter aortic valve implantation. *Eur Heart J* 2012;33:947–8.
32. Alli OO, Booker JD, Lennon RJ, Greason KL, Rihal CS, Holmes DR Jr. Transcatheter aortic valve implantation: assessing the learning curve. *J Am Coll Cardiol Interv* 2012;5:72–9.
33. Centers for Medicare and Medicaid Services. 2012. Decision memo for transcatheter aortic valve replacement. Available at: [http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?ncid=257&ver=5&ncaname=transcatheter+aortic+valve+replacement+\(tavr\)&bc=aaaaaaaaaaaa&](http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?ncid=257&ver=5&ncaname=transcatheter+aortic+valve+replacement+(tavr)&bc=aaaaaaaaaaaa&). Accessed November 30, 2012.
34. Haute Autorité de Santé. 2011. Transcatheter aortic valve implantation by the transfemoral or transapical route. Available at: <http://www.has-sante.fr>. Accessed November 30, 2012.
35. College voor zorgverzekeringen. 2011. Transcatheter aortakleppervingang. Available at: <http://www.cvz.nl/hetcvz/zoeken?query=transcatheter+aortakleppervingang>. Accessed November 30, 2012.
36. Kramer DB, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. *N Engl J Med* 2012;366:848–55.

TRANSCATHETER AORTIC VALVE REPLACEMENT IN EUROPE: ADOPTION TRENDS AND FACTORS INFLUENCING DEVICE UTILIZATION

Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization

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ABSTRACT

Objectives

The authors sought to examine the adoption of transcatheter aortic valve replacement (TAVR) in Western Europe and investigate factors that may influence the heterogeneous use of this therapy.

Background

Since its commercialization in 2007, the number of TAVR procedures has grown exponentially.

Methods

The adoption of TAVR was investigated in 11 European countries: Germany, France, Italy, United Kingdom, Spain, the Netherlands, Switzerland, Belgium, Portugal, Denmark, and Ireland. Data were collected from 2 sources: 1) lead physicians submitted nation-specific registry data; and 2) an implantation-based TAVR market tracker. Economic indexes such as healthcare expenditure per capita, sources of healthcare funding, and reimbursement strategies were correlated to TAVR use. Furthermore, we assessed the extent to which TAVR has penetrated its potential patient population.

Results

Between 2007 and 2011, 34,317 patients underwent TAVR. Considerable variation in TAVR use existed across nations. In 2011, the number of TAVR implants per million individuals ranged from 6.1 in Portugal to 88.7 in Germany (33 ± 25). The annual number of TAVR implants performed per center across nations also varied widely (range 10 to 89). The weighted average TAVR penetration rate was low: 17.9%. Significant correlation was found between TAVR use and healthcare spending per capita ($r = 0.80$; $p = 0.005$). TAVR-specific reimbursement systems were associated with higher TAVR use than restricted systems (698 ± 232 vs. 213 ± 112 implants/million individuals ≥ 75 years; $p = 0.002$).

Conclusions

The authors' findings indicate that TAVR is underutilized in high and prohibitive surgical risk patients with severe aortic stenosis. National economic indexes and reimbursement strategies are closely linked with TAVR use and help explain the inequitable adoption of this therapy.

Keywords: aortic stenosis, transcatheter aortic valve implantation, transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) gained Conformité Européenne (CE) mark approval in 2007, and the number of patients undergoing TAVR in Europe has increased exponentially in subsequent years. Despite the encouraging results from randomized, controlled trials and registries (1–4), there is anecdotal evidence that the use of TAVR varies markedly across European nations. Disparate adoption of medical technology is pervasive and results in inequitable patient access (5). Adoption kinetics of a novel medical technology such as TAVR and the factors influencing these variables have not been previously described. Regional differences in TAVR adoption are likely to have emerged because of variations in social, regulatory, economic, and political circumstances, as well as disease prevalence and longevity. This information may be of interest to patients, healthcare professionals, regulatory authorities, the medical device industry, and healthcare payers. In addition, these data may have implications for healthcare resource allocation, service development planning, assessment of equitable patient access, and physician training.

We sought to address this information gap by examining the trends in both the number of TAVR implants and number of centers across 11 European countries since CE mark approval. In addition, we investigated factors that may influence the heterogeneous adoption of this novel technology across nations.

METHODS

Data sourcing

We investigated TAVR use in 11 European countries: Germany, France, Italy, United Kingdom (including Northern Ireland), Spain, the Netherlands, Switzerland, Belgium, Portugal, Denmark, and Ireland. Data were collected from 2 distinct sources. First we identified data from published national registries and large databases in countries in which reimbursement is linked to registry inclusion (3,4,6–8). Lead physicians from each nation submitted data from national registries regarding the annual number of patients treated with TAVR and the annual number of implanting centers from 2007 to 2011. Lead physicians take responsibility for the integrity of the data (Online Table 1).

Secondly, we present data from BIBA MedTech (London, United Kingdom), a cardiovascular market analysis group tracking TAVR use since mid-2009. These data were gathered through specifically designed questionnaires and prearranged telephone interviews with an extensive research panel comprising interventional cardiologists, cardiac surgeons, and administrators from a large number of TAVR centers throughout Europe. National implant estimates were extrapolated using an algorithm that incorporated the following variables: device pricing, national guidelines, national reimbursement policies, portfolio, spread, and trend. This final data set was cross-referenced with published registries.

Table 1 TAVR Implants in Each Nation

	TAVR Implants per Annum, % increase					Cumulative TAVR	Cumulative TAVR, %
	2007	2008	2009	2010	2011		
Germany	157	921 (487)	2,566 (179)	4,859 (89)	7,252 (49)	15,755	45.9
France	58	82 (41)	320 (290)	1,523 (376)	2,447 (61)	4,430	12.9
Italy	71	450 (534)	1,138 (153)	1,581 (39)	1,879 (19)	5,119	14.9
United Kingdom	66	295 (347)	561 (90)	778 (39)	1,037 (33)	2,737	8.0
Spain	12	151 (1,158)	426 (182)	655 (54)	770 (18)	2,014	5.9
the Netherlands*	40	123 (208)	226 (84)	329 (46)	438 (33)	1,156	3.4
Switzerland	18	127 (606)	277 (118)	382 (38)	501 (31)	1,305	3.8
Belgium*	10	100 (900)	163 (63)	257 (58)	289 (12)	819	2.4
Portugal	4	13 (225)	52 (300)	67 (29)	65 (-3)	201	0.6
Denmark	9	81 (800)	126 (56)	190 (51)	239 (26)	645	1.9
Ireland	0	12	61 (408)	34 (-44)	29 (-15)	136	0.4
Total (% increase)	445	2,355 (429)	5,916 (151)	10,655 (81)	14,946 (40)	34,317	100

Values are n (%).

* Excludes 1 low-implant volume center (<30 TAVR implants per annum) in both the Netherlands and Belgium. TAVR = transcatheter aortic valve replacement.

Nation-specific data were combined with European Union– derived year-end population estimates (9) to calculate the: 1) annual and cumulative number of TAVRs performed in each nation; 2) annual number of TAVR implants per million population and TAVR implants per million population of age ≥ 75 years; 3) annual and cumulative number of TAVR centers in each nation; 4) number of TAVR centers per million population; and 5) mean number of TAVR implants per center for each nation.

TAVR penetration

The penetration rate of a therapy is a descriptor of the use of that therapy among eligible patients. Thus, TAVR penetration in each nation was determined as a measure of actual TAVR use relative to potential use. The numerator for calculating penetration was the number of living TAVR recipients at year end in each country. This was calculated as the sum of patients receiving TAVR in that calendar year and the number of living TAVR recipients from previous years. Annual mortality rates at 1, 2, 3, and 4 years following TAVR were assumed to be 24%, 33%, 49%, and 57%, respectively (10). The denominator was an estimate of the prevalence of patients with symptomatic severe aortic stenosis at high or excessive surgical risk that could potentially be treated with TAVR (11). Briefly, the proportion of elderly inhabitants of each country of age ≥ 75 years with severe aortic stenosis (3.4%) was determined by a random-effects meta-analysis. Among these patients, 75.6% were estimated to be symptomatic, 40.5% were deemed to be inoperable due to excessive surgical risk, and 5.2% were determined to be at high operative risk among the patients who received surgical aortic valve replacement

(Society of Thoracic Surgeons risk of mortality $\geq 10\%$). Finally, 40.3% of inoperable patients and 80.0% of the high-risk patients were deemed to be potential TAVR candidates.

Economic indexes

National economic indexes and healthcare parameters for 2011 were obtained from European Union and Organisation for Economic Co-operation and Development databases (12). To establish economic factors associated with TAVR use, we correlated the number of TAVR implants per million population (age ≥ 75 years) to the volume indexed gross domestic product (GDP) per capita in purchasing power standards. GDP per capita in purchasing power standards is obtained by converting GDP per capita to a fictive currency using purchasing power parities that eliminate differences in currency and price levels between countries, thereby allowing meaningful volume comparisons of GDP. In addition, we correlated the number of TAVR implants per million population (age ≥ 75 years) with the percentage of GDP spent on health care and the purchasing power parities-adjusted total healthcare expenditure per capita (U.S.\$). In Europe, health care is funded either by taxation or by social insurance institutions, which are largely outside the commercial marketplace. We classified healthcare financing in each country according to the principal source of funding and compared TAVR use between these systems.

TAVR reimbursement

Medical device reimbursement in Europe is inconsistent because healthcare regulators with diverse policies dictate the method of reimbursement (12). We divided existing 2011 TAVR reimbursement into 2 categories and compared TAVR use between these schemes: 1) “TAVR-specific” systems, in which TAVR is completely reimbursed via a therapy-specific national diagnosis-related group (DRG) tariff; and 2) “constrained” systems, in which TAVR reimbursement is only partially funded by an existing national DRG tariff or the cost is borne by a local healthcare trust or hospital budget.

Statistics

Continuous variables are presented as mean \pm SD or median with interquartile range according to distribution. Normally distributed variables were compared with the Student *t* test and non-normally distributed variables compared with the Wilcoxon rank-sum test. Categorical variables are presented as numbers and percentages. Bland-Altman plots were used to graphically compare the 2 sources of TAVR implant data. Correlation between economic indexes and TAVR implants per million population (age ≥ 75 years) was assessed using the Pearson or Spearman correlation according to distribution. A probability value < 0.05 was considered to indicate statistical significance. Analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Data sourcing

With the exception of 1 small center (<30 TAVR implants per annum) in both the Netherlands and Belgium, complete data were available from the 11 study nations. Herein, we report the results from the national databases which include TAVR implant data since CE mark approval in 2007. The BIBA MedTech data set includes data from 2009 to 2011 and is presented in the Online Appendix.

Implantation rates

Between January 2007 and December 2011, 34,317 patients underwent TAVR in the 11 study nations (Fig. 1A). Almost half of all implants were performed in Germany (45.9%), with Italy (14.9%) and France (12.9%) the next most frequent implanters (Table 1). Ireland accounted for

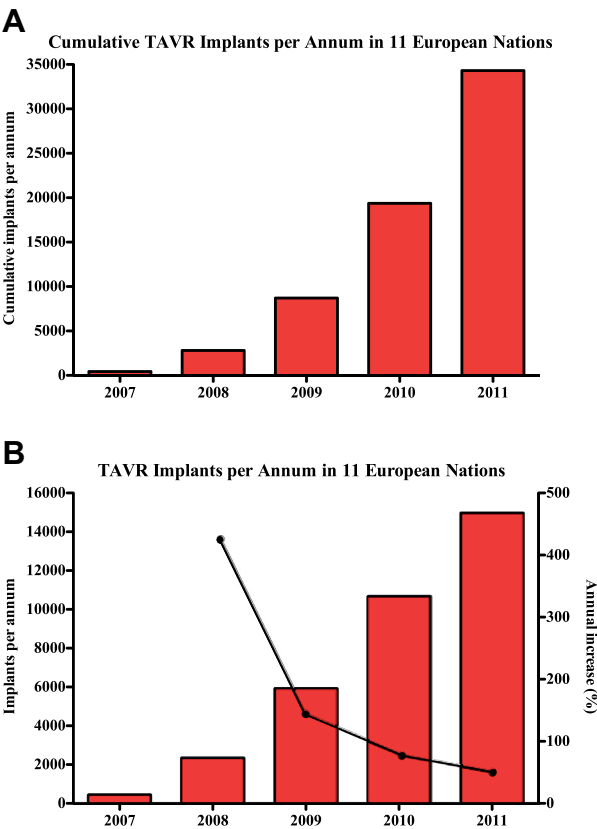


Figure 1 TAVR Adoption in Europe
(A) Cumulative transcatheter aortic valve replacement (TAVR) implants in 11 Western European nations between 2007 and 2011. (B) TAVR implants per annum and percentage annual increase (solid line).

the smallest proportion of implants (0.4%). In 2011, the highest annual increases in procedural volume were observed in France (61%) and Germany (49%), whereas Ireland (−15%) and Portugal (−3%) were the only nations to experience declines. The annual number of implants increased 33-fold from 455 in 2007 to 14,946 in 2011 (Fig. 1B). Although the annual procedural volume growth rate decreased from 429% in 2008 to 40% in 2011, it remained positive.

We observed a wide variation in the number of TAVR implants per million population (Figs. 2A and 2B). Germany (88.7) and Portugal (6.1) accounted for the highest and lowest

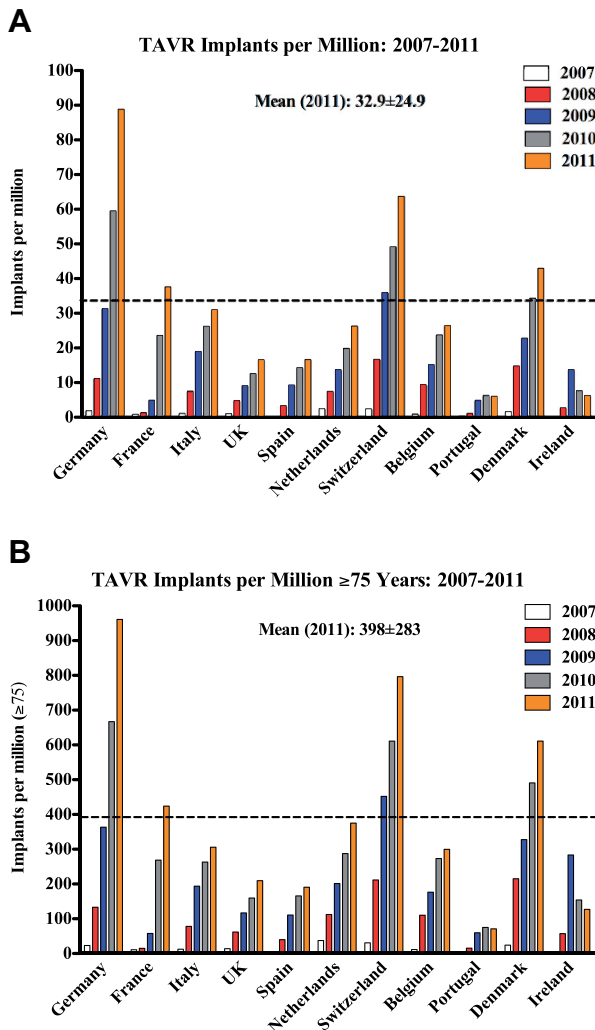


Figure 2 TAVR Implants per Million Population in the Study Nations

TAVR implant dynamics in the study nations between 2007 and 2011. (A) TAVR implants per million population. (B) TAVR implants per million population age ≥ 75 years. **Broken line** represents mean. Abbreviation as in Figure 1.

number of TAVR implants per million population in 2011, respectively. Among the 11 study nations, the mean number of TAVR implants per million population was 32.9 ± 24.9 and the mean number of TAVR implants per million population age ≥ 75 years was 398 ± 283 .

Implanting centers

The number of centers performing TAVR increased approximately 9-fold from 37 in 2007 to 342 in 2011 (Fig. 3A). In 2011, Germany (90) and Italy (87) had the highest number of TAVR centers, whereas Portugal, Denmark, and Ireland (3 each) had the lowest (Table 2). Belgium had the highest number of TAVR centers per million population (2.1) and Portugal (0.3) the lowest (Fig. 3B). On average, there were 0.9 ± 0.6 TAVR centers per million population. These numbers led to an average of 41 ± 28 TAVR implants per center in 2011, with estimates in individual countries ranging from 10 in Ireland to 89 in Germany (Fig. 3C). On account of the high number of TAVR centers per million population, Belgium had the second lowest number of TAVR implants per center (13).

Table 2 Implant Centers

	Cumulative TAVR Centers					TAVR Centers, 2011, %	TAVR Centers per Million Population, 2011	TAVR Implants per Center, 2011
	2007	2008	2009	2010	2011			
Germany	6	36	61	80	90	26.3	1.1	81
France	6	12	16	33	33	9.6	0.5	74
Italy	8	21	50	75	87	25.4	1.4	22
United Kingdom	6	19	26	31	33	9.6	0.5	31
Spain	2	10	20	39	48	14.0	1.0	16
the Netherlands	3	6	7	7	7	2.0	0.4	63
Switzerland	1	7	8	11	12	3.5	1.5	42
Belgium	2	7	13	20	23	6.7	2.1	13
Portugal	1	2	3	3	3	0.9	0.3	22
Denmark	2	3	3	3	3	0.9	0.5	80
Ireland	0	1	3	3	3	0.9	0.7	10
Total	37	124	210	305	342	100	0.9 ± 0.6	41 ± 28

TAVR penetration

In 2011, we estimated that there were 28,400 living TAVR recipients and 158,371 potential TAVR candidates in the 11 study nations (Table 3). Thus, the calculated weighted average TAVR penetration rate in 2011 was 17.9%. The estimated collective and nation-specific TAVR penetration rates are presented in Figures 4A and 4B. Germany (36.2%) and Switzerland (34.5%) had the highest TAVR penetration rates; Portugal (3.4%) and Spain (8.4%) had the lowest penetration rates.

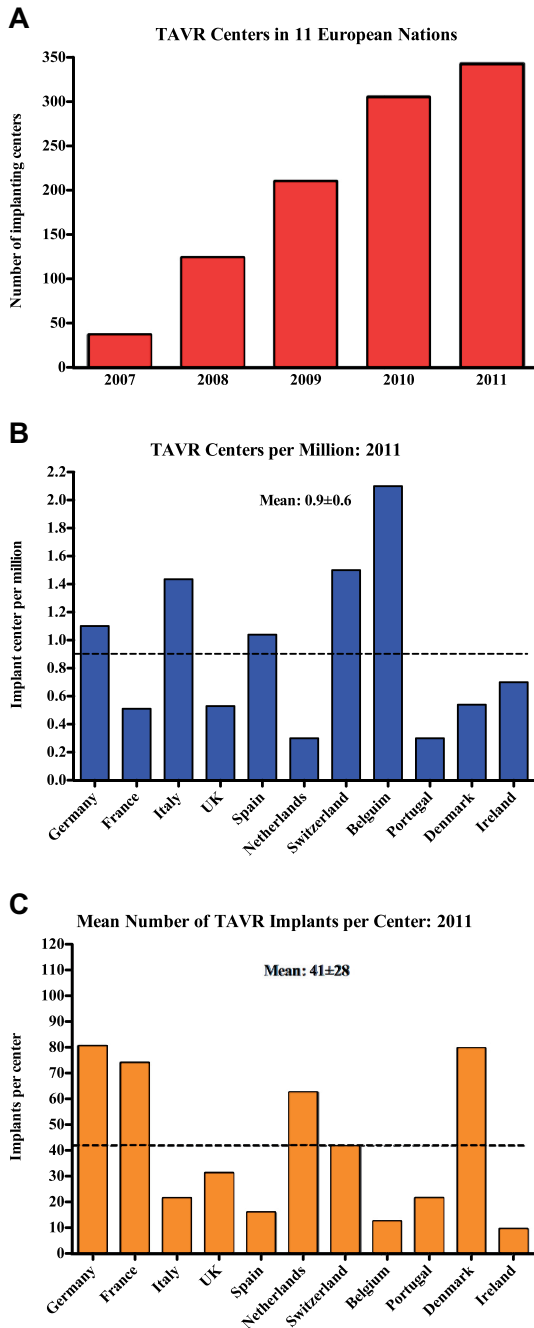


Figure 3 TAVR Centers in Europe

(A) Cumulative TAVR centers in 11 Western European nations from 2007 to 2011. (B) TAVR centers per million population in 2011. (C) Mean number of TAVR implants per center in each nation in 2011. **Broken line** represents mean. Abbreviation as in Figure 1.

Table 3 TAVR Penetration, 2011

	Total Population, 2011	Population Age > 75 years, 2011	Severe AS (3.4%)	Symptomatic Severe AS (75.6%)	Ineligible for SAVR (40.5%)		Eligible for SAVR (59.5%)		Total TAVR Eligible	TAVR Penetration, 2011, %
					Ineligible for SAVR (40.5%)	TAVR Eligible (40.3%)	Eligible for SAVR (5.2%)	High Risk (80%)		
Germany	81,751,602	7,546,760	256,590	193,982	78,563	31,661	115,419	6,002	4,801	36.2
France	65,048,412	5,771,830	196,242	148,359	60,085	24,214	88,274	4,590	3,672	13.9
Italy	60,626,442	6,147,116	209,002	158,005	63,992	25,789	94,013	4,889	3,911	13.8
United Kingdom	62,498,612	4,947,416	168,212	127,168	51,503	20,756	75,665	3,935	3,148	9.1
Spain	46,152,926	4,031,995	137,088	103,638	41,947	16,915	61,665	3,207	2,565	8.4
the Netherlands	16,655,799	1,166,868	39,647	29,993	12,147	4,895	17,846	928	742	16.3
Switzerland	7,870,134	629,004	21,386	16,168	6,548	2,639	9,620	500	400	34.5
Belgium	10,951,266	954,607	32,457	24,537	9,938	4,005	14,600	759	607	14.1
Portugal	10,529,255	964,125	32,780	24,782	10,037	4,045	14,745	767	613	3.4
Denmark	5,560,628	391,138	13,299	10,054	4,072	1,641	5,982	311	249	27.1
Ireland	4,569,864	227,917	7,749	5,858	2,373	956	3,486	181	145	9.2
Total	376,049,328	32,778,776	1,114,478	842,546	341,230	137,516	501,315	26,068	20,855	Weighted average: 17.9

Population data derived from EU sources (9). Estimates of TAVR-eligible patients derived from Osnabrügge (11).

AS = aortic stenosis; SAVR = surgical aortic valve replacement; other abbreviation as in Table 1.

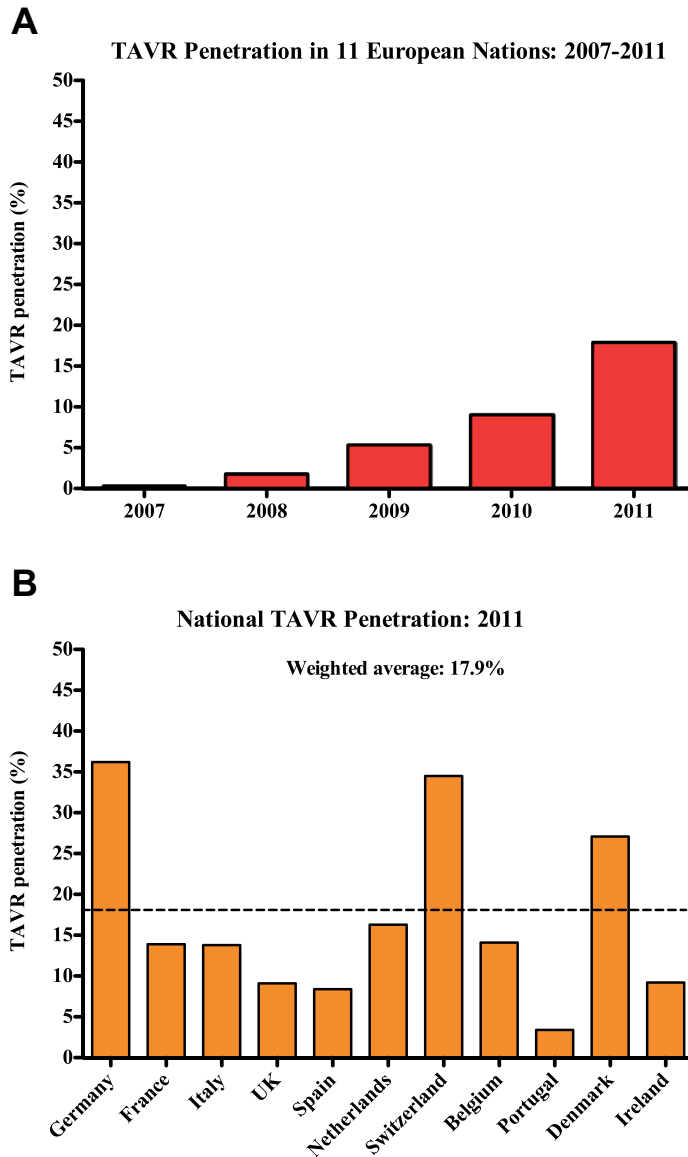


Figure 4 TAVR Penetration in Europe

(A) Estimated TAVR penetration among the 11 study nations from 2007 to 2011. (B) TAVR penetration in each nation in 2011. Broken line represents weighted average. Abbreviation as in Figure 1.

Economic indexes

We assessed the association between several economic indexes and TAVR use (Table 4). The volume-indexed GDP per capita, which is considered to be a reliable indicator of a country's standard of living, was not associated with TAVR use ($r = 0.53$; $p = 0.10$) (Fig. 5A). In contrast,

Table 4 Economic Indexes and Reimbursement Schemes

	Volume Indexed GDP per Capita (PPP)	Healthcare Spend, % of GDP	Healthcare Spend per Capita, 2010, US\$ (PPP)	Principle Source of Healthcare Funding	TAVR Reimbursement
Germany	120	11.6	4,338	Social insurance	National TAVR DRG
France	107	11.6	3,974	Taxation	National TAVR DRG
Italy	101	9.3	2,964	Taxation	Region dependent
United Kingdom	108	9.6	3,433	Taxation	Cost borne by local trust
Spain	99	9.6	3,056	Taxation	Cost borne by hospital
the Netherlands	131	12.0	5,056	Social insurance	Cost borne by hospital
Switzerland	151	11.5	5,270	Social insurance	National TAVR DRG
Belgium	118	10.5	3,969	Social insurance	Cost borne by hospital
Portugal	77	10.7	2,728	Taxation	National SAVR DRG.; remainder of cost borne by hospital
Denmark	125	11.1	4,464	Taxation	National TAVR DRG
Ireland	127	9.2	3,718	Taxation	Cost borne by hospital

Values are actual numbers.

DRG = diagnosis-related group; GDP = gross domestic product; PPP = purchasing power parity; other abbreviations as in Tables 1 and 3.

a significant linear correlation was found between the number of TAVR implants per million population (age ≥ 75 years) and healthcare spending as a percentage of GDP ($r = 0.68$; $p = 0.025$) (Fig. 5B) and healthcare spending per capita ($r = 0.80$; $p = 0.005$) (Fig. 5C). We also found an association between the principal source of healthcare funding and the number of TAVR implants per million population (Fig. 5D). Although not statistically significant, there was a trend toward increased TAVR use in those nations in which healthcare was funded principally by social insurance (Germany, France, the Netherlands, Switzerland, and Belgium) than those principally funded by taxation (Italy, United Kingdom, Spain, Portugal, Denmark, and Ireland) (571 ± 290 vs. 252 ± 192 implants per million population age ≥ 75 years; $p = 0.056$).

TAVR reimbursement

TAVR reimbursement strategies across the study nations were heterogeneous (Fig. 6, Table 4). TAVR-specific national DRG-based reimbursement occurs in Germany, France, Switzerland, and Denmark. Constrained reimbursement systems were noted for the United Kingdom, Spain, the Netherlands, Belgium, Portugal, and Ireland, where the cost of TAVR is borne by a local healthcare trust (United Kingdom) or by the hospital budget. Reimbursement systems

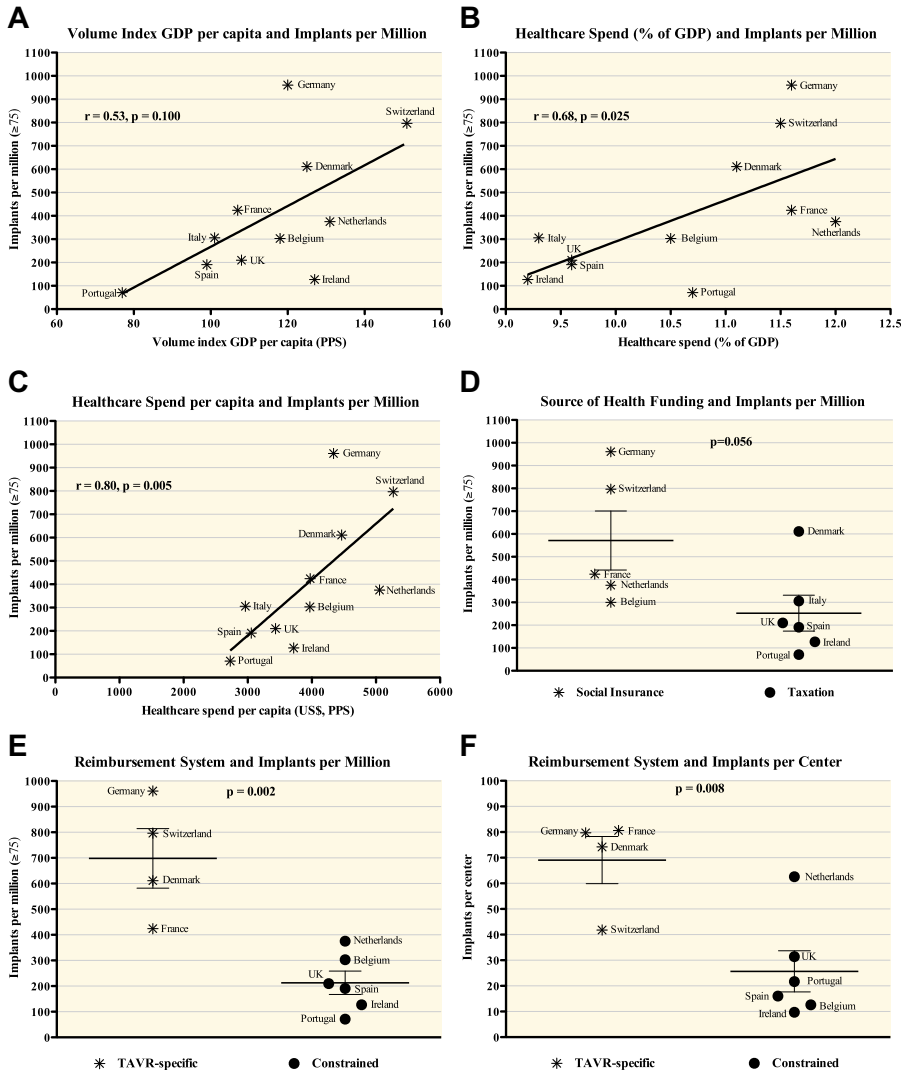


Figure 5 Factors Influencing TAVR Adoption in Europe

Correlation between TAVR implants per million population (age ≥ 75 years) and (A) volume-indexed gross domestic product (GDP); (B) healthcare expenditure (% of GDP); and (C) annual healthcare spend per capita (U.S.\$). Number of TAVR implants per million population (age ≥ 75 years) according to (D) the principal source of healthcare funding (social insurance or taxation) and (E) the system of reimbursement (TAVR specific or constrained). (F) The average number of TAVR implants per center in 2011 and the system of reimbursement. DRG = diagnosis-related group; PPS = purchasing power standards; other abbreviation as in Figure 1.

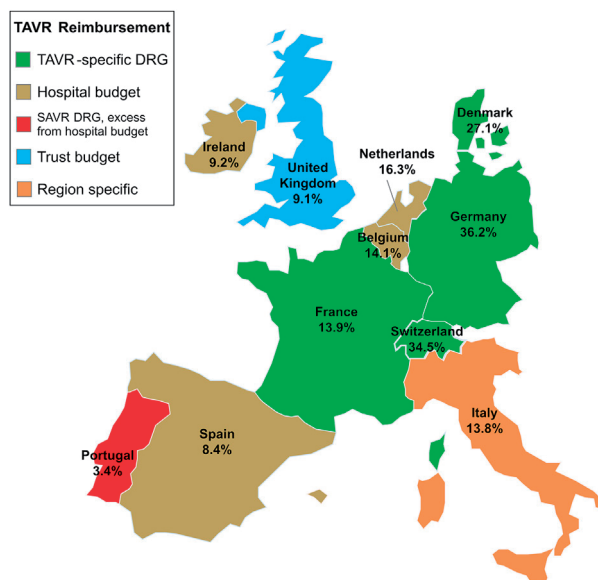


Figure 6 Reimbursement Systems and TAVR Penetration Across Europe

Map of the 11 study nations depicting estimated TAVR penetration rate and the 2011 TAVR reimbursement systems. SAVR = surgical aortic valve replacement; other abbreviations as in Figures 1 and 5.

evolved over the course of the study. For example, a TAVR-specific DRG was introduced in Germany in January 2008 as opposed to France, where it was introduced in December 2009.

We investigated the association between reimbursement system and both TAVR use (implants per million population age ≥ 75 years) and the number of TAVR implants per center. Italy was excluded from the analysis because reimbursement strategies varied across provinces. TAVR-specific reimbursement systems were associated with a 3.3-fold higher number of TAVR implants per million population (age ≥ 75 years) than constrained systems (698 ± 232 vs. 213 ± 112 ; $p = 0.002$) (Fig. 5E). Furthermore, TAVR-specific reimbursement systems were associated with 2.5 times more TAVR implants per center than constrained systems (69 ± 18 vs. 26 ± 20 implants per center; $p = 0.008$) (Fig. 5F).

Comparison between registry and BIBA data sets

The correlation between national registry and BIBA MedTech data sets for TAVR implant numbers is presented in a Bland-Altman plot (Online Fig. 1). There was satisfactory agreement between the 2 sources of information, and both provided similar results and conclusions (Online Figs. 2 to 6, Tables 2 to 4).

Values are n or mean \pm SD, unless otherwise indicated. Abbreviation as in Table 1.

DISCUSSION

This study described the adoption of TAVR in 11 Western European nations since the 2007 CE mark approval of the Edwards Sapien (Edwards Lifesciences Inc., Irvine, California) and Medtronic CoreValve (Medtronic Inc., Minneapolis, Minnesota) systems. The main findings are: 1) more than 34,000 patients received TAVR between 2007 and 2011; 2) there is substantial variation in the adoption of TAVR across nations; 3) there is disparity in the annual number of TAVR implants per center across nations (mean 41 ± 28); 4) TAVR remains greatly underutilized, with an estimated weighted penetration rate of 17.9%; and 5) economic and reimbursement indexes may help explain the variability in TAVR adoption across nations.

We found considerable variation in TAVR use across nations. Germany had more than 2 times the implant rate of all other nations except Switzerland and 14 times the implant rate of Ireland and Portugal. Regional variation in the adoption of medical technology is not unique to TAVR. In Europe, disparate use of drug-eluting stents and implantable cardioverter-defibrillators (ICDs) has previously been described (5,14,15). The identification of inequitable access to medical technologies is important because it generates discussion and initiatives to address inequalities and the corresponding impact on patient outcomes through payer- and physician-led programs (e.g., Stent for Life initiative [16]).

Explanations for the divergence in TAVR adoption among countries are numerous and varied. The economic challenge of providing progressive care for an aging population has mandated that the use of new medical device technologies be not only determined by the expectation of improved clinical outcomes but also by cost effectiveness. It is axiomatic, therefore, that the magnitude of healthcare resources influences the adoption of new medical device technology. Consistent with our findings that healthcare expenditure correlated with TAVR use, the use of ICDs in Europe has also been associated with national economic performance (5,14). Not surprisingly, the lowest TAVR implantation rates were found in Spain, Portugal, and Ireland, who are currently experiencing substantial economic hardship. In these nations, the medical device industry could provide additional support to develop and maintain TAVR programs. As was the case with drug-eluting stents and ICDs, the introduction of competitive TAVR systems should decrease procedural costs and consequently increase TAVR adoption.

Procedural reimbursement and healthcare funding are critical factors in determining the adoption of new medical device technology. Previously, these factors were shown to influence the use of ICDs and coronary stents. In the current study, TAVR use and the number of TAVR implants per center were found to be higher in the presence of nationwide TAVR-specific reimbursement schemes than restrictive reimbursement schemes. The impact of restrictive reimbursement systems was evident in the United Kingdom, Spain, the Netherlands, Belgium, Portugal, and Ireland. We also observed a trend toward increased TAVR use in nations in which social insurance rather than taxation was the principal source of healthcare funding ($p = 0.056$).

Our estimates of TAVR penetration suggest that TAVR remains underutilized in Western Europe. Although the TAVR penetration rate in 2011 was >30% in Germany and Switzerland, the weighted average penetration among the 11 nations studied was 17.9%, and penetration rates were <15% in two-thirds of countries. The adoption of new technology can be a slow process. It requires a threshold of robust clinical evidence, device iteration, physician training, and clinical and financial planning. Moreover, the cultural change required to embrace new therapies often evolves gradually. Given the therapeutic benefit associated with TAVR in inoperable patients (number needed to treat = 5) (1), the demonstrable cost effectiveness in both excessive and high-risk cohorts (17–19), and the less invasive nature of TAVR procedures, the protracted uptake of TAVR technology may have negative consequences for patients, physicians, and administrators. Although TAVR penetration is not necessarily a surrogate for quality of medical care, it may suggest the need for enhanced patient access to novel and potentially life-saving therapies. Indeed, it is interesting to speculate that in nations with higher TAVR penetration rates, a move toward treating patients at less extreme surgical risk may be emerging (20).

The impressive clinical trial outcomes with TAVR are attributable, in part, to the participation of experienced physicians and institutions. These outcomes are not necessarily reproducible in lower-volume settings (21–23). For these reasons, volume-based guidelines for catheter-based and surgical procedures exist (24,25). The recommended centralization of TAVR procedures in high-volume tertiary referral centers aims to ensure adequate operator and center volume for these complex procedures (26–28). National health technology assessments and position papers have suggested that each center perform a minimum of 24 TAVR procedures per annum (27,29,30). We observed centers with low procedural volume and therefore nonadherence to these criteria in several nations. In particular, centers in Ireland, Belgium, and Spain performed on average less than 20 implants in 2011. Two distinct observations explain the low procedural volume: 1) low number of TAVR implants per million population (Ireland); and 2) excessive number of TAVR centers (Belgium and Spain). The reasons for the variation in the number of TAVR centers per million population and center volume across nations are unclear. National political and financial concerns, healthcare policy, population density and profile, reimbursement strategy, and cultural factors may be important in determining the number of centers in each nation.

The way complex medical technology is disseminated has been revolutionized by TAVR. Clinical site selection, mandatory physician and team training, and detailed algorithms outlining patient selection have become the standard of care. Nevertheless, the variation in the adoption of TAVR in Western Europe is clear. Physicians, medical societies, the medical device industry, and other stakeholders have a responsibility to ensure the appropriate use and sensible dispersion of this innovative technology.

Study limitations

Several limitations are of note. First, although every attempt was made to ensure the validity of the implant data, both data sources should be considered to be estimates. Registry data may underestimate the true scale of TAVR use because some cases or small implant centers may not have been included. Secondly, the estimates of TAVR use are likely to have included patients treated for off-label indications, such as patients at lower surgical risk, which may have affected the estimates of TAVR penetration.

CONCLUSIONS

Despite the rapid adoption of TAVR across Europe, our findings indicate that a sizeable treatment gap remains for high/prohibitive surgical risk patients with severe aortic stenosis. National economic indexes and reimbursement strategies are closely linked with TAVR use and may explain the inequitable adoption of TAVR across nations.

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ABBREVIATIONS AND ACRONYMS

CE	= Conformité Européenne
DRG	= diagnosis-related group
GDP	= gross domestic product
TAVR	= transcatheter aortic valve replacement

APPENDIX

For supplemental tables and figures, please see the online version of this article.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607.
2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364: 2187–98.
3. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol* 2011;58: 2130–8.
4. Gilard M, Eltchaninoff H, Iung B, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012; 366:1705–15.
5. Ryden L, Stokoe G, Breithardt G, Lindemans F, Potgieter A. Patient access to medical technology across Europe. *Eur Heart J* 2004;25: 611–6.
6. Bosmans JM, Kefer J, De Bruyne B, et al. Procedural, 30-day and one year outcome following CoreValve or Edwards transcatheter aortic valve implantation: results of the Belgian national registry. *Interact Cardiovasc Thorac Surg* 2011;12:762–7.
7. Díaz JF, de la Torre JM, Sabaté M, Goicolea J. [Spanish cardiac catheterization and coronary intervention registry. 20th official report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990–2010)]. *Rev Esp Cardiol* 2011;64:1012–22.
8. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation* 2011;123:299–308.
9. European Commission: Eurostat. Available at: <http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database>. Accessed November 30, 2012.
10. Rodes-Cabau J, Webb JG, Cheung A, et al. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicentre experience. *J Am Coll Cardiol* 2012;60:1864–75.
11. Osnabrugge RL, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modelling study. *J Am Coll Cardiol* 2013. 62: 1002–1012.
12. OECD Health Data: Health Status. Organisation for Economic Cooperation and Development. Available at: http://www.oecd-ilibrary.org/social-issues-migration-health/data/oecd-health-statistics/oecd-health-data-health-status_data-00540-en. Accessed November 30, 2012.
13. Health Systems in Transition (HiT) Series. European Observatory on Health Systems and Policies. Available at: <http://www.euro.who.int/en/who-we-are/partners/observatory/health-systems-in-transition-hit-series>. Accessed November 30, 2012.
14. Lubinski A, Bissinger A, Boersma L, et al. Determinants of geographic variations in implantation of cardiac defibrillators in the European Society of Cardiology member countries—data from the European Heart Rhythm Association White Book. *Europace* 2011;13:654–62.
15. Ramcharitar S, Hochadel M, Gaster AL, Onuma Y, Gitt A, Serruys PW. An insight into the current use of drug eluting stents in acute and elective percutaneous coronary interventions in Europe. A report on the EuroPCI Survey. *EuroIntervention* 2008;3:429–41.
16. Kristensen SD, Fajadet J, Di Mario C, et al. Implementation of primary angioplasty in Europe: Stent for Life initiative progress report. *EuroIntervention* 2012;8:35–42.

17. Reynolds MR, Magnuson EA, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (cohort B). *Circulation* 2012;125:1102–9.
18. Reynolds MR, Magnuson EA, Lei Y, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (cohort A). *J Am Coll Cardiol* 2012; 60:2683–92.
19. Watt M, Mealing S, Eaton J, et al. Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement. *Heart* 2012;98:370–6.
20. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2011;59:280–7.
21. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346: 1128–37.
22. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003;349:2117–27.
23. Opatowsky AR, Landzberg MJ, Kimmel SE, Webb GD. Percutaneous closure of patent foramen ovale and atrial septal defect in adults: the impact of clinical variables and hospital procedure volume on in-hospital adverse events. *Am Heart J* 2009;157:867–74.
24. Bridgewater B, Hooper T, Munsch C, et al. Mitral repair best practice: proposed standards. *Heart* 2006; 92:939–44.
25. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44–122.
26. Holmes DR Jr., Mack MJ. Transcatheter valve therapy: a professional society overview from the American College of Cardiology Foundation and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011; 58: 445–55.
27. Tommaso CL, Bolman RM 3rd, Feldman T, et al. Multisociety (AATS, ACCF, SCAI, and STS) expert consensus statement: operator and institutional requirements for transcatheter valve repair and replacement, part 1: transcatheter aortic valve replacement. *J Am Coll Cardiol* 2012;59:2028–42.
28. Vahanian A, Alfieri O, Al-Attar N, et al. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2008;29:1463–70.
29. Blekkenhorst B. Transcatheter Aortaklepvervang. College voor Zorgverzekeringen. Available at: http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/standpunten/2011/sp1110-transcatheter-aortaklepvervang-v3b.pdf. Accessed November 30, 2012.
30. Medical Devices Assessment Department. Transcatheter Aortic Valve Implantation by the Transfemoral or Transapical Route: Reassessment Report, October 2011. Haute Autorité de Santé. Available at: http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-11/assessment_of_tavi_-_summary_vdef.pdf. Accessed November 30, 2012.

INTRODUCTION OF OBJECTIVE PERFORMANCE CRITERIA FOR TRANSCATHETER AORTIC HEART VALVE DEVICE APPROVAL

Considerations and Recommendations for the Introduction of Objective Performance Criteria for Transcatheter Aortic Heart Valve Device Approval

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ABSTRACT

In the United States, new surgical heart valves can be approved on the basis of objective performance criteria (OPC). In contrast, the US Food and Drug Administration traditionally requires stricter criteria for transcatheter heart valve (THV) approval, including randomized, clinical trials. Recent US Food and Drug Administration approval of new-generation THVs based on single-arm studies has generated interest in alternative study approaches for THV device approval. This review evaluates whether THV device approval could follow a pathway analogous to that of surgical heart valves by incorporating OPC and provides several considerations and recommendations. Factors to be taken into account in the construction of OPC include the maturity of THV technology, variability in transcatheter aortic valve replacement practice, end points included as OPC, follow-up terms for specific OPC, patient populations to which these OPC apply, and (statistical) methods for OPC development. We recommend that approval of THV devices in the United States for low-and intermediate-risk patients or for new indications should provisionally rely on data from randomized, clinical trials. However, it is recommended that formal OPC be applied for approval of new-generation THVs for use in high- and extreme-risk patient populations.

Keywords: aortic valve, aortic valve stenosis, device approval, heart valve prosthesis implantation, transcatheter aortic valve replacement

Since the introduction of prosthetic surgical heart valves in the 1950s, a great number of valve prostheses have been developed for surgical aortic valve replacement (SAVR), with continuous improvement in outcomes by advances in valve design.^{1,2} More recently, transcatheter aortic valve replacement (TAVR) has rapidly been adopted as an alternative therapy for high- or extreme-surgical-risk patients with severe aortic stenosis (AS).

In Europe, THV devices and surgical prostheses share a common market approval process. The Conformité Européenne (CE) mark provides authorization for a manufacturer to sell a product in the European Economic Area by affirming that it complies with prespecified legal requirements. Importantly, the level of scientific evidence required to achieve CE mark requires a single-arm demonstration of short-term safety and efficacy in ≈ 50 patients. In contrast, the approval process for new-generation surgical or transcatheter prostheses in the United States is very different. For surgical prostheses, the development of objective performance criteria (OPC) by the US Food and Drug Administration (FDA) has superseded the requirement to perform randomized, clinical trials (RCTs) because of the maturity of the device field and the minimal changes in new iterations of previously approved valves (predicate devices). Until recently, approval of THVs has required randomized comparisons with standard FDA-approved therapies because the technology is immature, device design is significantly different, and device development is still iterating rapidly. However, similar to the development of surgical prostheses, the established efficacy of TAVR as shown in multiple RCTs of high-risk patients has potentially made the requirement for lengthy RCTs before the introduction of new THV devices unacceptable from societal, patient, and physician standpoints. It may place patients at unnecessary risk by delaying access to improved safer and more efficient technology. Therefore, alternative study approaches should be considered for new THV device approval.

The FDA recently also approved several THVs on the basis of single-arm studies, the first one being the CoreValve device, which was tested in the CoreValve Extreme Risk Pivotal trial.³ Innovative trial designs, perhaps incorporating OPC, have been proposed but not formally introduced as alternatives to RCTs for new THV device approval.⁴ This review provides an overview of OPC, considers the potential role of OPC for THV device approval, and discusses the challenges associated with such an approach. Several recommendations for the future implementation of OPC for THV devices are provided.

OBJECTIVE PERFORMANCE CRITERIA

Traditionally, 2 methods of establishing a comparator for single-arm studies have been used: OPC and performance goals (PGs; Table 1). OPC are linearized event rates of safety end points that are derived from historical controls included in meta-analyses of available data. A PG, on the other hand, represents a single point estimate considered sufficient as a comparator.

In general, the process of developing a PG is less formal than the process of developing OPC. Therefore, compared with PGs, OPC are thought to be superior because of the increased maturity of device technology and the more robust data from which the comparator is developed.⁵ For the FDA to allow a device to be considered for approval with OPC, it should fulfill a number of criteria: (1) The device technology should be sufficiently mature; (2) the meta-analysis from which event rates are derived should include an accumulation of studies and all relevant literature from different devices; (3) the OPC should not be developed by companies using only their own data; and (4) the OPC must be contemporary and updated regularly because technology may become obsolete over time, thereby attenuating the rigor and relevance of the OPC.

Table 1 Different Methods Used as Comparators in Single-Arm Studies

	OPC for Heart Valves	PG	OPG in the CoreValve Trial ³
Comparator	Other similar devices	Other similar devices	Standard nondevice therapy
Development of comparator estimates	Historical controls in a meta-analysis of available data on existing similar devices	Often based on upper or lower confidence limit of efficacy or safety end point of existing similar device(s)	Meta-analysis of standard nondevice therapy, corrected for outcome of nondevice arm in a single randomized trial
Outcome	Linearized rate (%/patient-y)	Point estimate (X% at X [time])	Point estimate (43% at 1 y)
Composition of end point(s)	14 Single-component end points (7 for biological and 7 for mechanical valves)	1 Single-component or composite end point	1 Composite end point of death and major stroke
Nature of end point	Safety	Safety or efficacy	Efficacy
No. of criteria	14	1	1
Statistical comparison	Upper 95% CI of preapproval study should be less than twice the established OPC rate	Upper 1- or 2-sided 95% CI of preapproval study should be less than comparator point estimate	Upper 95% CI of preapproval study should be less than comparator point estimate

CI indicates confidence interval; OPC, objective performance criteria; OPG, objective performance goal; and PG, performance goal.

OPC Development

The OPC for surgical valves were conceived, subsequently developed, and then implemented after 2 major RCTs evaluating mechanical and biological prostheses did not identify significant safety concerns.¹ It was thus recognized that traditional randomized evaluations were not feasible because of the large sample sizes required to identify infrequent events. Such large RCTs would also greatly impede the timely introduction of technological advancements to

the market.⁷ In 1993, the FDA convened an expert workshop to consider alternative study designs for regulatory approval of new valves. This forum proposed a strategy of comparing new valves with valve-related adverse event rates of existing valves occurring after the immediate postoperative 30-day period. These rates were to be derived from meta-analyses of historical data.^{5,8}

An initial meta-analysis was performed, including >60 000 valve implantations and >200 000 patient-years of follow-up. A subselection of studies was based on previously FDA-approved valves in reports adhering to reporting guidelines.⁹ Expert consensus identified 7 procedure-related complications that were to be assessed for new device approval, the so-called OPC (Table 2).¹⁰ Because events occurred at a rate of 0.2% to 3.5% per 100 patient-years, this would demand an unduly large 4860 patient-years of follow-up for approval of each new valve in a study with 80% power and a 1-sided significance level of 0.05. The FDA agreed to evaluate these complication rates in studies with a minimum of 800 patient-years of patient follow-up to allow enough statistical power for events that occur at a rate of 1.2%/y, thus representing at least 9 of 14 OPC end points (eg, 7 for biological and 7 for mechanical prostheses; Table 2).

Table 2 OPC for Surgical Prostheses

	Original OPC				Proposed New OPC			
	Mechanical Valve		Tissue Valve		Mechanical Valve		Tissue Valve	
					Aortic		Mitral	
	OPC*	Patient-Years†	OPC*	Patient-Years†	OPC*		OPC*	
Thromboembolism	3.0	323	2.5	388	1.6	2.2	1.5	1.3
Valve thrombosis	0.8	1,213	0.2	4,850	0.1	0.2	0.04	0.03
All hemorrhage	3.5	277	1.4	693
Major hemorrhage	1.5	647	0.9	1,078	1.6	1.4	0.6	0.7
All PVL	1.2	808	1.2	808
Major PVL	0.6	1,617	0.6	1,617	0.3	0.5	0.3	0.2
Endocarditis	1.2	808	1.2	808	0.3	0.3	0.5	0.4

OPC indicates objective performance criteria; and PVL, paravalvular leak.

* Events per 100 patient-years (%/y).

† Patient-years required to satisfy the requirement of establishing that the observed rate is <2 times the OPC, with 80% power and $\alpha=0.05$.

Adopted from Grunkemeier et al¹⁰ and Wu et al.¹¹

Requirements for Device Approval Based on OPC

For a new valve to be approved, the upper 95% confidence interval of linearized complication rates should be less than twice the established OPC rate for each of the complications. In addition to these clinical event rates, a new valve must show functional improvement in patients (eg, New York Heart Association classification) and fulfill certain hemodynamic criteria.

Subsequently added criteria include the need to have follow-up of ≥ 300 patients for ≥ 1 year, with an equal distribution of included patients over 3 centers.

Newly Developed OPC

Since the introduction of OPC, numerous prosthetic valves have been approved with this approach.⁴ However, new OPC based on more contemporary evidence have recently been proposed.¹¹ With the use of the same study selection criteria, rate estimates were produced from an updated meta-analysis. Improved valve design, contemporary therapeutics, and closer patient follow-up have clearly decreased the expected complication rates (Table 2). In contrast to the original OPC, it has been proposed that separate OPC for valves in the aortic and mitral position be reported.

OPC for Coronary Stents

The process of using OPC for device approval in cardiovascular disease has not been limited to heart valves. New-generation coronary stents may be evaluated and approved with OPC (Table I in the online-only Data Supplement). However, the process of OPC development and the requirements for device approval are very different from those for surgical heart valves (Figure). Important differences that may be adopted for THV device approval include that OPC for coronary stents are based on complex statistical modeling whereas OPC for surgical heart valves include no statistical modeling; that, depending on the treatment indication or degree of design modification, either OPC are used or a randomized equivalence trial is required for approval; and that events are a combination of safety and efficacy whereas OPC for surgical heart valves include only safety end points.^{12,13}

COREVALVE EXTREME RISK PIVOTAL TRIAL

The methodology for approving the CoreValve THV for use in extreme-risk patients in the United States has been considered somewhat controversial.³ The trial did not use OPC in the traditional sense but introduced a new terminology: the objective performance goal (OPG) (Table 1). The OPG was based on outcomes analyzed in a meta-analysis of studies evaluating balloon aortic valvuloplasty as a stand-alone therapy for AS. These were adjusted for the standard treatment arm of the Placement of Aortic Transcatheter Valves (PARTNER) 1B trial, which included medical therapy, and balloon aortic valvuloplasty in 88% of patients.¹⁴ Even though this treatment has been deemed ineffective for severe AS, it formed the statistical basis for the CoreValve Extreme Risk Pivotal trial was to determine whether TAVR with the CoreValve THV was not significantly worse than the lower 95% confidence interval of standard treatment with the objective PG used as a comparator point estimate. However, because its primary goal was therefore to determine the efficacy of the CoreValve THV, the trial reflects a

measure similar to a PG. Its sole purpose was to quantify an improvement in patient outcome (mainly survival in this group) compared with the conservative management of severe AS, which was the standard of care in this patient population. The OPG did not, as is the case for OPC for surgical valve prostheses, derive data from available THV devices and evaluate the safety of the THV device in terms of multiple complication rates. As a result, it cannot be determined whether the CoreValve is comparable to the previously approved SAPIEN valve, particularly in terms of safety end points related to the valve.

HURDLES AND CONSIDERATIONS FOR CURRENT OPC USE FOR THV APPROVAL

SAVR and TAVR are considered to be complementary treatment options for select patients with native severe AS. It would therefore seem reasonable that the quality of both transcatheter and surgical heart valves be measured with the same criteria. However, the nature and rates of complications differ between SAVR and TAVR, complicating the potential application of surgical OPC to THV devices. For example, if OPC for surgical prostheses were applied to the PARTNER or CoreValve trial data, these devices would not have been approved on the basis of significantly increased paravalvular leak (PVL) with the transcatheter devices.¹⁵ Therefore, specific OPC for the approval of THV devices would be more appropriate. A number of factors need to be considered in the development of such OPC.

Maturity of Technology

The maturity of the device technology is one of the most important criteria for the FDA to consider the use of OPC. A great deal of TAVR research has been devoted to refining patient selection, improving procedural safety, and delivering better clinical outcomes. Such information has been instrumental in the development of new-generation THV devices that overcome technical and procedural issues related to first-generation devices. Indeed, direct comparisons between first- and new-generation devices have reported lower complication rates with more contemporary valves.¹⁶ Recent introductions to the European market of new repositionable, recapturable, and retrievable THVs and THVs that often contain sealing cuffs to reduce PVL have similarly shown promising clinical outcomes.¹⁷

Despite these promising results with new-generation THV, the majority of published TAVR outcome data relate to first-generation THVs that are no longer in use. The rapid evolution of THV technology may have already rendered the initial SAPIEN and CoreValve randomized trial outcome data superseded. A meta-analysis of all relevant data for the development of TAVR OPC would largely include obsolete THV devices and include only limited patient follow-up with new THVs. The inferiority bar that would be set as OPC would be so low that virtually any new device, however flawed, would not have significant trouble meeting

this antiquated bar. These data may thus be unsuitable for determining adverse events rates and treatment goals. A meta-analysis for TAVR OPC development should be up to date and include a variety of new-generation THV devices. It should not be based on a single device type or old-generation devices. Therefore, it is questionable whether TAVR practice and THV devices have matured sufficiently to allow the development of OPC.

Variability in TAVR Practice

The quality of new THV devices is often measured by a comparison of rates of procedural complications.¹⁸ However, whether these complication rates truly reflect an improvement in only the valve design is debatable. Procedural complications may be heavily influenced by operator experience and skill, by variability in TAVR practice, by procedure development, and importantly by variability in patient selection criteria. Compared with a relatively stable SAVR practice, standard practices for TAVR are rapidly changing as a result of new data.

Patient selection is hospital, heart team, and even operator dependent. The selection of lower-risk patients or the exclusion of “futile” patients will be associated with significant outcome improvements.^{19,20} Second, the rigor of preoperative assessment and valve sizing is variable. Third, although the majority of centers use a transfemoral-first approach to TAVR, other centers have favored alternative routes.²¹ Each access route will be associated with specific procedural complications. Fourth, variability in use of ancillary devices (eg, embolic protection) may have an impact on adverse events.²² Fifth, increased operator experience has been linked to reductions in procedural complications. Experienced operators can often avoid scenarios in which complications can occur or better manage them if they do occur. Moreover, algorithms for management of complications often differ, which may affect outcomes. For example, thresholds for blood transfusions after access site complications can be highly variable. Lastly, end-point adjudication according to the Valve Academic Research Consortium remains a challenge for some of these end points, resulting in misclassifications and overestimation or underestimations of outcomes.^{23,24}

Patient Population

Current large registries and RCTs of TAVR have essentially included high-risk populations with multiple severe comorbidities. Long-term follow-up is limited by the high rates of non-cardiovascular and cardiovascular non-valve-related deaths. Although valve hemodynamic performance is maintained,²⁵ information on actual valve durability and safety remains scarce.

Data from high-risk patients should not form the basis for the development of OPC for the approval of THV devices that are also to be used in lower-risk patients. Short- and medium-term outcomes are significantly improved in lower-risk patients.¹⁹ Development of OPC based solely on high-risk trial data risks the approval of THV devices that perform unsatisfactorily in lower-risk patient populations.

Therefore, it may be appropriate to develop TAVR OPC for specific patient populations (ie, separate low-, intermediate-, high-, or extreme-risk OPC). Specific procedural complications may have a greater impact in cohorts of high- than low-risk patients. For example, conversion to open surgery should be very low in populations of extreme-risk patients, who are not surgical candidates by default. This is less relevant in low-risk patients, who will have excellent results of SAVR despite the complication. In contrast, the impact of PVL and the requirement for new permanent pacemaker implantation may become more crucial in low-risk patients with a long life expectancy as opposed to high-risk patients in whom prognosis is already severely impaired as a result of comorbidities. Other complications such as coronary obstruction are likely to be of equal importance in all populations.

Follow-Up

Traditionally, OPC for prosthetic valves have focused on long-term events, not on procedural events. Technically, SAVR is relatively straightforward, and the design of the prosthetic valve has minimal impact on the operative technique and procedural outcome. The technical aspect of the procedure itself is considered to be less relevant for the actual safety of the valve. In contrast, design features of the THV delivery system and the THV have a significant impact on the TAVR procedure. Moreover, specific complications that should be considered as OPC may be a result of major differences in design features of THV devices, related to balloon expandability or self-expandability and specifically the height of devices, stent matrixes, presence and length of a skirt, and sealing rings.

OPC for TAVR should be a combination of short- and long-term criteria. To have sufficient statistical power to detect outcome differences, it should be mandatory to have a minimum length of follow-up and a minimum number of patients included in preapproval studies, similar to the practice of surgical OPC.

End Points

OPC for heart valves emphasize the long-term safety of new valves, as measured by events related to the device design: Thrombogenicity and bleeding are intertwined and related to valve design, the need for oral anticoagulation, and the targeted International Normalized Ratio; rates of PVL can be a measure of structural valve deterioration; and endocarditis evaluates the susceptibility of a valve for the colonization of organisms.

The poor prognosis of many high-risk patients has necessitated an end-point focus on death and strokes in TAVR trials rather than device-related safety. Indeed, stroke and PVL have been addressed adequately in numerous studies. However, many other complications have been reported only anecdotally.²⁶ Studies have just recently scrutinized rates of valve thrombosis, bleeding, and endocarditis during follow-up.^{25,27–29} These traditional OPC end points remain clinically relevant because their occurrence is associated with prognosis.^{25,28} Considering death as an end point itself, however, should be avoided. Analyses of predictors

of death after TAVR demonstrate that comorbidities are the most important predictors of mortality.^{30,31} Procedural complications that are operator dependent such as bleeding and vascular complications have also been shown to predict mortality. Therefore, death as an OPC would not necessarily represent a measure of valve safety (eg, prosthetic inadequacy or design).

Similar to OPC for coronary stents that require collection of 30-day major adverse cardiac events, procedural safety events related to specific valve designs should be considered in OPC. Alternatively, a 30-day early safety PG may also be sufficient for the rapid introduction of new technology. These may include but are not limited to the following events: conversion to open surgery, coronary obstruction, annular rupture, ventricular septal perforation, mitral valve apparatus damage or dysfunction, early valve migration or embolization, PVL, and permanent pacemaker implantation. Other procedural end points related to specific approaches (eg, transapical or transaortic TAVR) should be considered less relevant.

In addition to traditional heart valve OPC that should be required to test the safety of THV devices, long-term evaluation should include hemodynamic performance of THVs and the freedom from structural valve deterioration. These end points are crucial to assess the efficacy of TAVR.

The use of composite end points as OPC should be avoided. Potential risks related to valves will not become apparent because lower and higher event rates of specific complications in the composite will even out.

Statistical Analysis

Multivariate adjustment for OPC in coronary stent approval is performed on the basis of clinical and procedural characteristics (Figure). TAVR outcomes are highly dependent on patient selection, practice variability, and patient comorbidities. For OPC of THVs, it would therefore also be appropriate to provide outcome adjustment based on clinical profiles and procedural characteristics of TAVR patients. A disadvantage of this approach is the lack of clear predictors for surgical OPC end points (eg, endocarditis or valve thrombosis). Little predictability is derived from patient, procedural, or postprocedural characteristics available in the immediate perioperative phase. Similarly, numerous TAVR-specific outcomes that could be considered for OPC occur rarely. Identification of clear predictors is therefore limited, and outcome adjustment would be insufficient.

NON-OPC ALTERNATIVES FOR DEVICE APPROVAL

Propensity score analysis using historical controls has been proposed as an alternative to OPC for device approval. Multivariate analyses have demonstrated TAVR outcomes to be dependent largely on patient baseline characteristics, except for the impact of PVL, different

	Prosthetic valves	Coronary stents	
Disease aspects	No specific OPC for different disease (e.g. stenosis or regurgitation)	No specific OPC for different disease (e.g. native coronary or graft stenosis)	Patient and device specifics
Anatomical aspects	No differentiation in anatomical specifics*	Considers current stent labeling for treatment of specific lesions	
Design aspects	All valves have the exact same OPC requirements	Requirements differ according to the degree of design modification	
Patients required	800 patient-years	No requirements	OPC specifics
Follow-up length	≥1 year for 300 patients	Up to 6 months†	
Endpoints	Primarily safety events	Safety and efficacy events	
Statistical model	Standard pooled meta-analysis	Bayesian hierarchical modeling	OPC development
Adjustment	No adjustment for covariates	Adjusted for clinical, lesion, and post-procedural covariates associated with specific endpoints	

Figure Differences in development and specifics of objective performance criteria (OPC) for prosthetic valves and coronary stents. *Newly developed OPC take into consideration whether a valve is located in the aortic or mitral position, but the US Food and Drug Administration has not yet adopted these. †Depending on the degree of stent device design modifications, with longest follow-up required being 6 months.

access routes, and procedural adverse events.^{30,31} These variables would allow for appropriate propensity matching. However, TAVR research has focused largely on evaluating prognostic results of TAVR in a comorbid patient population. Besides hemodynamic performance during follow-up, reports and predictors of valve function and safety have been scarce. Even with propensity score analysis or propensity matching, analyses would focus predominantly on efficacy, not safety. This highlights the need for further maturity of device technology and research to reduce the “noise” in current outcome studies that obscures actual valve safety during follow-up.

Should RCTs be mandatory for specific indications, bayesian and adaptive trial designs over a frequentist’s superiority approach may be alternatives that can potentially reduce sample size or trial duration and costs.³² Such trial designs mandate satisfactory information from previous RCTs and informative large registries, which are available for TAVR. Other RCT designs using composite end points and noninferiority trials have been proposed to reduce sample sizes.³³ However, liberal noninferiority margins to artificially claim noninferiority should be avoided.³⁴ Furthermore, composite end points pose several limitations, although

they may be overcome by application of hierarchical statistical methodology.³⁵ The concept of registry-based RCTs has recently been introduced in cardiovascular medicine to ease trial planning and execution.³⁶ This may certainly be possible in the setting of the many existing large-scale TAVR registries.

CONSIDERATIONS FOR TAVR OPC DEVELOPMENT

Despite the numerous hurdles currently related to developing OPC for THV device approval, it is likely that there will not be an ideal time for introducing OPC. Challenges will remain and new hurdles will arise. OPC for THV device approval will need to be introduced at some point and subsequently optimized. Regular updates when new evidence becomes available will be required.

The causes, interventional techniques, and devices differ significantly between TAVR and transcatheter mitral valve interventions. Therefore, separate OPC for aortic and mitral procedures should be developed.

Important recommendations relate to the risk profile of distinct patient populations because OPC should be patient group specific. New treatment indications for TAVR require data from an RCT on which OPC can subsequently be developed. With robust data from RCTs, approval of new THV devices for use in high- and extreme-risk patients should be made possible by the introduction of formal OPC (Table 3). The use of OPC cannot currently be justified for low- or intermediate-risk patient populations for whom randomized data with a surgical AVR control are scarce; only large, powered RCTs can demonstrate whether TAVR can be recommended for use in intermediate-risk patients.³⁷ With the ongoing PARTNER II and Surgical Replacement and Transcatheter Aortic Valve Implantation (*SURTA*VI) trials,

Table 3 Proposal for Current THV Device Approval Based on OPC, PGs, and Data From RCTs

Patient Population	Early Safety	Long-Term Safety and Efficacy
Low risk	Similar safety as a propensity-matched surgical cohort, or as determined by a 30-d PG once a THV has been approved for use in these patients	Show both similar results in an RCT comparing TAVR versus SAVR and fulfill surgical OPC
Intermediate risk	Similar safety as a 30-d PG	Through a non-inferiority or superiority THV vs THV RCT if TAVR is superior to SAVR in ongoing TAVR vs SAVR RCTs, or fulfill OPC that can be derived from these ongoing trials
High and extreme risk	Similar safety as a 30-d PG	Through noninferiority or superiority THV vs THV RCT, or fulfill specific THV OPC in a single-arm registry

OPC indicates objective performance criteria; PG, performance goal; RCT, randomized, clinical trial; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; and THV, transcatheter heart valve.

contemporary data on the best strategy for intermediate-risk patients will be available shortly. These data can function as new standards and form the basis for the development of OPC for intermediate-risk patients. In the future, the development of 30-day PGs will help rapidly integrated new-generation iterative THVs into clinical practice and will be available on short notice from large national and company databases such as the Transcatheter Valve Therapeutics registry.³¹ For low-risk patients, long-term performance of THVs should at least match that of surgical prostheses and fulfill surgical OPC.

Table 4 contains a summary of recommendations for OPC development. Importantly, OPC development should be done in close collaboration with regulatory bodies in charge of device approval.⁴

Table 4 Considerations and Recommendations for OPC Development

Procedure

Separate surgical and transcatheter heart valve OPC

Separate aortic and mitral valve OPC

Uniform for different access approaches

OPC for THV development

Based on TAVR data only

Based on multiple new-generation THVs

Regular updates

May include covariate adjustment

Patient populations

Separate OPC according to risk populations

No OPC for new treatment indications

Follow-up

Specific short- and long-term criteria

A minimum length of follow-up requirement

End points

Avoid composite end points

Composed of valve-related events

Exclude events specifically related to the patient population, access approach, or operator experience

Events may differ according to risk profiles of patient populations

Short term: focus on safety

Long term: combination of safety and efficacy

Identification of valve design features related to specific adverse events

AVR indicates aortic valve replacement; OPC, objective performance criteria; RCT, randomized, controlled trial; TAVR, transcatheter aortic valve replacement; and THV, transcatheter heart valve.

CONCLUSIONS

It is recommended that applying formal OPC for the approval of new-generation THVs for use in high- and extreme-risk patient populations in the United States be considered. For now, approval of THV devices for use in low- and intermediate-risk patients or for new indications should provisionally be considered only with data from RCTs. However, in the near future, data from specific RCTs (PARNTER II and SURTAVI) can form the basis for development of additional OPC for intermediate-risk patients. Development of these and future OPC should include considerations of technology maturity, short- and long-term data, specific events likely to be related to particular THV designs, patient risk profile, and statistical methods to produce OPC.

Supplemental Table 1 Objective Performance Criteria for coronary stents

Engineering evaluation compared to approved conventional stainless steel stents		Patient factors	Lesion factors	Stent factors	New stent: frequentist evaluation technique	Modified stent: Bayesian evaluation technique
Conventional stent design or minimal design deviation		Elective coronary or vein graft	3.0-5.0mm reference	Balloon expandable; stainless steel; slotted tube, welded, coil	Registry: 30-day MACE and acute angiographic predicted restenosis rate compared against OPC	Update prior similar stent experience for direct probability comparison with acute MACE and predicted restenosis OPC
Moderate design deviation		Elective coronary or vein graft	3.0-7.0mm reference	Balloon or self-expandable; stainless steel nitinol, coated, new metal, covered; tube, welded, coil	Registry: 30-day MACE and 6-month angiographic endpoints compared to OPC	Update prior similar stent experience for direct probability comparison to acute MACE and 6-month OPC
New patient population or new untested stent design	Severe design deviation	Elective coronary or vein graft	3.0-7.0mm reference	Balloon or self-expandable; stainless steel nitinol, coated, new metal, covered; tube, welded, coil	Randomized equivalence trial against standard approved stent, 8/9-month angiography and clinical follow-up	
	Conventional design or moderate or severe design deviation	Elective coronary	<2.75mm reference or lesion >35mm	Balloon or self-expandable; stainless steel nitinol, coated, new metal, covered; tube, welded, coil	Randomized superiority trial against balloon angioplasty, 8/9-month angiography and clinical follow-up	

OPC = Objective Performance Criteria; MACE = major adverse cardiac event

REFERENCES

1. Grunkemeier GL, Li HH, Naftel DC, Starr A, Rahimtoola SH. Long-term performance of heart valve prostheses. *Curr Probl Cardiol*. 2000;25:73–154.
2. Dunning J, Gao H, Chambers J, Moat N, Murphy G, Pagano D, Ray S, Roxburgh J, Bridgewater B. Aortic valve surgery: marked increases in volume and significant decreases in mechanical valve use: an analysis of 41,227 patients over 5 years from the Society for Cardiothoracic Surgery in Great Britain and Ireland national database. *J Thorac Cardiovasc Surg*. 2011;142:776–782e3.
3. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J Jr, Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh JK; CoreValve United States Clinical Investigators. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63:1972–1981. doi: 10.1016/j.jacc.2014.02.556.
4. Chen E, Sapirstein W, Ahn C, Swain J, Zuckerman B. FDA perspective on clinical trial design for cardiovascular devices. *Ann Thorac Surg*. 2006;82:773–775. doi: 10.1016/j.athoracsur.2006.07.044.
5. Johnson DM, Sapirstein W. FDA's requirements for in-vivo performance data for prosthetic heart valves. *J Heart Valve Dis*. 1994;3:350–355.
6. US Food and Drug Administration. *Design Considerations for Pivotal Clinical Investigations for Medical Devices: Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff*. Issued on November 7, 2013. <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373750.htm>. Accessed April 27, 2016.
7. Sapirstein W. Designing trials for testing prosthetic cardiac valves: a Food and Drug Administration perspective. *Am Heart J*. 2001;141:861–863. doi: 10.1067/mhj.2001.114980.
8. Division of Cardiovascular and Neurological Devices. *Draft Replacement Heart Valve Guidance, Version 4.1*. In: *Center for Devices and Radiological Health, Food and Drug Administration*. Washington, DC; US Food and Drug Administration. 1994: 1–134.
9. Edmunds LH Jr, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. *Eur J Cardiothorac Surg*. 1996;10:812–816.
10. Grunkemeier GL, Jin R, Starr A. Prosthetic heart valves: objective performance criteria versus randomized clinical trial. *Ann Thorac Surg*. 2006;82:776–780. doi: 10.1016/j.athoracsur.2006.06.037.
11. Wu Y, Butchart EG, Borer JS, Yoganathan A, Grunkemeier GL. Clinical evaluation of new heart valve prostheses: update of objective performance criteria. *Ann Thorac Surg*. 2014;98:1865–1874. doi: 10.1016/j.athoracsur.2014.05.006.
12. O'Malley AJ, Normand SL, Kuntz RE. Application of models for multivariate mixed outcomes to medical device trials: coronary artery stenting. *Stat Med*. 2003;22:313–336. doi: 10.1002/sim.1337.
13. Byrne RA, Serruys PW, Baumbach A, Escaned J, Fajadet J, James S, Joner M, Oktay S, Jüni P, Kastrati A, Sianos G, Stefanini GG, Wijns W, Windecker S. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. *Eur Heart J*. 2015;36:2608–2620. doi: 10.1093/eurheartj/ehv203.
14. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607. doi: 10.1056/NEJMoa1008232.

15. Hahn RT, Pibarot P, Stewart WJ, Weissman NJ, Gopalakrishnan D, Keane MG, Anwaruddin S, Wang Z, Bilsker M, Lindman BR, Herrmann HC, Kodali SK, Makkar R, Thourani VH, Svensson LG, Akin JJ, Anderson WN, Leon MB, Douglas PS. Comparison of transcatheter and surgical aortic valve replacement in severe aortic stenosis: a longitudinal study of echocardiography parameters in cohort A of the PARTNER trial (Placement of Aortic Transcatheter Valves). *J Am Coll Cardiol*. 2013;61:2514–2521. doi: 10.1016/j.jacc.2013.02.087.
16. Grube E, Buellesfeld L, Mueller R, Sauren B, Zickmann B, Nair D, Beucher H, Felderhoff T, Iversen S, Gerckens U. Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving system. *Circ Cardiovasc Interv*. 2008;1:167–175. doi: 10.1161/CIRCINTERVENTIONS.108.819839.
17. Seiffert M, Conradi L, Kloth B, Koschyk D, Schirmer J, Schnabel RB, Blankenberg S, Reichenspurner H, Diemert P, Treede H. Single-centre experience with next-generation devices for transapical aortic valve implantation. *Eur J Cardiothorac Surg*. 2015;47:39–45. doi: 10.1093/ejcts/ezu041.
18. Maxwell YL. FDA Approves 2 New TAVR Systems for High- Risk, Inoperable Patients. June 23rd, 2015. www.tctmd.com/show.aspx?id=129626. Accessed on August 28, 2015.
19. Wenaweser P, Stortecky S, Schwander S, Heg D, Huber C, Pilgrim T, Gloekler S, O'Sullivan CJ, Meier B, Jüni P, Carrel T, Windecker S. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. *Eur Heart J*. 2013;34:1894–1905. doi: 10.1093/eurheartj/ehv086.
20. Arnold SV, Reynolds MR, Lei Y, Magnuson EA, Kirtane AJ, Kodali SK, Zajarias A, Thourani VH, Green P, Rodés-Cabau J, Beohar N, Mack MJ, Leon MB, Cohen DJ; PARTNER Investigators. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation*. 2014;129:2682–2690. doi: 10.1161/CIRCULATIONAHA.113.007477.
21. Amrane H, Porta F, van Boven AJ, Boonstra PW, Hofma SH, Head SJ, Kappetein AP. Transcatheter aortic valve implantation using a direct aortic approach: a single-centre heart team experience. *Interact Cardiovasc Thorac Surg*. 2014;19:777–781. doi: 10.1093/icvts/ivu247.
22. Lansky AJ, Schofer J, Tchetché D, Stella P, Pietras CG, Parise H, Abrams K, Forrest JK, Cleman M, Reinöhl J, Cuisset T, Blackman D, Bolotin G, Spitzer S, Kappert U, Gilard M, Modine T, Hildick-Smith D, Haude M, Margolis P, Brickman AM, Voros S, Baumbach A. A prospective randomized evaluation of the TriGuard™ HDH embolic DEFLECTION device during transcatheter aortic valve implantation: results from the DEFLECT III trial. *Eur Heart J*. 2015;36:2070–2078. doi: 10.1093/eurheartj/ehv191.
23. Kappetein AP, Head SJ, Génèreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB; Valve Academic Research Consortium (VARC)-2. Updated standardized end-point definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg*. 2012;42:S45–S60. doi: 10.1093/ejcts/ezs533.
24. Erlebach M HS, Mylotte D, Leon MB, Serruys PW, Kappetein AP, Martucci G, Genereux P, Windecker S, Lange R, Piazza N. VARC end-point definition compliance rates in contemporary transcatheter aortic valve implantation studies. *EuroIntervention*. 2016;12:375–80.
25. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG; PARTNER 1 Trial Investigators. 5-Year outcomes of transcatheter aortic valve replacement or surgical

- aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–2484. doi: 10.1016/S0140-6736(15)60308-7.
26. Mylotte D, Andalib A, Thériault-Lauzier P, Dorfmeister M, Girgis M, Alharbi W, Chetrit M, Galatas C, Mamane S, Sebag I, Buithieu J, Bilodeau L, de Varennes B, Lachapelle K, Lange R, Martucci G, Virmani R, Piazza N. Transcatheter heart valve failure: a systematic review. *Eur Heart J*. 2015;36:1306–1327. doi: 10.1093/eurheartj/ehu388.
 27. Latib A, Naganuma T, Abdel-Wahab M, Danenberg H, Cota L, Barbanti M, Baumgartner H, Finkelstein A, Legrand V, de Lezo JS, Kefer J, Messika-Zeitoun D, Richardt G, Stabile E, Kaleschke G, Vahanian A, Laborde JC, Leon MB, Webb JG, Panoulas VF, Maisano F, Alfieri O, Colombo A. Treatment and clinical outcomes of transcatheter heart valve thrombosis. *Circ Cardiovasc Interv*. 2015;8.
 28. Généreux P, Cohen DJ, Williams MR, Mack M, Kodali SK, Svensson LG, Kirtane AJ, Xu K, McAndrew TC, Makkar R, Smith CR, Leon MB. Bleeding complications after surgical aortic valve replacement compared with transcatheter aortic valve replacement: insights from the PARTNER I Trial (Placement of Aortic Transcatheter Valve). *J Am Coll Cardiol*. 2014;63:1100–1109. doi: 10.1016/j.jacc.2013.10.058.
 29. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, Kapadia S, Lerakis S, Cheema AN, Gutiérrez-Ibanes E, Munoz-Garcia AJ, Pan M, Webb JG, Herrmann HC, Kodali S, Nombela-Franco L, Tamburino C, Jilaihawi H, Masson JB, de Brito FS Jr, Ferreira MC, Lima VC, Mangione JA, Iung B, Vahanian A, Durand E, Tuzcu EM, Hayek SS, Angulo-Llanos R, Gómez-Doblas JJ, Castillo JC, Dvir D, Leon MB, Garcia E, Cobiella J, Vilacosta I, Barbanti M, R Makkar R, Ribeiro HB, Urena M, Dumont E, Pibarot P, Lopez J, San Roman A, Rodés-Cabau J. Infective endocarditis after transcatheter aortic valve implantation: results from a large multicenter registry. *Circulation*. 2015;131:1566–1574. doi: 10.1161/CIRCULATIONAHA.114.014089.
 30. Ludman PF, Moat N, de Belder MA, Blackman DJ, Duncan A, Banya W, MacCarthy PA, Cunningham D, Wendler O, Marlee D, Hildick-Smith D, Young CP, Kovac J, Uren NG, Spyt T, Trivedi U, Howell J, Gray H; UK TAVI Steering Committee and the National Institute for Cardiovascular Outcomes Research. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. *Circulation*. 2015;131:1181–1190. doi: 10.1161/CIRCULATIONAHA.114.013947.
 31. Holmes DR Jr, Brennan JM, Rumsfeld JS, Dai D, O'Brien SM, Vemulapalli S, Edwards FH, Carroll J, Shahian D, Grover F, Tuzcu EM, Peterson ED, Brindis RG, Mack MJ; STS/ACC TVT Registry. Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA*. 2015;313:1019–1028. doi: 10.1001/jama.2015.1474.
 32. US Food and Drug Administration. *FDA Guidance for Industry and FDA Staff: Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials*. Issued on February 5, 2010. <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071121.pdf>. Accessed April 27, 2016.
 33. Parides MK, Moskowitz AJ, Ascheim DD, Rose EA, Gelijns AC. Progress versus precision: challenges in clinical trial design for left ventricular assist devices. *Ann Thorac Surg*. 2006;82:1140–1146. doi: 10.1016/j.athoracsurg.2006.05.123.
 34. Head SJ, Kaul S, Bogers AJ, Kappetein AP. Non-inferiority study design: lessons to be learned from cardiovascular trials. *Eur Heart J*. 2012;33:1318–1324. doi: 10.1093/eurheartj/ehs099.
 35. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*. 2012;33:176–182. doi: 10.1093/eurheartj/ehs352.
 36. Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angerås O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Kåregren A, Nilsson J, Rob-

- ertson L, Sandhall L, Sjögren I, Ostlund O, Harnek J, James SK; TASTE Trial. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;369:1587–1597. doi: 10.1056/NEJMoa1308789.
37. Thyregod HG, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engström T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Søndergaard L. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol*. 2015;65:2184–2194. doi: 10.1016/j.jacc.2015.03.014.

NOVEL ADAPTATIONS OF TAVI TECHNOLOGY

III

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Mylotte D, Osnabrugge RL, Martucci G, Lange R, Kappetein AP, Piazza N.
EuroIntervention. 2013;9 Suppl:S77-83.
- Chapter 11 TAVI for Failing Surgical Aortic Bioprotheses**
Mylotte D, Bapat V, Dvir D, Kornowski R, Lange R, Piazza, N.
The Clinical Atlas of Transcatheter Aortic Valve Therapies, First Edition. Edited by Serruys PW, Windecker S, Thomas M, Bax J, Piazza N, van Mieghem N, Leon M.
2014 Europa Digital & Publishing.
- Chapter 12 Transcatheter Aortic Valve Implantation Versus Re-do Surgery for Failing Surgical Aortic Bioprosthesis: a Multi-Center Propensity Score Analysis**
Spaziano M, Mylotte D, Thériault-Lauzier P, De Backer O, Søndergaard L, Bosmans J, Debry N, Modine T, Barbanti M, Tamburino C, Sinning JM, Grube E, Nickenig G, Mellert F, Bleiziffer S, Lange R, de Varennes B, Lachapelle K, Martucci G, Piazza N. 2016
EuroIntervention. 2017;13:1149-1156.
- Chapter 13 Transcatheter aortic valve replacement in bicuspid aortic valve disease**
Mylotte D, Lefevre T, Søndergaard L, Watanabe Y, Modine T, Dvir D, Bosmans J, Tchetché D, Kornowski R, Sinning JM, Thériault-Lauzier P, O'Sullivan CJ, Barbanti M, Debry N, Buithieu J, Codner P, Dorfmeister M, Martucci G, Nickenig G, Wenaweser P, Tamburino C, Grube E, Webb JG, Windecker S, Lange R, Piazza N.
J Am Coll Cardiol. 2014;64:2330-9.
- Chapter 14 First-in-human experience with the Medtronic CoreValve Evolut R**
Piazza N, Martucci G, Lachapelle K, de Varennes B, Bilodeau L, Buithieu J, Mylotte D.
EuroIntervention. 2014;9:1260-3.
- Chapter 15 Transcatheter aortic valve replacement: feasibility and Safety.**
Mylotte D, Sudre A, Teiger E, Obadia JF, Spence M, Khamis H, Delhayé C, Koussa M, Debry N, Piazza N, Modine, T.
JACC Cardiovasc Interv. 2016;9:472-80.

TRANSCATHETER HEART VALVE IMPLANTATION FOR FAILING SURGICAL BIOPROSTHESES: TECHNICAL CONSIDERATIONS AND EVIDENCE FOR VALVE-IN-VALVE PROCEDURES

Transcatheter heart valve implantation for failing surgical bioprostheses: technical considerations and evidence for valve-in-valve procedures

Mylotte D, Lange R, Martucci G, Piazza N.
Heart. 2013;99:960-7.

Transcatheter aortic valve implantation (TAVI) represents a novel technology for treating patients with severe symptomatic calcific aortic stenosis at high or prohibitive surgical risk. In patients at excessive surgical risk, TAVI substantially reduces mortality compared to medical treatment,¹ and in high risk cohorts provides similar safety and efficacy to surgical aortic valve (SAV) replacement.²

More recently, the remit of transcatheter heart valve (THV) technology has been expanded beyond that initially conceived: patients at lower surgical risk are being treated despite a lack of evidence in this patient population^{w1}; and novel implantation techniques, such as the transaortic approach, have been developed.^{w2} Perhaps the most notable adaptation of this technology is the treatment of patients with failing surgical bioprosthetic valves. In 2007, Wenaweser and colleagues reported the implantation of a Medtronic CoreValve (Medtronic CV, Luxembourg S.a.r.l.) into a degenerated surgical aortic bioprosthesis.³ Since this first case, numerous transcatheter aortic valve in surgical aortic valve (TAV-in-SAV) procedures have been performed,^{4–7 w3–11} and experienced physicians are adapting current THVs for treatment of failing surgical atrioventricular^{8 w12} and pulmonary bioprostheses.⁹

DESIGN CHARACTERISTICS OF SURGICAL BIOPROSTHESES

Successful valve-in-valve (VIV) procedures are dependent on a thorough understanding of the design characteristics and failure modes of surgical bioprosthetic valves. Surgical bioprostheses are constructed as either stented or stentless valves (figure 1), while the valve leaflets are of xenograft (porcine aortic valve or bovine pericardium) or homograft origin.¹⁰

STENTED VALVES

Stented valves usually consist of a base ring covered by a fabric sewing cuff from which a stent or frame arises to support the valve leaflets (figure 2). The base ring may be circular or scalloped and is constructed from a variety of metal alloys or plastics. The stent frame is designed to reduce the loading stress of repeated valve closure on the tissue leaflets, and is composed of metallic or plastic materials. The base ring and/or frame are usually exteriorised by pericardium or another material that acts as an anchoring suture cuff.

Surgical valve sizing is performed intraoperatively using specific sizing tools, and may be affected by several factors including operator experience and the degree of leaflet resection or annular decalcification performed. The inner base ring diameter greatly influences the postoperative transvalvular gradient, while the outer suture ring diameter determines the maximum size of the valve chosen for implantation. Optimisation of these diameters can be achieved by implanting the valve above the native annulus, as the aortic sinuses can

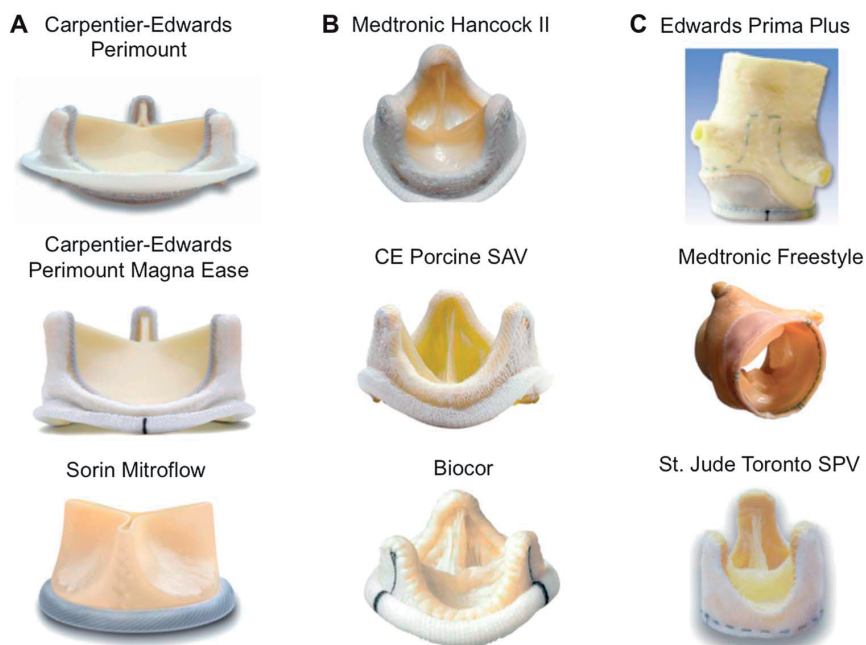


Figure 1 Stented and stentless bioprosthetic surgical valves. (A) Stented pericardial bovine bioprosthetic valves. (B) Stented porcine aortic valve bioprostheses. (C) Stentless bioprosthetic valves.

accommodate the bulky sewing cuff. Therefore, supra-annular implantation affords a larger inner base ring diameter for a given patient. Second and third generation valves, such as the Medtronic Mosaic (Medtronic Inc, Minneapolis, Minnesota, USA), Carpentier-Edwards (CE) Magna (Edwards Lifesciences Inc, Irvine, California, USA), and Sorin Soprano (Sorin Group, Milan, Italy), are designed for supra-annular implantation.

It is of particular importance to note that the manufacturer's labelled valve size does not correspond to the inner base ring diameter. Manufacturers can provide the inner stent diameter for a given labelled valve size. Of note, pannus and calcification can lead to a discrepancy between observed and expected inner stent diameters obtained by echocardiography/multislice CT and manufacturers, respectively.

STENTLESS VALVES

Stentless valves may be of autograft, homograft (a genetically non-identical donor of the same species), or xenograft origin (another species) (figure 1). These valves do not have a base ring or the stent/frame support for the leaflets, but may have a thin basal strip of fabric to cover

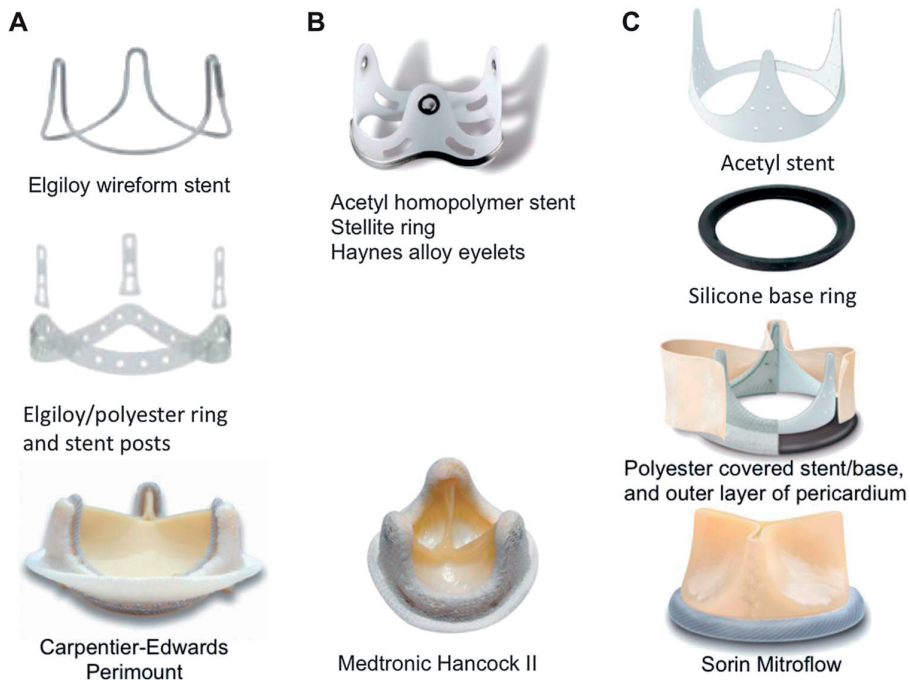


Figure 2 Design characteristics of stented bioprosthetic valves. (A) Carpentier-Edwards Perimount bovine pericardial valve. (B) Medtronic Hancock II porcine aortic valve. (C) Sorin Mitroflow bovine pericardial valve.

Understanding the dimensions of surgical bioprostheses is of crucial importance to the success of TAV-in-SAV procedures. The nomenclature of these measurements is based on the anatomical construction of the valve (figure 3). The inner base ring diameter (also known as the inner stent diameter) is the distance between the inner surfaces of the base ring. In the context of TAV-in-SAV procedures, this diameter represents the maximum available diameter for TAVI, as the ring is rigid and relatively non-distensible. The outer base ring diameter (outer stent diameter) is the distance between the outer surfaces of the base ring and does not include the thickness of the covering cloth (sewing cuff). The outer sewing ring diameter (external diameter) is the distance between the outer undisturbed sewing cuff surfaces.

the inflow tract and enable suturing of the valve into the site of the excised native valve. These valves are predominately used in the aortic position, as stentless mitral valves have found little clinical utility due to difficulty in insertion and poor durability.^{w13} Stentless valves were designed to improve important in small aortic roots.^{w15} To date, clinical postimplantation transvalvular gradients and flow characteristics compared to stented valves.^{w14} Theoretically, these characteristics are particularly studies have not demonstrated superiority of stentless over stented valves, though they have identified extensive aortic root calcification as a potential drawback to stentless valve reoperation.^{w16} The labelled size of stentless valves typically

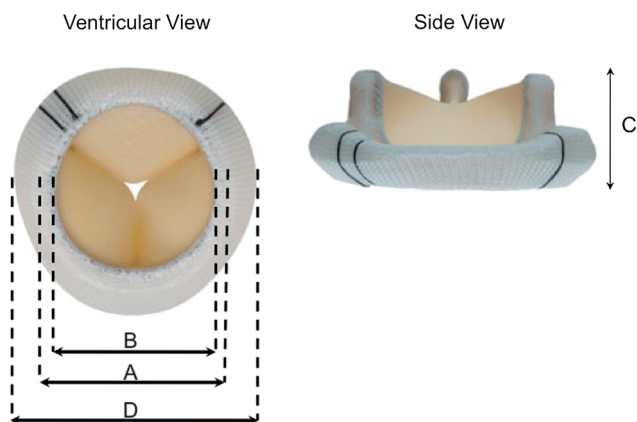


Figure 3 The dimensions of stented surgical bioprostheses. Ventricular and side views of a stented bioprosthesis: (A) outer base ring diameter; (B) inner base ring diameter; (C) prosthesis height; and (D) outer sewing ring diameter.

corresponds to the valve's outer diameter, though the inner diameter and height are usually available. The absence of a rigid base ring with these prostheses suggests that they are more compliant than stented valves when performing VIV procedures.

MECHANISMS OF BIOPROSTHETIC VALVE FAILURE

Compared to mechanical surgical valves, bioprosthetic valves are more susceptible to time dependant structural failure.^{w17} The aetiology of bioprosthetic valve dysfunction has been described in detail elsewhere.¹¹ Valve failure results from malfunction of the leaflets, the supporting structures (base ring or stent/frame), or both, and can be influenced by the design features of the valve (physical and biochemical), host metabolic pathways, and the mechanical loading stress exerted on the valve. Durability of bioprosthetic valves results from resistance to structural failure in response to repetitive cycling and resistance to calcification over time, particularly in young patients. In most cases, valve failure can be attributed to wear and tear, leaflet calcification, pannus formation, in situ thrombosis, or infective endocarditis.

Leaflet tissue deterioration is the most common aetiology of bioprosthetic valve failure.¹¹ Leaflet dysfunction is commonly precipitated by calcium deposition, which tends to occur at sites of greatest leaflet flexion and stress: the basal and commissural attachment points. All bioprosthetic valves undergo glutaral-dehyde fixation which promotes leaflet durability by enhancing collagen cross-linking and renders the heterograft biologically inert. However, residual glutaral-dehyde can promote calcium phosphate deposition and upregulate graft

and host pro-inflammatory pathways. Anticalcification processes (eg, Edwards TheraFix, Medtronic AOA) reduce calcium binding and improve leaflet longevity.

The development of inflammatory tissue, rich in fibroblasts, at the host-graft interface is known as pannus. Most valves exhibit some evidence of pannus; however, marked pannus formation can induce valve dysfunction if it extends and fixes the leaflet cusps. Valve thrombosis and endocarditis are uncommon causes of valve failure.

BIOPROSTHESES FAILURE: AN EMERGING CLINICAL PROBLEM?

Recent trends suggest that the relative use of surgical bioprosthetic valves has increased substantially in the last decade.¹² The advantage of surgical bioprosthetic valves over mechanical alternatives is the avoidance of long term anticoagulation, and therefore the associated risk of bleeding.^{w17} In contrast, the requirement for reoperation is greater with bioprosthetic valves.^{w17} Bioprosthetic valves have therefore traditionally been used in elderly patients, where the risk of bleeding is greatest, and where the life expectancy of the bioprosthesis is expected to exceed that of the patient. However, recent preclinical and clinical studies suggest reducing the age cutoff for bioprosthetic aortic valves from 65 to 60 years.^{w18} The actuarial freedom from reoperation for a degenerated bioprosthetic valve is approximately 95%, 90%, and 70% at 5, 10, and 15 years, respectively.¹⁰ Therefore, as the population ages and a greater proportion of younger patients are treated with bioprosthetic valves, we can expect to encounter a growing number of patients with degenerated surgical bioprostheses requiring reoperation.

Important comorbid conditions such as diabetes mellitus, renal impairment, congestive heart failure, pulmonary hypertension, and coronary and peripheral vascular disease are more common in redo cohorts.^{w19} Nevertheless, the mortality risk associated with redo valve surgery has decreased over the last number of decades. Operative mortality for an elective redo aortic valve surgery ranges from 2–7% and can be comparable to the primary valve surgery in low risk cases.^{w20 w21} In contrast, mortality can be as high as 30% in high risk and non-elective patients.^{w20–22} Redo valve surgery can also be associated with significant morbidity including blood transfusion, and delayed wound healing, mobilisation, and hospital discharge.

TAV-IN-SAV PROCEDURES

In selected cases, where the risk of redo surgery for a failing surgical bioprosthesis is deemed excessive by a dedicated heart team, TAV-in-SAV procedures offer a less invasive and potentially safer alternative to conventional surgery. As with TAVI for native aortic valve stenosis, patient selection is critical to the success of these procedures, and therefore the involvement of a team of interventional cardiologists, cardiac surgeons, cardiac anaesthetists, and imaging

specialists is essential. Currently, three THVs have been successfully implanted into failing bioprostheses: the Edwards Sapien/XT valve, the Medtronic CoreValve, and the Medtronic Melody valve.

PRECLINICAL STUDIES

Several important preclinical investigations have been undertaken to test the very concept of TAV-in-SAV¹³ procedures.^{w23 w24} Boudjemline *et al* reported the first successful VIV experience, having implanted a bovine jugular valve inside a surgically sited Medtronic Mosaic mitral valve in a sheep model.¹³ Subsequently, successful transapical implantation of the commercial Edwards Sapien THV inside CE porcine aortic and mitral valves was demonstrated in pigs.^{w24}

CLINICAL EXPERIENCE TAV-IN-SAV

First performed in 2007,⁵ TAV-in-SAV procedures represent innovative adaptation of TAVI technology. In the aortic position, TAVI has been performed within both stented and stentless surgical bioprosthetic valves. The Edwards Sapien/XT valve has been implanted using transfemoral, transapical and transaxillary approaches^{4 5 7 w3 w4 w8 w11} (figure 4). The transapical approach was initially the preferred strategy using the Edwards Sapien/XT valve, as greater stability and coaxial implantation of the THV was achieved,^{4 w8} though transfemoral procedures are becoming more common.¹² Medtronic CoreValve TAV-in-SAV procedures are performed via transfemoral, transaxillary, and direct transaortic approaches (figure 5).^{3 6 w6 w9}

Overall, results from small case series of high postprocedural gradients. Intuitively, valve underexpansion should also adversely affect leaflet and stent durability. In contrast, the rigid base ring of a stented valve may provide the necessary platform to produce a nearly circular TAVI that allows for optimal leaflet geometry and durability. The largest TAV-in-SAV series published to date has TAV-in-SAV procedures in high risk patients suggest an acceptable short term safety profile (75–100% 30 day survival).^{4 5 7 14 w5 w8 w10} Similar outcomes have been reported following TAV-in-SAV for stented and stentless (homograft and xenograft) valves; however, insufficient data are available to compare outcomes from these different valve designs. Significant paravalvular aortic regurgitation, which is associated with adverse outcomes in TAVI for de novo aortic stenosis, occurs infrequently in TAV-in-SAV procedures. Importantly, the acute haemodynamic results achieved with TAV-in-SAV procedures are suboptimal (approximately 20 mm Hg) compared to TAVI for de novo aortic valve stenosis (usually 10 mm Hg (see online supplementary table S1)). Thus, longer term follow-up is required to confirm the efficacy of these interventions, particularly if these procedures are to be considered in younger patients. An inability to completely expand the THV inside the rigid base ring

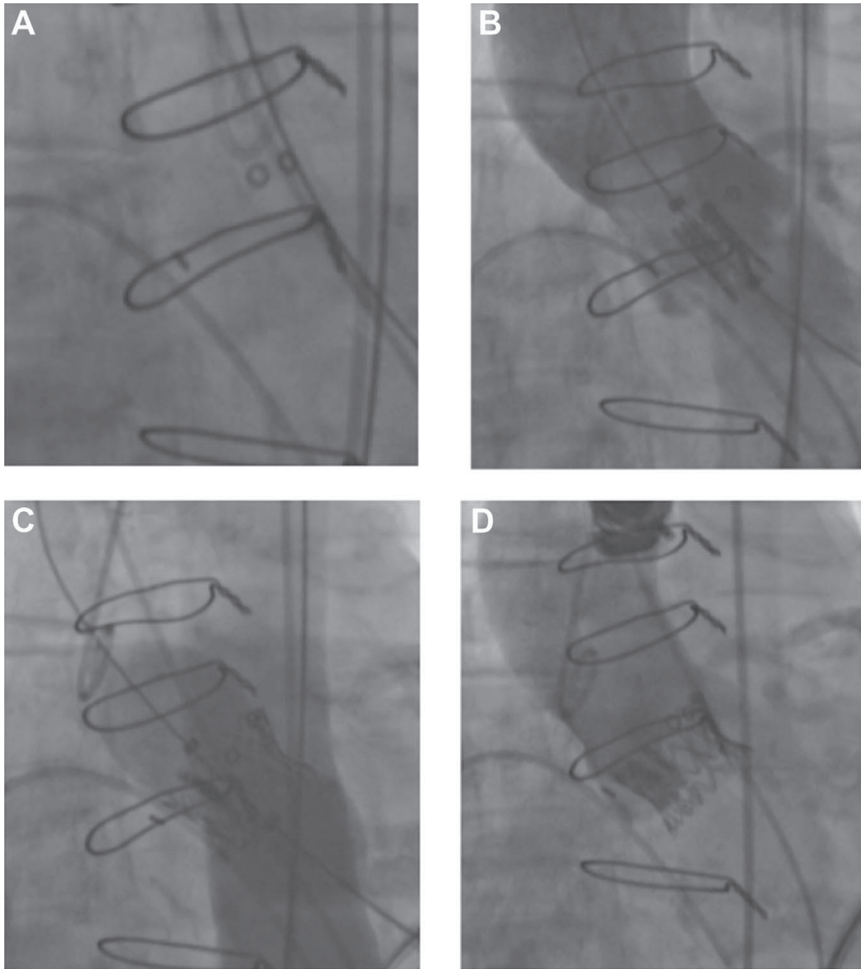


Figure 4 Edwards Sapien TAV-in-SAV procedure. Transapical implantation of a 23 mm Edwards Sapien TAV inside a 21 mm Medtronic Mosaic bioprosthesis. (A) Fluoroscopic identification of the Medtronic Mosaic valve. (B) Positioning of the Edwards Sapien valve. (C) Deployment of the Edwards SAPIEN valve. (D) Final contrast aortography. Images courtesy of German Heart Centre, Munich.

of the SAV may be responsible for these reported 100% technical procedural success, one periprocedural death due to low output cardiac failure, and transvalvular mean gradients ≥ 20 mm Hg in 44% of patients.^{w10} Mortality at 30 days was 17%.

A specific concern relating to TAV-in-SAV procedures is the risk of ostial coronary occlusion with bioprosthetic valves where tissue is mounted external to the valve frame or in prostheses with no stent frame (stentless valves).⁵ In particular, THV deployment within the Mitroflow valve (Sorin Group, Burnaby, BC, Canada), where the leaflet tissue is mounted externally over the stent, has been associated with ostial left main stem occlusion.^{w27} Anecdotal

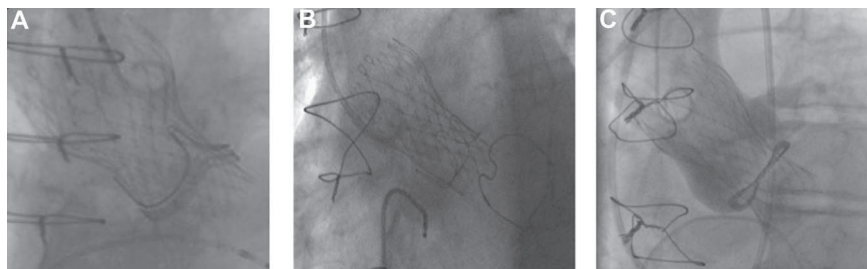


Figure 5 Medtronic CoreValve transcatheter aortic valve in surgical aortic valve (TAV-in-SAV) procedures. Medtronic CoreValve prosthesis implantation within (A) Edwards Perimount, (B) Carpentier-Edwards Porcine Supra-Annular Valve, and (C) Sorin Soprano bioprosthesis. Images courtesy of German Heart Centre, Munich.

evidence suggests that supravulvar implantation, a short distance between the coronary ostia and the bioprosthesis, and extensive pannus formation are risks for ostial coronary occlusion.

TAV in surgical mitral valve

To date, only the Edwards Sapien/XT valve has been implanted into failing surgical bioprostheses in the mitral position.^{4 8 15 w5 w28 w29} The Medtronic CoreValve is not suitable for this purpose due to its height. The majority of cases have been performed via the transapical approach, although transvenous transseptal and open direct visualisation transatrial approaches have been described. In the largest series available (n=11), Cheung and colleagues report 100% 30 day survival in a high risk cohort with a mean age of 81 ± 5 years, and a mean Society of Thoracic Surgeons (STS) mortality risk score of $16.1\% \pm 5.8\%$.¹⁵ The median postprocedural transvalvular gradient was 7 mm Hg. The narrow range of currently available THV sizes relative to surgical mitral bioprosthetic valves represents an important limitation for TAV in surgical mitral valve (TAV-in-SMV) procedures. Surgical mitral prostheses range from 25–31 mm; however, given that the 29 mm (internal stent diameter 26–28 mm) and 31 mm (internal stent diameter 28–30 mm) valves are the most commonly implanted, the largest Edwards Sapien valve (29 mm) may be unsuitable for use in a number of patients.

TAV in surgical annuloplasty ring

Surgical mitral valve repair using an annuloplasty ring is frequently performed in patients with severe mitral regurgitation (MR). In patients with ischaemic MR, undersizing of the annuloplasty ring can result in recurrent MR in a significant proportion of patients. Animal experiments have demonstrated the feasibility of TAV in surgical annuloplasty ring (TAV-in-SAR) procedures using the Edwards Sapien/XT valve^{w30} or the Melody valve.^{w31} Successful transapical TAV-in-SAR procedures have also been performed in high risk patients using the Edwards Sapien/XT valve.¹⁶

TAV in surgical tricuspid valve

Both the Edwards Sapien/XT^{4 8 w12} and Medtronic Melody^{w32} THVs have been successfully implanted into failing bioprostheses in the tricuspid position. Percutaneous transvenous access using the femoral, subclavian, and jugular veins, and open direct visualisation transatrial approaches, have been described. The largest reported series (n=15) reported significant reductions in transvalvular gradients (12.9 to 3.9 mm Hg) postimplantation of the Medtronic Melody valve within failing surgical tricuspid bioprostheses, without significant procedural complications.¹⁷

TAV in surgical pulmonary valve

The first VIV procedures related to implantation of the Medtronic Melody valve. This valve was implanted in the pulmonary position for failing valved conduits that had been used for right ventricular outflow tract reconstruction.¹⁸ The first large series using this valve (n=58) demonstrated significant improvement in postoperative transvalvular gradients, right ventricular end-diastolic volume (EDV) and effective stroke volume, and increased left ventricular EDV.¹⁸ No significant procedural complications or 30 day mortality was reported. The Edwards Sapien/XT valve has also been used in this position with promising short and medium term (median 22.5 months) results.¹⁵

TAV-IN-SAV: TECHNICAL CONSIDERATIONS

Transcatheter valve sizing

Details of the primary valve surgery, including the type and size of prosthesis used, the site of implantation (annular or supra-annular), and the degree of aortic root calcification are crucial to the success of TAV-in-SAV procedures. Reference tables are available for consultation if the inner base ring diameter of the bioprosthesis is not listed.¹⁰ However, the availability of these details does not diminish the key role of multimodal imaging in THV size selection. Multidetector CT and transoesophageal and transthoracic echocardiography should be used to establish the mode of bioprosthesis failure, and to determine the presence of severe calcification or pannus formation that could result in a discrepancy in the manufacturer listed inner base ring diameter. The presence of valve thrombosis or infective endocarditis is a contraindication for VIV procedures.

Much debate surrounds the choice of imaging modality for optimal measurement of the non-circular aortic valve annulus and THV sizing. Transoesophageal echocardiography is the most practical and frequently used modality; however, two dimensional measurements of the three dimensional aortic annulus can lead to underestimation of the true dimensions of the annulus.^{w33} This may result in valve undersizing and increase the risk of paravalvular aortic regurgitation.^{w34} Multidetector CT reconstruction of the annulus orthogonal to the centre

axis of the left ventricular outflow tract allows for the assessment of minimal and maximal diameter, circumference, and area measurements. As such, multidetector CT is becoming the default imaging modality to assess aortic annular dimensions.

In the setting of native aortic valve stenosis, TAVIs are oversized relative to the annulus diameter by 10–30%. Oversizing creates enough interference between the bioprosthesis and the aortic valvar complex to ensure adequate anchoring and sealing. It is not known if sizing rules should differ for TAV-in-SAV cases, or indeed if they should differ between non-distensible stented valves and somewhat distensible stentless valves. The authors continue to advocate manufacturer based sizing principles in the absence of any firm evidence. Other investigators have suggested that the TAVI external diameter does not necessarily have to be larger than the bioprosthesis internal diameter and can even match the internal diameter.⁷

One important preclinical study using a pulse generator evaluated the haemodynamic consequences of implanting a 23 mm TAVI within degenerated small sized CE Perimount bioprostheses (19, 12, and 23 mm).^{w23} In all cases, the rigid base ring and stent posts prevented complete expansion of the THV. Postimplantation transvalvular gradients were significantly reduced in the 23 mm and 21 mm bioprostheses; however, there was no improvement within the 19 mm Perimount bioprosthesis, which also demonstrated considerable central aortic regurgitation. More recently, preliminary data suggest that the balloon expandable Edwards Sapien/XT valve may yield greater postoperative transvalvular gradients in small surgical bioprostheses (<20 mm) than the self-expanding thinner strut Medtronic CoreValve.^{w35} The difference in postoperative gradients is probably a reflection of the intra-annular versus supra-annular leaflet location of the Edwards Sapien/XT versus Medtronic CoreValve prosthesis.

The predilatation conundrum

Balloon aortic valvuloplasty (BAV) is routinely performed before TAVI in native aortic valve stenosis. The rationale for aortic valve predilatation includes improving the annular seating space and assisting maximal THV expansion. In TAV-in-SAV procedures, practice patterns are more heterogeneous. The clinical utility of dilating a non-distensible stented valve can be debated. Where severe calcification is the mode of failure, there is probably some merit in performing preimplantation predilatation; however, this may increase the risk of annulus rupture in stentless valves, or the risk of embolisation of friable material. In light of these potential risks, most experienced operators avoid preimplantation BAV unless deemed an absolute necessity (see online supplementary table S1). The American College of Cardiology/American Heart Association and European Society of Cardiology valvular heart disease guidelines contraindicate percutaneous balloon interventions in the treatment of stenotic aortic bioprostheses,^{w36 w37} and so routine preimplantation BAV is not recommended for VIV procedures.

Surgical bioprosthetic valve recognition

Stented surgical bioprostheses can be recognised by identifying the radiopaque components of the base ring and/or stent on fluoroscopy (figure 6).^{19 20} If the base ring is metallic, one should assess its shape (circular, boat, or scallop shaped) and ascertain if it is open or closed. If the stent/frame is radiopaque, assess its design, shape and the angle it arises from the base ring. In some cases, the stent/frame is radiolucent except for circular eyelets near the apices (Medtronic Hancock II or Mosaic prosthesis). Stentless valves are not radiopaque and cannot be identified in the catheterisation laboratory; calcification of the prosthesis, if present, may provide anatomical landmarks for valve positioning.

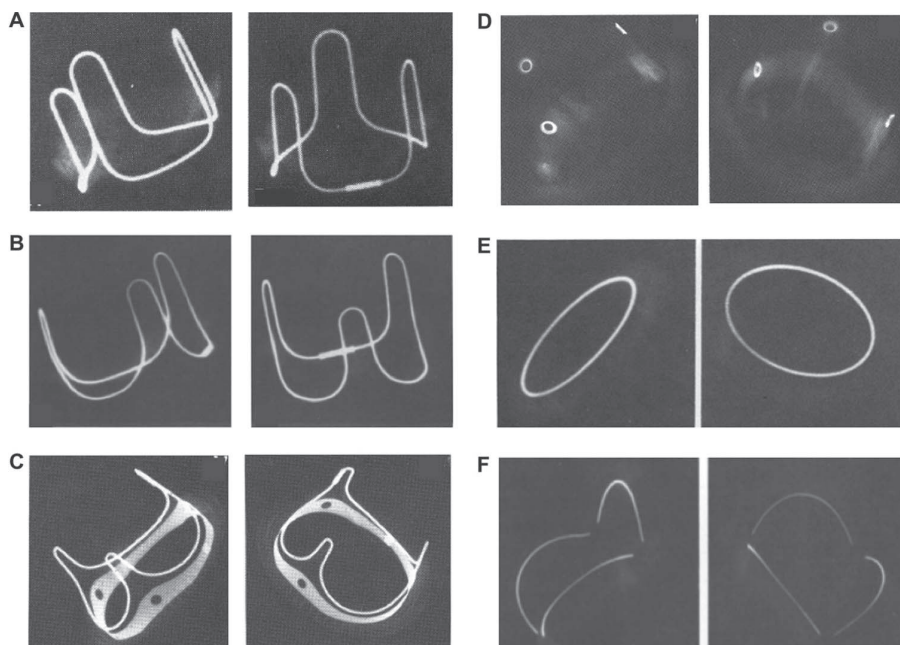


Figure 6 Fluoroscopic identification of stented surgical bioprostheses. (A) The Carpentier-Edwards (CE) Porcine Standard valve has a radiopaque wire that outlines the stent posts (U shaped loops) and the base ring. (B) The CE Porcine Supra-Annular Valve is similar to the CE Porcine Standard valve (A) except that it has less defined transition angles between the base ring and stent posts. (C) The CE Pericardial valve has a flattened radiopaque base ring with three holes, and a narrow wire that outlines the three stent posts and the base ring. (D) The Medtronic Mosaic valve has radiopaque metal eyelets only. (E) The Hancock standard valve has a radiopaque Haynes alloy flat base ring. (F) The Ionescu-Shiley low profile valve has three narrow wire arcs separated by radiolucent areas. Figures 6A–E are reprinted, with permission, from Mehlman *et al.*^{19 20}

THV positioning

As with TAVI for native aortic valve stenosis, implant positioning is crucial to procedural success. If radiopaque, the surgical bioprosthesis offers stable markers for positioning the TAV (figure 4). If radiolucent, THV positioning is performed in the usual fashion using aortic an-

giography, transoesophageal echocardiography, a pigtail catheter lying in the base of the prosthetic leaflets, and/or identification of calcific spots. The fluoroscopic viewing angle should be perpendicular to the base ring, or selected in the usual fashion using contrast angiography. If possible, the THV should be coaxial within and lie 3–4 mm below the base ring of the surgical prosthesis. Transapical implantation may offer superior coaxial alignment than retrograde access; however, both access routes have been associated with acceptable procedural success rates.^{4 7}

Significant aortic regurgitation, a common occurrence with degenerated bioprosthetic valves, may compromise the stability of the THV during implantation and increase the risk of valve embolisation.⁴ In such cases, rapid pacing is advised to reduce cardiac output and stabilise the position of the THV. Postimplant dilation may be required in cases of significant paravalvular aortic regurgitation or underexpansion of the prosthesis associated with elevated transvalvular gradients.

FUTURE PERSPECTIVES: CHALLENGES AND OPPORTUNITIES

To date, the published results of VIV procedures have been encouraging, and advocate the continued development of this innovative adaptation of THV technology. However, there remain important knowledge gaps that must be addressed: patient selection criteria; VIV sizing criteria; understanding the clinical impact of elevated transvalvular gradients; potential galvanic (metal-on-metal) corrosion; the potential for THV thrombosis following VIV procedures; and durability issues. Dedicated prospective trials are required to further our understanding of these procedures and are currently being considered by the THV manufacturers in order to secure expanded clinical indications for their products.

Although in their infancy, VIV procedures have the potential to revolutionise the manner in which we treat valvular heart disease. Less invasive and perhaps safer redo procedures may mitigate against the upfront use of metallic surgical valves and their associated requirement for anticoagulation. Indeed, anecdotal evidence suggests that in specific cases, cardiac surgeons are already applying a strategy of implanting a bioprosthetic surgical valve for patients <60 years old, with the intention of performing a subsequent VIV procedure if required. This strategy, although appealing on many fronts, requires further study. Undoubtedly, the future of VIV procedures lies in the development of customised surgical bioprosthesis and/or dedicated VIV transcatheter aortic, mitral, and pulmonary valves. The unrelenting evolution of transcatheter valve technology suggests that this future may soon become a reality.

CONCLUSIONS

An ageing population, longer life expectancy, and increased use of bioprosthetic valves has led to an increase in elderly and high risk patients with degenerated surgical bioprostheses. Transcatheter implantation of commercially available TAVs represents an emerging and potentially advantageous alternative to redo surgery. Indeed, TAV-in-SAV procedures have the potential to become the standard of care for structural valve dysfunction, though large prospective comparisons with long term follow-up are fundamental to the development of the field.

Contributors All authors have contributed significantly to the submitted work.

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Transcatheter heart valve implantation for failing surgical prostheses: key points

Bioprosthetic surgical aortic valve construction

- ▶ A thorough understanding of the design characteristics of bioprosthetic surgical aortic valves is crucial for the success of transcatheter aortic valve in surgical aortic valve (TAV-in-SAV) procedures.
- ▶ Stented valves consist of a base ring covered by a fabric sewing cuff from which a stent or frame arises to support the valve leaflets.
- ▶ The inner base ring diameter (inner stent diameter) is the distance between the inner surfaces of the base ring, and represents the maximum available diameter for TAV implantation.
- ▶ Stentless valves do not have a base ring or the stent/frame support for the leaflets, and may be of heterograft, autograft or homograft origin. TAV-in-SAV procedures
- ▶ Both the Edwards Sapien/XT and Medtronic CoreValve have been used successfully for TAV-in-SAV procedures.
- ▶ Results from small case series suggest TAV-in-SAV implantation is associated with acceptable medium term results with an acceptable safety profile (75–100% 30 day survival).
- ▶ Dedicated prospective trials with longer term follow-up are required to confirm the efficacy of TAV-in-SAV procedures. Other valve-in-valve procedures
- ▶ The Edwards Sapien/XT transcatheter heart valve has been implanted into failing surgical bioprostheses in the mitral, tricuspid and pulmonary positions with acceptable medium term outcomes.
- ▶ The Edwards valve has also been successfully implanted into failing surgical annuloplasty rings in the mitral and tricuspid positions.

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REFERENCES

1. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012;366:1696–704.
 - ▶ PARTNER cohort B trial: two-year outcomes. A randomised trial of TAV implantation versus medical therapy for severe symptomatic native aortic stenosis in patients at excessive surgical risk.
2. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686–95.
 - ▶ PARTNER cohort A trial: two-year outcomes. A randomised trial of TAV implantation versus SAV replacement for severe symptomatic native aortic stenosis in high risk surgical patients.
3. Wenaweser P, Buellesfeld L, Gerckens U, et al. Percutaneous aortic valve replacement for severe aortic regurgitation in degenerated bioprosthesis: the first valve in valve procedure using the Corevalve Revalving system. *Catheter Cardiovasc Interv* 2007;70:760–4.
 - ▶ Case report of the first TAV-in-SAV procedure.
4. Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation* 2010;121:1848–57.
 - ▶ The first published case series of valve-in-valve procedures, including TAV implantation for failing aortic, mitral, pulmonary and tricuspid bioprostheses.
5. Piazza N, Bleiziffer S, Brockmann G, et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 2). *JACC Cardiovasc Interv* 2011;4:733–42.
 - ▶ A large case series of TAV-in-SAV procedures and review of available literature.
6. Descoutures F, Himbert D, Radu C, et al. Transarterial Medtronic CoreValve system implantation for degenerated surgically implanted aortic prostheses. *Circ Cardiovasc Interv* 2011;4:488–94.
7. Latib A, Ielasi A, Montorfano M, et al. Transcatheter valve-in-valve implantation with the Edwards SAPIEN in patients with bioprosthetic heart valve failure: the Milan experience. *EuroIntervention* 2012;7:1275–84.
 - ▶ A recently published series of transfemoral Edwards Sapien TAV-in-SAV procedures.
8. Cerillo AG, Chiamonti F, Murzi M, et al. Transcatheter valve in valve implantation for failed mitral and tricuspid bioprosthesis. *Catheter Cardiovasc Interv* 2011;78:987–95.
9. Boone RH, Webb JG, Horlick E, et al. Transcatheter pulmonary valve implantation using the Edwards SAPIEN transcatheter heart valve. *Catheter Cardiovasc Interv* 2010;75:286–94.
10. Piazza N, Bleiziffer S, Brockmann G, et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 1). *JACC Cardiovasc Interv* 2011;4:721–32.
 - ▶ A comprehensive review of the design and failure modes of SAVs and the procedural steps involved in TAV-in-SAV procedures.
11. Roselli EE, Smedira NG, Blackstone EH. Failure modes of the Carpentier-Edwards pericardial bioprosthesis in the aortic position. *J Heart Valve Dis* 2006;15:421–7.
12. Brown JM, O'Brien SM, Wu C, et al. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg* 2009;137:82–90.
13. Boudjemline Y, Pineau E, Borenstein N, et al. New insights in minimally invasive valve replacement: description of a cooperative approach for the off-pump replacement of mitral valves. *Eur Heart J* 2005;26:2013–17.

14. Chan PH, Di Mario C, Davies SW, et al. Transcatheter aortic valve implantation in degenerate failing aortic homograft root replacements. *J Am Coll Cardiol* 2011;58:1729–30.
15. Cheung AW, Gurvitch R, Ye J, et al. Transcatheter transapical mitral valve-in-valve implantations for a failed bioprosthesis: a case series. *J Thorac Cardiovasc Surg* 2011;141:711–15.
16. de Weger A, Ewe SH, Delgado V, et al. First-in-man implantation of a trans-catheter aortic valve in a mitral annuloplasty ring: novel treatment modality for failed mitral valve repair. *Eur J Cardiothorac Surg* 2011;39:1054–6.
17. Roberts PA, Boudjemline Y, Cheatham JP, et al. Percutaneous tricuspid valve replacement in congenital and acquired heart disease. *J Am Coll Cardiol* 2011;58:117–22.
18. Khambadkone S, Coats L, Taylor A, et al. Percutaneous pulmonary valve implantation in humans: results in 59 consecutive patients. *Circulation* 2005;112:1189–97.
19. Mehlmán DJ. A guide to the radiographic identification of prosthetic heart valves: an addendum. *Circulation* 1984;69:102–5.
 - ▶ An important guide to the fluoroscopic identification of bioprosthetic SAVs.
20. Mehlmán DJ, Resnekov L. A guide to the radiographic identification of prosthetic heart valves. *Circulation* 1978;57:613–23.

**FAILING SURGICAL
BIOPROSTHESIS IN AORTIC
AND MITRAL POSITION**

Failing surgical bioprosthesis in aortic and mitral position

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ABSTRACT

Bioprosthetic heart valves are preferentially selected over mechanical prostheses in the majority of patients undergoing valve replacement surgery. These bioprostheses are prone to structural degeneration, and hence an increasing number of patients are presenting with bioprosthetic failure requiring redo surgery. In selected high-risk cases, successful implantation of a transcatheter aortic valve (TAV) within the failing bioprosthetic surgical aortic valve (SAV) or mitral valve (SMV) has been performed. Herein, we summarise the available evidence, describe the technical challenges, and highlight important procedural considerations for these innovative interventions.

Keywords: aortic stenosis, surgical bioprosthesis, TAVI, TAV-in-SAV, TAVR, valve-in-valve, valve replacement surgery

INTRODUCTION

In the 1970s, commercialisation of bioprosthetic surgical heart valves revolutionised the treatment of aortic and mitral valve disease. These devices afforded elderly patients and others at considerable risk of bleeding the opportunity for curative surgical aortic or mitral valve replacement. Today, these prostheses are more frequently used than their mechanical equivalent¹. Indeed, recent guidelines have recognised bioprosthetic heart valves to be the standard of care for patients ≥ 60 years of age requiring aortic valve replacement and those ≥ 65 years old undergoing mitral valve replacement².

In the last decade we have seen another paradigm shift in the treatment of patients with valvular heart disease. Transcatheter aortic valve implantation (TAVI) has again extended the promise of curative intervention to patients with severe aortic stenosis (AS) at excessive risk for aortic valve replacement³. As with most medical innovations, the remit of this technology has been extended beyond that initially conceived.

Perhaps the most interesting adaptation of TAVI is the treatment of patients with degenerative surgical bioprostheses. Most recently, the Medtronic CoreValve® (Medtronic, Minneapolis, MN, USA) has received Conformité Européenne approval for implantation within failing aortic bioprosthetic valves. This article aims to provide an update on the available evidence supporting this innovative use of transcatheter heart valve (THV) technology.

SURGICAL BIOPROSTHESIS FAILURE

Bioprosthetic heart valves are increasingly preferred to mechanical prostheses as lifelong anticoagulation can be avoided. This advantage is mitigated by structural deterioration of bioprosthetic valves, which have an average lifespan of between 12 and 20 years^{4,5}. Improved bioprosthetic valve design has reduced the rate of structural deterioration and has resulted in these valves being used in younger patient cohorts². Hence, patients with failing surgical bioprostheses are more frequently encountered. Redo aortic or mitral valve replacement surgery is the treatment of choice for these patients. Operative mortality for an elective redo aortic valve surgery is between 2% and 7%, and is comparable to the primary valve surgery in low-risk cohorts⁶. However, a significant number of high-risk patients are declined redo surgery, or have protracted postoperative recovery and adverse outcomes⁷. In these cases, implantation of a transcatheter aortic valve (TAV) within a surgical aortic valve (SAV) or mitral valve (SMV) may offer a less invasive and effective alternative to conventional surgery (**Figure 1**).

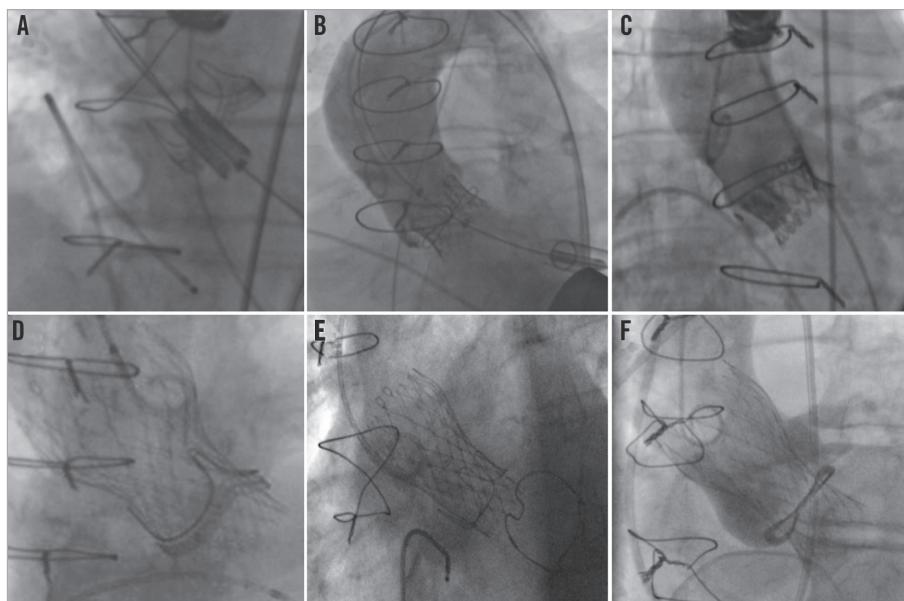


Figure 1 Case examples of TAV-in-SAV procedures. Transapical implantation of an Edwards SAPIEN valve inside: (A) Carpentier-Edwards Perimount; (B) Sorin Soprano; and (C) Medtronic Mosaic. Implantation of a Medtronic CoreValve within (D) Edwards Perimount; (E) Carpentier-Edwards porcine supra-annular valve; and (F) Sorin Soprano.

CLASSIFICATION OF SURGICAL BIOPROSTHETIC VALVES

Understanding the construction of surgical bioprostheses and their failure modes is fundamental to successful valve-in-valve (VIV) procedures. These valves may be classified as stented or stentless, with the stented prostheses being more frequently encountered. Stented valves usually have a rigid base ring from which a stent or frame arises to support the valve leaflets (**Figure 2**)⁸. The base ring and support frame are covered by pericardium or a synthetic material that protects the frame, and acts as an anchoring suture cuff. The base ring and frame are composed of metal alloys or plastics and can be radiolucent or radiopaque. The valve leaflets are of xenograft or homograft origin, and can be mounted inside (PERI-MOUNT™ [Edwards Lifesciences, Irvine, CA, USA], Epic [St. Jude Medical, St. Paul, MN, USA], Hancock II® [Medtronic, Minneapolis, MN, USA]) or outside (Mitroflow® [Sorin Group, Milan, Italy] Trifecta™ [St. Jude Medical, St. Paul, MN, USA]) the frame (**Figure 3**). Bioprosthetic valves are usually placed at the level of the native aortic annulus though specific supra-annular designs are available (Magna [Edwards Lifesciences], Mosaic® [Medtronic]) to maximise the effective orifice area.

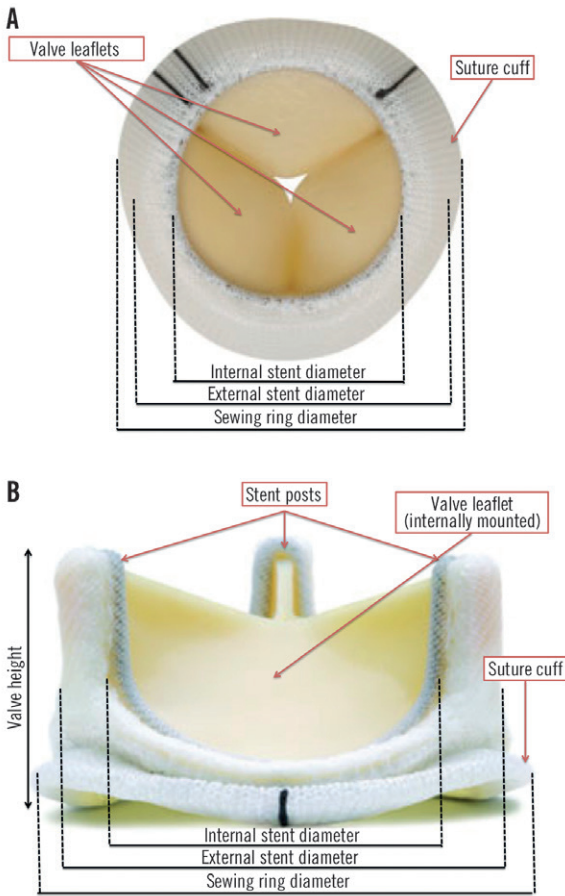


Figure 2 Carpentier-Edwards Perimount Magna Ease aortic valve. A & B) Dimensions and design features of a stented bioprosthetic valve.

Stentless valves do not have a base ring or frame to support the leaflets and are of heterograft, autograft or homograft origin (**Figure 4**). A fabric suture cuff covers the inflow portion of the valve, thereby enabling fixation at the site of the excised native valve.

SIZE LABELLING OF SURGICAL BIOPROSTHESIS

The labelled size of stented surgical bioprostheses corresponds to the external diameter of the base ring rather than the internal stent diameter that is relevant for THV sizing for VIV procedures (**Figure 2**). The internal stent diameter represents the available diameter for THV implantation within the relatively non-distensible base ring. Tables detailing these diameters in all surgical bioprostheses are available⁹; however, pannus and calcification can lead to a discrepancy between observed and expected inner stent diameters. Thus, pre-implantation

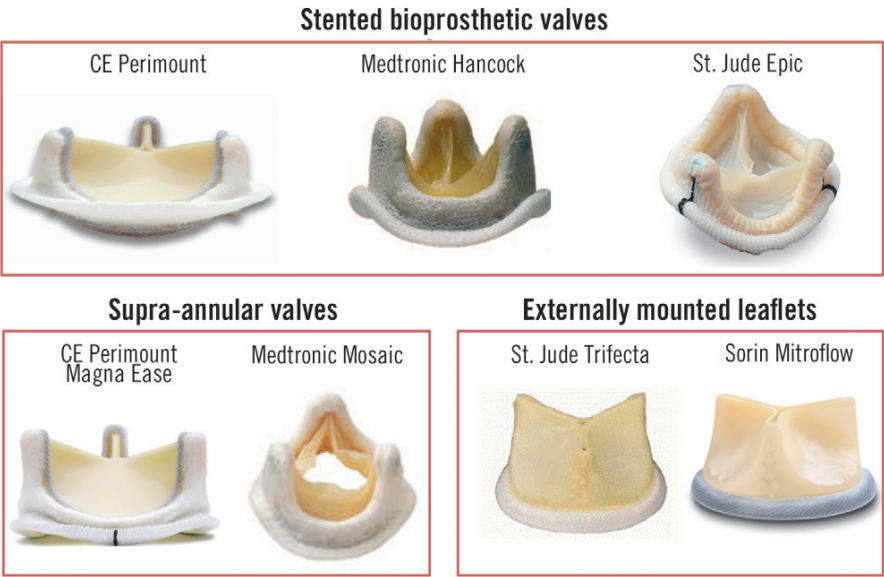


Figure 3 Stented bioprosthetic valves. CE: Carpentier-Edwards.

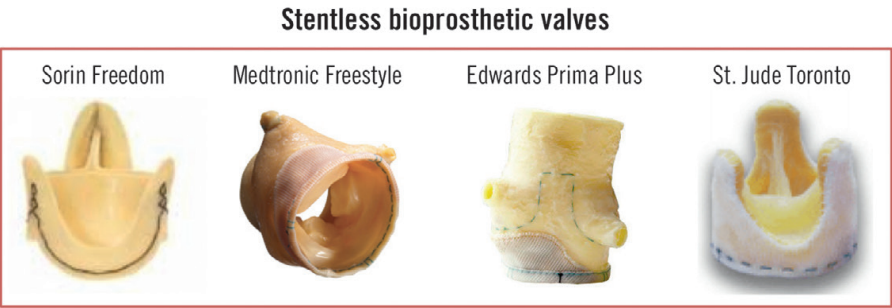


Figure 4 Stentless bioprosthetic valves.

multislice computed tomography remains crucial for THV sizing. Similar to stented valves, the labelled size of stentless valves and homografts usually corresponds to the valve's outer diameter. The inner diameter of the valve is usually available though the absence of a base ring makes these prostheses more compliant than stented valves. Thus THV sizing can be performed in a manner akin to TAVI for native aortic valve stenosis.

MECHANISMS OF SURGICAL BIOPROSTHESIS FAILURE

Bioprosthetic valve failure results from malfunction of the leaflets or the supporting structures (base ring or frame). Common mechanisms of valve failure include wear and tear, leaflet calcification, pannus formation, thrombosis, and infective endocarditis¹⁰. Leaflet tissue deterioration is the most common cause of bioprosthetic valve failure. Although leaflet failure usually occurs insidiously, failing leaflets can tear off the frame and can result in abrupt aortic or mitral insufficiency.

PERCUTANEOUS TREATMENT OF FAILING SURGICAL AORTIC BIOPROSTHETIC VALVES: TAV-IN-SAV

Evidence critically evaluating the safety and efficacy of TAV-in-SAV procedures remains limited. While randomised trials comparing redo surgery with THV implantation have not been performed, several small case series and the Global Valve-in-Valve Registry have reported encouraging and intriguing results^{9,11–17}. The latter is a voluntary registry that currently includes 459 TAV-in-SAV cases and 88 TAV-in-SMV cases performed in 55 centres worldwide. In this registry, high-risk patients (mean Society of Thoracic Surgeons [STS] risk of mortality score >11.9%) underwent TAV-in-SAV procedures for bioprosthetic regurgitation (30.7%), stenosis (39.2%), or mixed regurgitation and stenosis (30.1%). Most patients (79.7%) had failing stented surgical bioprosthetic valves.

CLINICAL OUTCOMES

30-day outcomes

Patients successfully discharged from the hospital following TAV-in-SAV experience improvement in symptoms, as demonstrated by a reduction in New York Heart Association (NYHA) functional class¹⁷. At 30 days, more than 85% of patients report NYHA Class I/II symptoms¹⁴. Reported 30-day mortality rates are between 4.2% and 17%^{11,15}. The Global Valve-in-Valve Registry has reported 30-day rates of all-cause and cardiovascular mortality of 7.6% and 6.5%, respectively (Ran Kornowski EuroPCR 2013, personal communication). These results are comparable to other TAVI cohorts and appear to confirm the safety of these complex interventions^{18–20}. Importantly, physician experience is associated with improved acute procedural results^{15,17}.

Long-term results

Six-month and one-year survival rates range from 86% to 94% and 84% to 92%, respectively^{13,14,16,17}. In the Global Valve-in-Valve Registry, survival at one year was 85% in Medtronic CoreValve patients and 81.3% in Edwards SAPIEN patients ($p=0.44$) (Ran Kornowski EuroPCR 2013, personal communication). Transvalvular gradients also appear to be stable out to one-year follow-up^{14,17}. According to the indication for VIV implantation, one-year survival was 91.2% in patients with aortic regurgitation, 83.9% in those with mixed disease, and 76.6% in patients with bioprosthetic stenosis ($p=0.01$). Indeed, baseline bioprosthetic stenosis was the strongest predictor of mortality at one year (Hazard Ratio: 4.8; 95% confidence interval 1.8 to 12.5, $p=0.002$) (Ran Kornowski EuroPCR 2013, personal communication).

Longer-term follow-up is required to confirm the efficacy of TAV-in-SAV procedures. This is especially true in patients with high post-procedural transvalvular gradients, as underexpansion of the THV can lead to suboptimal valve function, impaired leaflet coaptation, and increased leaflet stress and dysfunction^{21,22}.

Stroke

The reported incidence of major 30-day stroke ranges from 0% to 2.4%^{9,13,15,16}. Thus, it appears that periprocedural stroke may be less common with VIV procedures than with TAVI for native AS (3.8% to 5.0%)^{18,19}. The lower than expected incidence of stroke in TAV-in-SAV procedures is probably multifactorial: patients tend to be younger than those undergoing TAVI for native AS; bioprosthetic regurgitation usually involves less extensive aortic calcification than native AS; and pre-implantation balloon dilatation is performed more sparingly and less aggressively in TAV-in-SAV procedures.

PROCEDURAL OUTCOMES

Coronary obstruction

Coronary obstruction following TAVI for native AS is rare (0.35%)²³. In contrast, the reported incidence of coronary occlusion is ten times higher (3.5%) in patients undergoing TAV-in-SAV¹⁴. The higher incidence may be explained by: 1) the position of the surgical bioprosthesis (annular or supra-annular: the latter reduces the distance to the coronary ostia); 2) the design features of the bioprosthesis (stented or stentless; internal or external leaflet mounting; leaflet length); and 3) the presence of bulky pannus. In particular, Mitroflow stented valves, which have externally mounted, elongated leaflets, and Freedom stentless valves (Sorin Group) have a higher incidence of left main occlusion^{14,16,24}.

Left main rather than right coronary occlusion predominates due to the lower position of the left coronary ostium relative to the aortic annulus. Rapid haemodynamic instability, ST-segment changes, and ventricular arrhythmias are common²³. Coronary occlusion compli-

cating TAVI for native AS can usually be effectively treated percutaneously with success rates of 90% and in-hospital mortality of 8.3%²³. In contrast, percutaneous intervention during TAV-in-SAV is more challenging, as the bioprosthetic valve posts or leaflets inhibit guidewire passage (**Figure 5**)²⁴. In-hospital mortality due to coronary occlusion in the Global Valve-in-Valve Registry was 57.1%¹⁴.

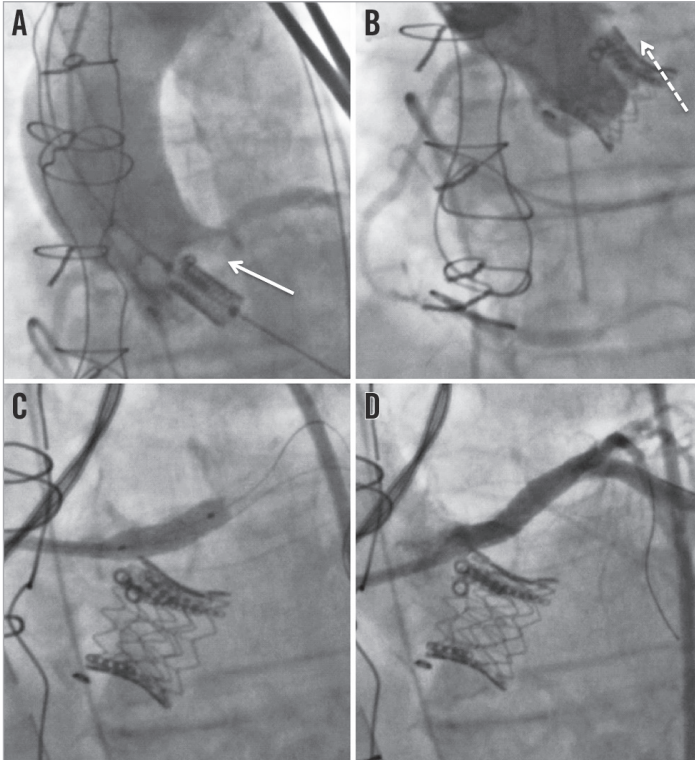


Figure 5 Left main coronary occlusion following TAV-in-SAV. Fluoroscopic images of a stenotic Medtronic Mosaic valve in the aortic position being treated by TAV-in-SAV with an Edwards SAPIEN valve. A) Positioning of the Edwards SAPIEN valve inside the failing bioprosthesis. Note the impressive calcification adjacent to the left main (arrow). B) Aortography following TAV-in-SAV demonstrates left main occlusion (dashed arrow). C) Stenting of the left main. D) Final result of left main stenting.

Requirement for pacemaker

Approximately 10-40%²⁵⁻²⁷ and 4-7%^{28,29} of patients require a permanent pacemaker after CoreValve and Edwards SAPIEN implantation for native AS, respectively. The requirement for pacemaker following TAV-in-SAV procedures is lower. In the Global Valve-in-Valve Registry pacemakers were implanted in 12.2% of CoreValve and 4.9% of Edwards SAPIEN recipients, respectively (Ran Kornowski EuroPCR 2013, personal communication). The non-distensible base ring of the surgical prosthesis, paravalvular fibrotic change, and relatively high implanta-

tion of the THV probably protect the conduction apparatus from the full distension force of the THV and mitigate against conduction disturbance.

Transvalvular gradients

Elevated post-implantation transvalvular gradients appear to be the Achilles heel of TAV-in-SAV procedures. Mean gradients are higher following TAV-in-SAV procedures (≈ 15 – 20 mmHg) than TAVI for native AS (≈ 10 mmHg)^{9,14,15}. High post-procedural gradients (mean gradient ≥ 20 mmHg) were reported in 28.4% in the Global Valve-in-Valve Registry¹⁴. This observation results in a large proportion of cases failing to meet the updated Valve Academic Research Consortium (VARC) definition of acute procedural success³⁰. Elevated gradients may be explained by pre-existing prosthesis patient mismatch, which occurs in up to 52% of patients with a stented aortic bioprosthesis³¹, or by incomplete expansion of the THV within the rigid base ring of the surgical prosthesis²². This problem is most frequently encountered in those with surgical prostheses of small internal diameter (< 20 mm). The limited number of available THV sizes has resulted in many patients being treated with THVs that would conventionally have been considered too large for the measured internal diameter of the failing surgical bioprosthesis. Thus, the relation of the THV diameter to the surgical bioprosthesis diameter (“prosthesis-to-prosthesis match”³²) may be associated with elevated transvalvular gradients. It is interesting to speculate that the introduction of the 23 mm CoreValve and 20 mm Edwards SAPIEN valve may yield a reduction in postprocedural transvalvular gradients, especially in those with small surgical bioprostheses.

Mean postprocedural gradients are also ≈ 5 mmHg higher with TAV-in-SAV using the Edwards SAPIEN than with the CoreValve ($p < 0.0001$)¹⁴. This difference is most apparent inside small surgical bioprostheses, where 43% of Edwards SAPIEN cases had transvalvular gradients > 20 mmHg compared to 24% of CoreValve cases (Ran Kornowski EuroPCR 2013, personal communication). It is likely that the supra-annular functionality of the CoreValve provides a larger potential orifice area than the intra-annular position of the Edwards SAPIEN valve. Hence, the CoreValve is the preferred THV for patients with smaller surgical bioprostheses.

Elevated transvalvular gradients and prosthesis-patient mismatch following SAVR are associated with congestive heart failure, perioperative and long-term mortality³³. However, the advanced age and comorbid status of patients undergoing TAV-in-SAV may render the long-term consequences of prosthesis-patient mismatch less significant. Close patient follow-up and further study are required to establish the long-term clinical significance of prosthesis-patient mismatch³⁴.

Paravalvular leak

Moderate to severe paravalvular leak occurs less frequently with TAV-in-SAV than TAVI for native AS. However, important (grade ≥ 2) paravalvular leaks continue to occur in approximately 5% of cases¹⁴. Moderate paravalvular leak appears to occur more commonly following

CoreValve implantation (8.9%) than with the Edwards SAPIEN valve (2.5%). Paravalvular leaks may occur between the THV and the surgical bioprosthesis or between the surgical bioprosthesis and the native annulus.

PROCEDURAL CONSIDERATIONS

Pre-implantation balloon valvuloplasty

Opinions remain divided on the role of pre-implantation balloon aortic valvuloplasty (BAV) for TAV-in-SAV procedures. In cases where extensive calcification is present, BAV may be logical. However, the merit of BAV within the non-distensible base ring of stented bioprostheses or in cases of primary aortic regurgitation is uncertain. Surgical bioprostheses are more susceptible to tearing than native aortic leaflets and ensuing haemodynamic instability can render TAV-in-SAV procedures more challenging³⁵. More importantly, intervention on degenerated surgical bioprostheses carries a higher risk of debris embolisation and stroke. Indeed, balloon dilatation of prosthetic left-sided heart valves is contraindicated by societal guidelines^{2,36}. Despite these recommendations, BAV was performed in 27.7% of cases in the Global Valve-in-Valve Registry (16.1% CoreValve; 46.2% Edwards SAPIEN)¹⁴.

Malposition of the THV

THV malposition during TAV-in-SAV procedures occurs frequently. The Global Valve-in-Valve Registry reported initial malposition in 15.3%, additional manoeuvres to retrieve the CoreValve in 8.9%, and implantation of a second THV in 8.4%¹⁴. Malposition occurs more commonly during intervention on stentless surgical bioprostheses and particularly with the Medtronic Mosaic valve¹⁴. Several factors may account for the high rates of malposition. Firstly, the large variety of surgical valves with different constructions and fluoroscopic markers creates uncertainty in identifying the optimal position for implantation³⁷. Second, in patients with predominant aortic regurgitation, the elevated stroke volume contributes to prosthesis instability during implantation. Third, the limited number of available THV sizes has necessitated the implantation of relatively larger THVs than in TAVI for native AS, thus making the implant more difficult.

A thorough understanding of the design and fluoroscopic identification of the surgical bioprosthesis is therefore essential. An iPhone app that helps identify the features of currently available surgical bioprostheses is available (<http://www.ubqo.com/viv>). Rapid ventricular pacing should be considered in patients with significant aortic regurgitation to reduce stroke volume and valve instability. In cases with limited fluoroscopic implantation landmarks, transoesophageal echocardiography should be used for device positioning. It is satisfying to note that the most recent data presented from the Global Valve-in-Valve Registry demonstrate

that the requirement for implantation of a second THV has fallen to 4.4% (Ran Kornowski EuroPCR 2013, personal communication).

PERCUTANEOUS TREATMENT OF FAILING SURGICAL MITRAL BIOPROSTHETIC VALVES: TAV-IN-SMV

Successful implantation of the Edwards SAPIEN valve within a failing surgical mitral valve was first reported in 2009³⁸. In subsequent years, several case reports and small series have demonstrated the feasibility and safety of this technique with both Edwards SAPIEN and Medtronic Melody THVs^{38–41}.

Safety and efficacy

Cheung et al have recently reported their institutional experience of 23 transapical TAV-in-SMV cases⁴². In this high-risk cohort (mean STS score $12.2 \pm 6.9\%$) declined conventional redo mitral valve replacement surgery, the mechanism of bioprosthetic failure was stenosis in 30.4%, regurgitation in 39.1%, and mixed in 30.4%. VARC-defined device success was achieved in 100% of cases and there was no 30-day mortality. The mitral transvalvular gradient significantly decreased from 11.1 ± 4.6 mmHg to 6.9 ± 2.2 mmHg following the VIV procedure, and all patients had no more than mild paravalvular mitral regurgitation. Haemodynamic or structural deterioration was not observed during follow-up, though one patient underwent a further valve-in-valve-in-valve procedure due to atrial migration of the Edwards SAPIEN valve. Heart failure symptoms improved in all but one patient (NYHA Class I/II). At a median follow-up of 753 days the Kaplan-Meier survival rate was 90.4%. Long-term durability and efficacy require further study.

Procedural considerations

The majority of TAV-in-SMV cases have been performed using the transapical approach which provides direct and coaxial access to the failing mitral bioprosthesis. Alternative access routes are more technically challenging and include the transatrial approach using a right-sided thoracotomy⁴³, and the transvenous transseptal approach¹¹. As stentless bioprostheses are used very infrequently in the mitral position, THV implantation can usually be performed using fluoroscopy. In cases where the sewing ring is radiopaque, the use of transoesophageal echocardiography is recommended. Similar to TAV-in-SAV procedures, THV sizing for failing mitral bioprostheses has been guided primarily by the manufacturers' reported internal stent diameter, as well as screening computed tomography and intraprocedural echocardiography. These latter imaging modalities add important information regarding the failure mode of the surgical valve. In the series by Cheung and colleagues, 10% oversizing of the Edwards SAPIEN valve relative to the surgical bioprosthesis was considered appropriate⁴².

Unanswered questions

Although the frequency of VIV interventions is growing, it is important to note that there remain significant gaps in our understanding of these procedures. Long-term efficacy and durability remain unknown, particularly in patients with underexpanded THVs and high transvalvular gradients. A comparative effectiveness analysis comparing VIV with redo surgery has not yet been performed. The optimal degree of THV oversizing inside the surgical bioprosthesis is unknown. Antiplatelet and anticoagulant regimens are untested. In which anatomical or patient groups are these procedures best avoided? Which THV should be preferentially used for annular or supra-annular surgical bioprosthesis? What are the implications of prosthesis-patient mismatch in this patient population? Should specific VARC outcomes be developed for VIV procedures? Further study is required to address these important questions.

CONCLUSIONS

Current data support the treatment of patients with failing surgical bioprostheses at high operative risk using THV technology in specialised centres. Although considerable gaps in our understanding of the long-term efficacy of these procedures remain, results to date suggest that these innovative procedures have the potential to become the standard of care for surgical bioprosthetic valve dysfunction.

Conflict of interest statement N. Piazza is a proctor and a consultant for Medtronic. The other authors have no conflicts of interest to report.

REFERENCES

1. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg.* 2009;137:82-90.
2. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J.* 2012;33:2451-96.
3. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation.* 2002;106:3006-8.
4. Ruel M, Chan V, Bedard P, Kulik A, Ressler L, Lam BK, Rubens FD, Goldstein W, Hendry PJ, Masters RG, Mesana TG. Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age. *Circulation.* 2007;116:1294-300.
5. Chan V, Malas T, Lapierre H, Boodhwani M, Lam BK, Rubens FD, Hendry PJ, Masters RG, Goldstein W, Mesana TG, Ruel M. Reoperation of left heart valve bioprostheses according to age at implantation. *Circulation.* 2011;124:S75-80.
6. Vogt PR, Brunner-LaRocca H, Sidler P, Zund G, Truniger K, Lachat M, Turina J, Turina MI. Reoperative surgery for degenerated aortic bioprostheses: predictors for emergency surgery and reoperative mortality. *Eur J Cardiothorac Surg.* 2000;17:134-9.
7. Akins CW, Buckley MJ, Daggett WM, Hilgenberg AD, Vlahakes GJ, Torchiana DF, Madsen JC. Risk of reoperative valve replacement for failed mitral and aortic bioprostheses. *Ann Thorac Surg.* 1998;65:1545-51; discussion 1551-2.
8. Mylotte D, Lange R, Martucci G, Piazza N. Transcatheter heart valve implantation for failing surgical bioprostheses: technical considerations and evidence for valve-in-valve procedures. *Heart.* 2013;99:960-7.
9. Piazza N, Bleiziffer S, Brockmann G, Hendrick R, Deutsch MA, Opitz A, Mazzitelli D, Tassani-Prell P, Schreiber C, Lange R. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 2). *JACC Cardiovasc Interv.* 2011;4:733-42.
10. Roselli EE, Smedira NG, Blackstone EH. Failure modes of the Carpentier-Edwards pericardial bioprosthesis in the aortic position. *J Heart Valve Dis.* 2006;15:421-7; discussion 427-8.
11. Webb JG, Wood DA, Ye J, Gurvitch R, Masson JB, Rodes-Cabau J, Osten M, Horlick E, Wendler O, Dumont E, Carere RG, Wijesinghe N, Nietlispach F, Johnson M, Thompson CR, Moss R, Leipsic J, Munt B, Lichtenstein SV, Cheung A. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation.* 2010;121:1848-57.
12. Kempfert J, Van Linden A, Linke A, Borger MA, Rastan A, Mukherjee C, Ender J, Schuler G, Mohr FW, Walther T. Transapical off-pump valve-in-valve implantation in patients with degenerated aortic xenografts. *Ann Thorac Surg.* 2010;89:1934-41.
13. Latib A, Ielasi A, Montorfano M, Maisano F, Chieffo A, Cioni M, Mussardo M, Bertoldi L, Shannon J, Sacco F, Covello RD, Figini F, Godino C, Grimaldi A, Spagnolo P, Alfieri O, Colombo A. Transcatheter valve-in-valve implantation with the Edwards SAPIEN in patients with bioprosthetic heart valve failure: the Milan experience. *EuroIntervention.* 2012;7:1275-84.
14. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, Descoutures F, Hengstenberg C, Moat NE, Bekerredjian R, Napodano M, Testa L, Lefevre T, Guetta V, Nissen H, Hernandez JM, Roy D,

- Teles RC, Segev A, Dumonteil N, Fiorina C, Gotzmann M, Tchetché D, Abdel-Wahab M, De Marco F, Baumbach A, Laborde JC, Kornowski R. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. *Circulation*. 2012;126:2335-44.
15. Eggebrecht H, Schafer U, Treede H, Boekstegers P, Babin-Ebell J, Ferrari M, Mollmann H, Baumgartner H, Carrel T, Kahlert P, Lange P, Walther T, Erbel R, Mehta RH, Thielmann M. Valve-in-valve transcatheter aortic valve implantation for degenerated bioprosthetic heart valves. *JACC Cardiovasc Interv*. 2011;4:1218-27.
16. Bedogni F, Laudisa ML, Pizzocri S, Tamburino C, Ussia GP, Petronio AS, Napodano M, Ramondo A, Presbitero P, Etori F, Santoro G, Klugman S, De Marco F, Brambilla N, Testa L. Transcatheter valve-in-valve implantation using CoreValve Revalving System for failed surgical aortic bioprostheses. *JACC Cardiovasc Interv*. 2011;4:1228-34.
17. Linke A, Woitek F, Merx MW, Schiefer C, Mobius-Winkler S, Holzhey D, Rastan A, Ender J, Walther T, Kelm M, Mohr FW, Schuler G. Valve-in-valve implantation of Medtronic CoreValve prosthesis in patients with failing bioprosthetic aortic valves. *Circ Cardiovasc Interv*. 2012;5:689-97.
18. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-607.
29. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-98.
20. Ussia GP, Barbanti M, Petronio AS, Tarantini G, Etori F, Colombo A, Violini R, Ramondo A, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, De Carlo M, Napodano M, Fiorina C, De Marco F, Antoniucci D, de Cillis E, Capodanno D, Tamburino C. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. *Eur Heart J*. 2012;33:969-76.
21. Azadani AN, Jaussaud N, Matthews PB, Ge L, Guy TS, Chuter TA, Tseng EE. Valve-in-valve implantation using a novel sup-ravalvular transcatheter aortic valve: proof of concept. *Ann Thorac Surg*. 2009;88:1864-9.
22. Azadani AN, Jaussaud N, Matthews PB, Ge L, Chuter TA, Tseng EE. Transcatheter aortic valves inadequately relieve stenosis in small degenerated bioprostheses. *Interact Cardiovasc Thorac Surg*. 2010;11:70-7.
23. Ribeiro HB, Nombela-Franco L, Urena M, Mok M, Pasian S, Doyle D, Delarochelliere R, Cote M, Laflamme L, Delarochelliere H, Allende R, Dumont E, Rodes-Cabau J. Coronary obstruction after transcatheter aortic valve implantation: a systematic review. *JACC Cardiovasc Interv*. 2013;6:452-61.
24. Gurvitch R, Cheung A, Bedogni F, Webb JG. Coronary obstruction following transcatheter aortic valve-in-valve implantation for failed surgical bioprostheses. *Catheter Cardiovasc Interv*. 2011;77:439-44.
25. Guetta V, Goldenberg G, Segev A, Dvir D, Kornowski R, Finckelstein A, Hay I, Goldenberg I, Glikson M. Predictors and course of high-degree atrioventricular block after transcatheter aortic valve implantation using the CoreValve Revalving System. *Am J Cardiol*. 2011;108:1600-5.
26. Khawaja MZ, Rajani R, Cook A, Khavandi A, Moynagh A, Chowdhary S, Spence MS, Brown S, Khan SQ, Walker N, Trivedi U, Hutchinson N, De Belder AJ, Moat N, Blackman DJ, Levy RD, Manoharan G, Roberts D, Khogali SS, Crean P, Brecker SJ, Baumbach A, Mullen M, Laborde JC, Hildick-Smith D. Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). *Circulation*. 2011;123:951-60.

27. Tchetché D, Modine T, Farah B, Vahdat O, Sudre A, Koussa M, Lereun C, Nejari M, Choby M, Ros-encher J, Sorbets E, Fajadet J. Update on the need for a permanent pacemaker after transcatheter aortic valve implantation using the CoreValve® Accutrak™ system. *EuroIntervention*. 2012;8:556-62.
28. Eltchaninoff H, Prat A, Gilard M, Leguerrier A, Blanchard D, Fournial G, Iung B, Donzeau-Gouge P, Tribouilloy C, Debrux JL, Pavié A, Guéret P. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. *Eur Heart J*. 2011;32:191-7.
29. Thomas M, Schymik G, Walther T, Himbert D, Lefevre T, Treede H, Eggebrecht H, Rubino P, Michev I, Lange R, Anderson WN, Wendler O. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation*. 2010;122:62-9.
30. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *EuroIntervention*. 2012;8:782-95.
31. Pibarot P, Honos GN, Durand LG, Dumesnil JG. The effect of prosthesis-patient mismatch on aortic bioprosthetic valve hemodynamic performance and patient clinical status. *Can J Cardiol*. 1996;12:379-87.
32. Ferrari E, Marcucci C, Sulzer C, von Segesser LK. Which available transapical transcatheter valve fits into degenerated aortic bioprostheses? *Interact Cardiovasc Thorac Surg*. 2010;11:83-5.
33. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation*. 2009;119:1034-48.
34. Clavel MA, Webb JG, Pibarot P, Altwegg L, Dumont E, Thompson C, De Larochelliere R, Doyle D, Masson JB, Bergeron S, Bertrand OF, Rodes-Cabau J. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. *J Am Coll Cardiol*. 2009;53:1883-91.
35. McKay CR, Waller BF, Hong R, Rubin N, Reid CL, Rahimtoola SH. Problems encountered with catheter balloon valvuloplasty of bioprosthetic aortic valves. *Am Heart J*. 1988;115:463-5.
36. Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006;114:e84-231.
37. Bapat V, Mydin I, Chadalavada S, Tehrani H, Attia R, Thomas M. A guide to fluoroscopic identification and design of bioprosthetic valves: a reference for valve-in-valve procedure. *Catheter Cardiovasc Interv*. 2013;81:853-61.
38. Cheung A, Webb JG, Wong DR, Ye J, Masson JB, Carere RG, Lichtenstein SV. Transapical transcatheter mitral valve-in-valve implantation in a human. *Ann Thorac Surg*. 2009;87:e18-20.
39. Cerillo AG, Chiamonti F, Murzi M, Bevilacqua S, Cerone E, Palmieri C, Del Sarto P, Mariani M, Berti S, Glauber M. Transcatheter valve in valve implantation for failed mitral and tricuspid bioprosthesis. *Catheter Cardiovasc Interv*. 2011;78:987-95.

40. Seiffert M, Conradi L, Baldus S, Schirmer J, Knap M, Blankenberg S, Reichenspurner H, Treede H. Transcatheter mitral valve-in-valve implantation in patients with degenerated bioprostheses. *JACC Cardiovasc Interv.* 2012;5:341-9.
41. Cullen MW, Cabalka AK, Alli OO, Pislaru SV, Sorajja P, Nkomo VT, Malouf JF, Cetta F, Hagler DJ, Rihal CS. Transvenous, Antegrade Melody Valve-in-Valve Implantation for Bioprosthetic Mitral and Tricuspid Valve Dysfunction: A Case Series in Children and Adults. *JACC Cardiovasc Interv.* 2013;6: 598-605.
42. Cheung A, Webb JG, Barbanti M, Freeman M, Binder RK, Thompson C, Wood DA, Ye J. 5-year experience with transcatheter transapical mitral valve-in-valve implantation for bioprosthetic valve dysfunction. *J Am Coll Cardiol.* 2013;61: 1759-66.
43. Cheung AW, Gurvitch R, Ye J, Wood D, Lichtenstein SV, Thompson C, Webb JG. Transcatheter transapical mitral valve-in-valve implantations for a failed bioprosthesis: a case series. *J Thorac Cardiovasc Surg.* 2011;141:711-5.

TAVI FOR FAILING SURGICAL AORTIC BIOPROSTHESES

11

Based on:

TAVI for Failing Surgical Aortic Bioprostheses

Mylotte D, Bapat V, Dvir D, Kornowski R, Lange R, Piazza, N.

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INTRODUCTION

Among elderly subjects undergoing surgical aortic valve replacement (SAVR), implantation of bioprosthetic heart valves is considered to be the standard of care.^{1,2} These prostheses are recommended for patients ≥ 60 years of age or in those at high risk of bleeding with systemic anticoagulation.^{1,2} Consequently, the use of bioprosthetic heart valves now greatly outweighs their mechanical equivalents.³ Despite advances in bioprosthetic design, valve durability remains the Achilles' heel; current iterations are expected to degenerate within 12 to 20 years and in some cases even sooner.^{4,5} Redo SAVR is recommended for stenotic or regurgitant bioprostheses, though surgery is often denied due to elevated operative risk in these elderly patients with comorbid medical conditions.⁶⁻⁸ In such patients, implantation of a transcatheter aortic valve (TAV) within the degenerated bioprosthetic surgical aortic valve (SAV) has proven to be feasible, safe, and effective.⁹⁻¹³ Nevertheless, limitations of TAV-in-SAV implantation include a relatively higher rate of malposition and coronary occlusion, device underexpansion, and residual aortic stenosis, compared to native aortic valve TAV implantation (TAVI). This chapter aims to describe the pre-procedural planning, implantation techniques, and evidence for these TAV-in-SAV procedures.

BIOPROSTHETIC SURGICAL AORTIC VALVE CONSTRUCTION

Bioprosthetic SAVs are comprised of two essential components: the valve leaflets and a supporting frame/structure (**Figure 1**).¹¹ The leaflets may be of xenograft or homograft origin. Xenografts are most frequently composed of bovine pericardium or are whole porcine aortic valves. Less frequently, thinner porcine pericardium may be used for leaflet construction. Typically, the leaflets are prepared with an anti-calcification treatment (e.g. ThermoFix™,

Figure 1. Stented Aortic Bioprosthesis

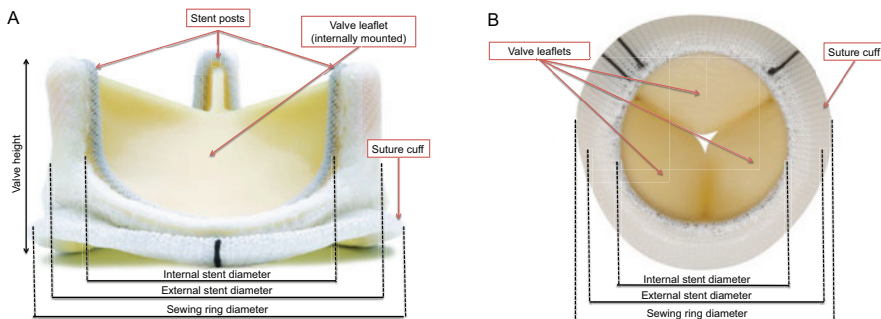


Figure 1. (A and B) Carpentier-Edwards Perimount Magna Ease aortic valve. Dimensions and design features of a stented bioprosthetic valve. With permission from Mylotte et al. *EuroIntervention*. 2013;9:S77-S83.

Edwards Lifesciences, Irvine, CA, USA) and preserved in glutaraldehyde. Bioprosthetic heart valves can be further categorized according to the leaflet support structure (**Figure 2**): A) stented prostheses where the leaflets are supported by a mechanical frame; or B) stentless prostheses where the leaflets are supported by xeno- or homograft tissue.

Figure 2. Stented and Stentless Bioprosthetic Valves

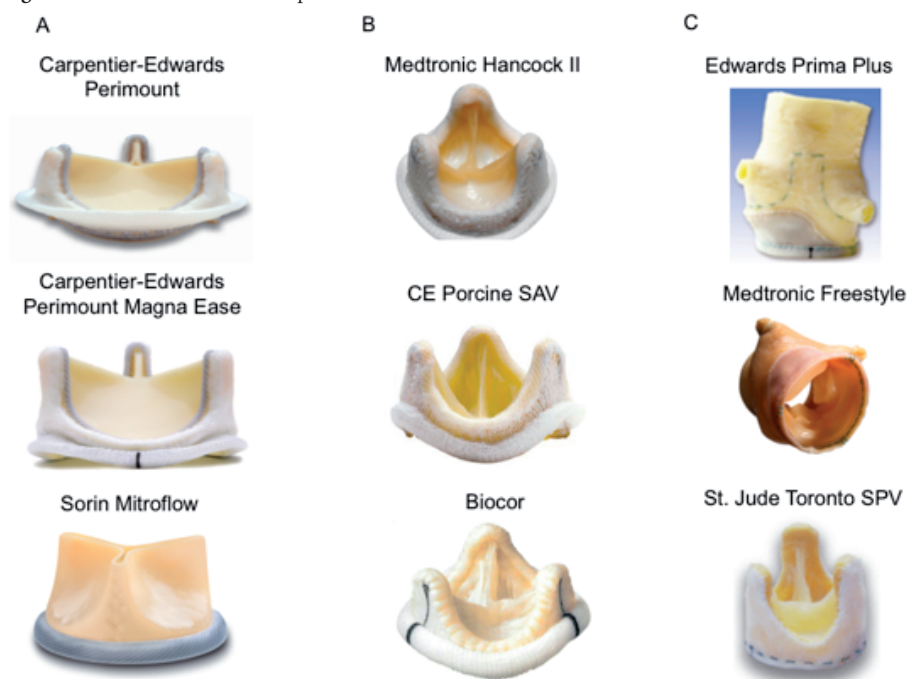


Figure 2. Stented and stentless bioprosthetic surgical valves. (A) Stented pericardial bovine bioprosthetic valves. (B) Stented porcine aortic valve bioprostheses. (C) Stentless bioprosthetic valves. With permission from Mylotte et al. *Heart* 2013 99: 960-967.

A) Stented Bioprostheses

The basic construction of all stented bioprosthetic heart valves is consistent: valve leaflets sutured to a rigid supporting frame constructed of metallic alloys (titanium or cobalt-chromium), pyrolytic carbon, or polymeric materials (polymers) (**Figure 3**).¹⁴ The stent frame or posts are covered by pericardium or by a synthetic material for protection. A circular or scallop shaped sewing ring is attached to the frame and is usually covered in by a fabric sewing cuff that is used to secure the bioprosthesis to the native aortic root. The valve leaflets may be sited either at the level of the annulus (intra annular Link below)) or above the annulus (supra annular (link to below)) (**Figure 4**). The latter is designed to increase the effective orifice area and improve the haemodynamics of the prosthesis. In most cases, the valve leaflets are sutured

inside the supporting frame, however the Mitroflow (Sorin, British Columbia, Canada) and Trifecta (St. Jude, St Paul, Minnesota, USA) (Link to individual images) bioprotheses have externally mounted leaflets wrapped as a sleeve around the frame.

Figure 3. Stented Bioprosthetic Valve Construction

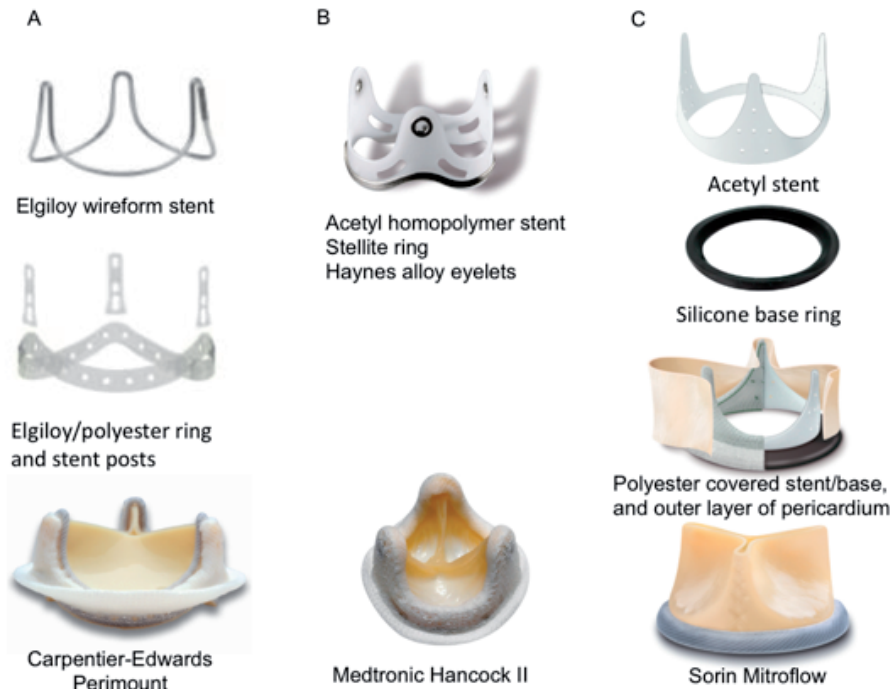


Figure 3. (A) Carpentier-Edwards Perimount bovine pericardial valve. (B) Medtronic Hancock II porcine aortic valve. (C) Sorin Mitroflow bovine pericardial valve. With permission from Mylotte et al. Heart 2013 99: 960-967.

Figure 4. Intra and Supra Annular Bioprotheses

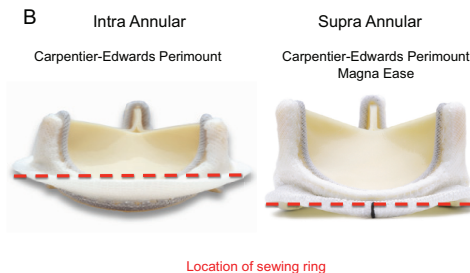


Figure 4. (A) Intra (Carpentier Edwards Perimount) and supra (Carpentier Edwards Perimount Magna Ease) annular bioprotheses. Note (B) the location of the sewing ring is different.

Fluoroscopic Identification of Stented Bioprosthesis

The stent frame or posts and the sewing ring may be radiolucent or radiopaque, according to their composition. Fluoroscopic identification of stented surgical bioprostheses is performed by discerning differences in the shape of the frame and/or the design and location of the sewing ring.¹¹ The Aortic Valve-in-Valve (VIV) application includes a user-friendly, comprehensive, guide that assists in the identification of aortic bioprosthetic valves.

B) Stentless Bioprostheses

Stentless bioprostheses do not have a supporting frame and/or ring. Rather, these valves are entirely constructed from human (homograft) or porcine (xenograft) aortic root tissue.¹⁵ Examples include: Edwards Prima; Medtronic Freestyle, Sorin Freedom; St Jude Toronto SPV. These prostheses were principally developed to yield superior haemodynamic results to their stented equivalents. Stentless bioprostheses have not been proven to enhance durability when compared to their stented equivalents.¹⁶ Furthermore, their propensity towards heavy aortic root calcification and lack of fluoroscopic markers can make TAV-in-SAV more challenging.¹⁷

FAILURE MODES OF SURGICAL BIOPROSTHESES

The increasing use of surgical bioprosthetic valves has resulted in physicians encountering bioprosthesis failure with greater frequency. First generation bioprosthetic heart valves were particularly prone to failure: up to one-third of younger patients underwent reoperation within 10 years.¹⁸ Technical advances have rendered these early prostheses obsolete, and have improved valve durability: freedom from structural valve failure at 15-years was reported in 43% of those treated with the first generation Hancock bioprosthesis (Medtronic, Minneapolis, Minnesota, USA) and in 19% treated with the second-generation Hancock valve.^{19,20} Current, third-generation bioprostheses are expected to further reduce the incidence of structural valve failure, though long-term durability data are not yet available. Overall, the median life-span of surgical bioprostheses is currently between 12 to 20 years with current prostheses,^{4,5} however there appears to be a cohort of patients that experience early valve failure: the median time to failure in the Global VIV registry was 9 years.¹² It is also conceivable that because many bioprosthetic recipients are elderly and high-risk for redo surgery, that the true incidence of aortic bioprosthesis failure may be under-reported. Smoking, younger age, persistent left ventricular hypertrophy and small prosthesis sizes are predictors of requirement for reoperation.^{4,6} In addition, metabolic syndrome, diabetes mellitus, renal insufficiency, and higher mean valve gradient at baseline significantly contribute to structural valve deterioration over time of bioprostheses.²¹

Valve leaflet deterioration, due to wear and tear, progressive calcification, infective endocarditis, thrombosis or extensive pannus formation is the most common mechanism of

bioprosthetic failure (**Figure 5**).^{11, 22} Structural fatigue of the valve frame or stent posts, and paravalvular regurgitation in the presence of a functionally normal prosthesis may also necessitate redo surgery. Isolated bioprosthetic stenosis is observed more frequently than isolated regurgitation in stented bioprostheses whereas stentless bioprostheses commonly fail with predominant regurgitation or mixed valve failure.¹² In the preliminary report of the Global VIV registry (n=202), bioprosthesis mode of failure was stenosis (42%), regurgitation (34%), or combined stenosis and regurgitation (24%).

Figure 5. Aetiology of Surgical Bioprosthesis Failure



Figure 5. Pathological specimens demonstrating the aetiology of bioprosthetic valve failure. (A) Wear and tear. (B) Calcific degeneration. (C) Pannus. (D) Endocarditis. (E) Thrombus. With permission from Piazza N et al. *JACC Interv* 2011;4:721–32.

SIZE LABELLING OF SURGICAL BIOPROSTHESES: IMPLICATIONS FOR TAV-IN-SAV

Understanding the sizing nomenclature of surgical bioprostheses is of utmost importance for planning and executing properly the TAV-in-SAV procedures (**Figure 1**). The internal stent diameter represents the internal diameter of the frame of stented surgical bioprostheses, without the valve leaflets. This measurement, among other scaffold dimensions (external stent diameter; sewing ring diameter), is commonly available from the prosthesis manufacturer. However, when the valve leaflets are considered, the dimensions of the bioprosthesis with internally mounted leaflets are smaller than the labelled inner stent diameter. This, “true” internal diameter is typically 2.0 mm smaller for valves with internally mounted porcine leaflets (Hancock II), Mosaic, CE Porcine SAV, Epic and Biocor) and 1.0 mm smaller in valves composed of pericardial tissue (Perimount, Perimount 2700, Magna, Magna Ease, Soprano).²³ With externally mounted leaflets, the internal stent diameter is equal to the “true” internal diameter.²³ The presence of heavy leaflet calcification and/or pannus can further reduce the diameter available for TAV implantation.

The manufacturer-labelled diameter of stentless valves typically corresponds to the external (aortic root diameter) of the valve. Although the labelled diameter can be somewhat variable, due to the ability to distend these pliable valves, the “true” internal diameter is approximately 1.5 mm (Prima), 3 mm (Freestyle), or 2 mm (Toronto SPV) smaller than the labelled size.²³

TAV SIZING

In TAVI for native aortic valve stenosis, oversizing the transcatheter heart valve (THV) relative to the aortic annulus is required (1) to anchor the prosthesis and prevent valve migration; (2) to provide sealing and avoid paravalvular leaks; and (3) to minimise patient-prosthesis mismatch. The degree of THV oversizing is prosthesis specific (Edwards SAPIEN: 4 to 20%; CoreValve 7 to 30%) and is greatly influenced by the imaging modality (echocardiographic vs. computed tomography [CT]) and by the method of diameter calculation (area; mean diameter; perimeter).

Currently, the amount of THV oversizing and the optimal method of THV-sizing for TAV-in-SAV procedures remain unknown. The required degree of THV oversizing relative to the degenerated bioprosthesis may be less than that advised for native aortic stenosis, as prosthesis anchoring and sealing appear to be superior within the frame of the surgical valve and the rate of significant post-procedural paravalvular aortic regurgitation appears low. Although the risk of excessive oversizing with regard to annular rupture is low in these cases, aggressive oversizing may hypothetically risk high post-implantation transvalvular gradients and may threaten longer-term valve durability. There is consensus, that CT evaluation of the “true diameter” of the degenerated bioprosthesis may be the most appropriate method of sizing.^{17, 24} CT affords assessment of the impact of the valve leaflets, calcification, and pannus formation on the manufacturer-labelled internal diameter. The authors strongly recommend the sizing algorithm proposed in the Aortic VIV application.

EVIDENCE FOR TAV-IN-SAV PROCEDURES

Evidence supporting the safety and efficacy of TAV-in-SAV procedures was initially derived from case reports and small series.^{10, 13, 25-30} In 2010, the Global VIV registry began collecting data from centres performing TAV-in-SAV procedures across the globe.¹² Most recently, this voluntary registry reported outcomes on 459 patients (n=213: CoreValve; n=246 Edwards SAPIEN) with a failed surgical aortic bioprosthesis treated by TAV-in-SAV.³¹

The complexity of these procedures was demonstrated by satisfactory procedural success and clinical results but also by high rates of TAVI malposition: stented prostheses (8%); stentless prostheses (14%); and by the requirement for a second transcatheter valve in 4.5%. Coronary artery obstruction occurred in 2% and conversion to surgical aortic valve replacement was required in 3.4%. Overall 30-day mortality was 7.6%, (7.0% CoreValve and 8.1% Edwards SAPIEN). At 1-year, 85% of CoreValve and 81.3% of Edwards SAPIEN treated patients were alive (p=0.44). The strongest independent predictors for post-procedural mortality were a small surgical valve size (label size ≤21mm) and stenosis as the failure mechanism.³¹

PROCEDURAL COMPLICATIONS

Post Implantation Gradients

In the setting of THV implantation for native aortic valve stenosis, mean transvalvular gradients average 5 to 15 mmHg. In contrast, mean transvalvular gradients following TAV-in-SAV are frequently higher: 10 – 25 mmHg. In the Global VIV registry, 28.4% of cases had elevated post-procedural gradients.¹² Consequently, a large proportion of TAV-in-SAV cases do not meet the Valve Academic Research Consortium (VARC) definition for acute procedural success³². The restricted area for THV expansion within the degenerated surgical bioprosthesis or pre-existing patient-prosthesis mismatch is the most likely explanations for these elevated gradients. Indeed, the smaller the surgical bioprosthesis, the higher the gradient that can be expected following THV implantation.³³ Importantly, the Medtronic CoreValve seems to deliver superior haemodynamic performance than the Edwards SAPIEN in surgical bioprostheses of small (< 20 mm) or intermediate (>20 < 23 mm) internal diameter.³¹ This discrepancy arises from the different design characteristics of these devices: the functional component of the Edwards SAPIEN system is located at the level of the native annulus while the CoreValve's leaflets are supra-annular (**Figure 6**). Thus, the CoreValve is ultimately less constrained by the rigid frame of the surgical bioprosthesis into which it is implanted and provides a larger effective orifice area. Whether this haemodynamic superiority translates into enhanced long-term clinical outcomes is not yet known. Going forward, it is expected that

Figure 6. Bench Morphology of TAV-in-SAV

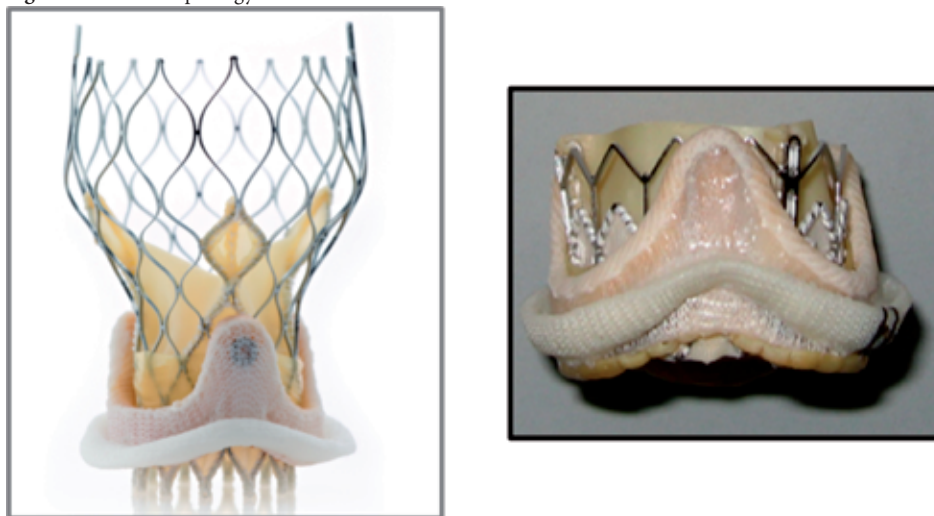


Figure 6. Bench morphology of the Medtronic CoreValve (left) and Edwards SAPIEN valve (right) within stented surgical bioprosthetic valves.

the newly developed 23mm CoreValve and 20mm Edwards SAPIEN prostheses will impact positively on post-implantation gradients.^{34, 35}

TAV-in-SAV procedures have been performed using a range of prostheses: Medtronic CoreValve,¹⁰ Medtronic CoreValve Evolut R,³⁴ Medtronic Melody,³⁶ Edwards SAPIEN,³⁷ St Jude Portico,³⁸ and Symetis Acurate.³⁹ Most procedures however, have been performed with either the Edwards SAPIEN or Medtronic CoreValve systems.¹²

THV Malposition

THV malposition was reported in 15.3% of cases in the Global VIV registry.¹² Consequently, high rates of additional manoeuvres to reposition or retrieve the valve or implantation of a second THV (8% of total cohort) were observed.¹² More recently, the requirement for implantation of a second THV appear to have fallen to 4.3%.³¹ Operator experience is likely to have had an important role in these improving results:²⁴ improved understanding of bioprosthesis construction and mode of failure; understanding the ideal implant position for a given bioprosthesis (e.g. different for annular and supra annular bioprostheses); and utilization of intra-procedural multimodality imaging. Stentless bioprostheses and stented valves with radiolucent sewing rings (Epic, St. Jude; Mosaic, Medtronic) provide the greatest challenge to accurate THV positioning.

Paravalvular Leak

Significant paravalvular regurgitation between the THV and the surgical bioprosthesis are uncommon (5%).¹² The frame of the surgical valve appears to improve THV sealing and thus the majority of cases of significant paravalvular regurgitation arise from THV malposition.²⁴ In the absence of malposition, incomplete THV expansion may be treated with post implantation balloon dilatation.

Coronary Obstruction

There is an elevated risk of coronary obstruction with TAV-in-SAV procedures compared to TAVI for native aortic stenosis.^{24, 40} Coronary obstruction was observed in 3.5% of cases in the initial publication of the Global VIV registry. Most recently, the rate of coronary obstruction in the expanded registry was reported to be 2%.³¹ Left coronary artery obstruction occurs more commonly and is usually associated with haemodynamic instability and ventricular arrhythmia.⁴⁰ The most common mechanism for coronary obstruction is thought to be displacement of the leaflets of the bioprosthesis towards the ostium of the coronary artery or towards the sinutubular junction. A reduced distance between the bioprosthetic leaflets and/or stent posts and the coronary ostia may increase the risk of coronary occlusion. Several factors may increase this risk: low-lying coronary arteries and/or sinutubular junction; narrow aortic sinuses of Valsalva; supra annular bioprosthesis; elongated leaflets; bulky pannus or calcification.²⁴ The design of the surgical bioprosthesis may increase the risk of coronary obstruction.

Stentless bioprostheses (Freedom, (Sorin, British Columbia, Canada) and Trifecta (St Jude, St. Paul, Minneapolis, USA) add links) or those with externally mounted leaflets (Mitroflow, Sorin) increase the risk of coronary obstruction as the leaflets may extend outward in a tubular fashion following TAV-in-SAV.

Stroke

Degenerated surgical bioprosthetic valve leaflets may be heavily calcified and/or friable, and prone to tearing, and therefore may have embolic potential. It was assumed therefore, that TAV-in-SAV procedures might carry a higher risk of stroke than TAVI for native aortic stenosis. The Global VIV registry reported major stroke rates of 0.9% for CoreValve and 2.4% for Edwards SAPIEN recipients. These rates are comparable to published series for TAVI in native aortic stenosis.⁴¹ Nonetheless, lack of pre-implantation valvuloplasty during TAV-in-SAV in most cases may have contributed to the low risk of stroke among failed bioprosthetic valve patients.

TAV-IN-SAV: PROCEDURAL TIPS AND TRICKS

Patient Selection

The patient work-up for a TAV-in-SAV procedure should be extensive and thorough. Details of the initial surgical procedure should be sought and the indication for surgery, type and size of the surgical prosthesis documented. The bioprosthetic stenosis or regurgitation, or both, requires confirmation with echocardiography. However, it must be demonstrated that the bioprosthesis is indeed failing and stenotic, rather than there being a chronically elevated gradient due to a small surgical valve. Similarly, in cases of significant bioprosthesis incompetence, it is important to demonstrate that the aortic regurgitation is transvalvular rather than paravalvular. Ruling out active bioprosthetic infective endocarditis or valve thrombosis as failure mechanisms can also be achieved with echocardiography and laboratory testing. We advocate that all patients under consideration for TAV-in-SAV undergo CT analysis for the purposes of THV-sizing and access route selection and transoesophageal echocardiography in cases with predominant regurgitation in order to exclude paravalvular leak.

THV Selection

The choice of THV for implantation should be individualized for each patient. In the majority of cases, the Edwards SAPIEN (**Figure 7**) or CoreValve (**Figure 8**) are likely to be equally efficacious. Patients with bioprostheses of small (<20 mm) internal diameter may benefit from the superior haemodynamic results associated with the CoreValve.³¹ Consideration of the risk of coronary ostial occlusion may also influence THV selection. New generation, fully retrievable THV devices or those with aortic leaflet clipping (Jena valve) may be preferable if the risk

Figure 7. Edwards SAPIEN TAV-in-SAV

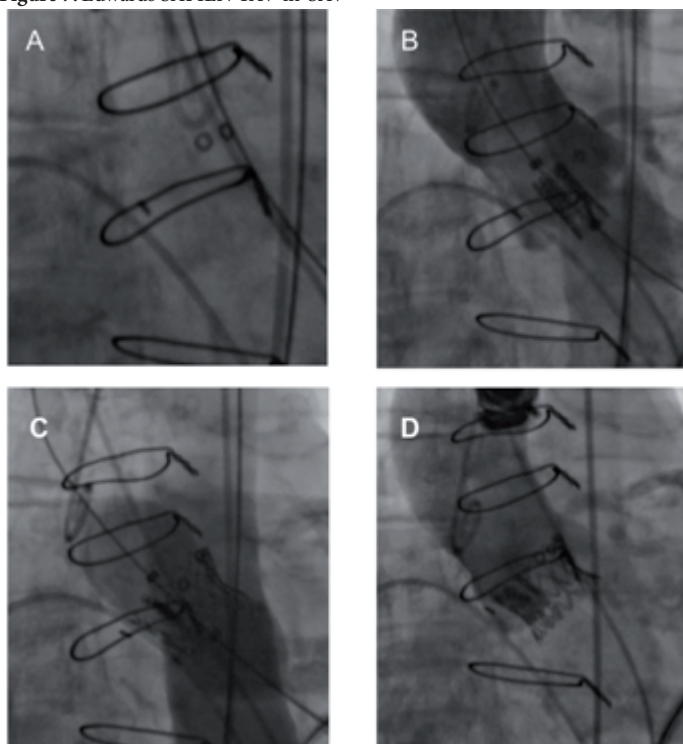


Figure 7. Edwards SAPIEN TAV-in-SAV procedure. Transapical implantation of a 23 mm Edwards SAPIEN TAV inside a 21 mm Medtronic Mosaic bioprosthesis. (A) Fluoroscopic identification of the Medtronic Mosaic valve. (B) Positioning of the Edwards SAPIEN valve. (C) Deployment of the Edwards SAPIEN valve. (D) Final contrast aortography. With permission from Mylotte et al. *Heart* 2013 99: 960-967.

Figure 8. Medtronic CoreValve TAV-in-SAV

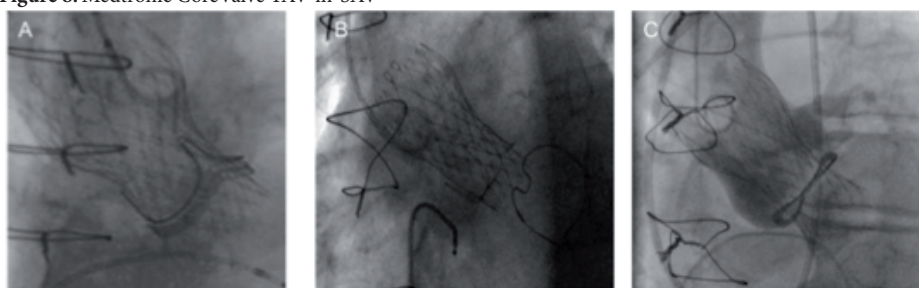


Figure 8. Medtronic CoreValve transcatheter aortic valve in surgical aortic valve (TAV-in-SAV) procedures. Medtronic CoreValve prosthesis implantation within (A) Edwards Perimount, (B) Carpentier-Edwards Porcine Supra-Annular Valve, and (C) Sorin Soprano bioprosthesis. With permission from Mylotte et al. *Heart* 2013 99: 960-967.

of coronary occlusion is deemed to be high. Furthermore, if the risk of coronary occlusion seems high, a safety wire (with/without a loaded stent) can be placed in the coronary arteries to facilitate and/or expedite percutaneous coronary intervention (**Figure 9**).

Figure 9. TAV-in-SAV with Prophylactic Left Main Coronary Protection.



Figure 9. Implantation of a Medtronic CoreValve within a 19 mm Sorin Mitroflow bioprosthesis, facilitated by placing a 0.014 guide wire into the distal left circumflex. Note the pre-mounted balloon in the left main stem.

Balloon Predilatation

Current guidelines discourage balloon valvuloplasty of degenerative bioprostheses on the left side of the heart as a single procedure because of a significant risk of hemodynamic compromise following inadvertent leaflet tear.^{2, 42} Certainly, there is little to be gained from pre-emptive balloon valvuloplasty in the setting of primary bioprosthesis regurgitation or in transapical cases with antegrade crossing of the aortic valve. In contrast, if difficulty crossing a stenotic bioprosthesis or if suboptimal THV expansion is envisaged due to severe calcification or pannus formation, then upfront valvuloplasty with an undersized balloon may be appropriate.

THV Positioning

As with TAVI for native aortic stenosis, the optimal fluoroscopic angle for implantation should be chosen. This is achieved by lining up the fluoroscopic markers, particularly the sewing ring along a single plane. Understanding the construction of the surgical bioprosthesis is axiomatic.¹⁰ The recently developed Aortic VIV Application (Link) provides a very useful

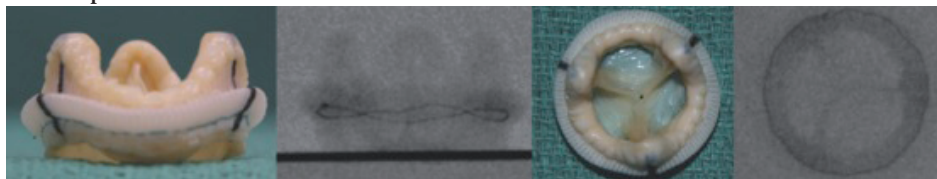
guide for THV positioning in available bioprostheses. In stented bioprostheses, the sewing ring is the most rigid structure and provides the anchor for THV implantation. For supra annular bioprostheses, the Edwards SAPIEN and the CoreValve should be positioned 15-20% and 4 mm below the lowest fluoroscopic part of the stent, respectively. For intra annular bioprostheses, the Edwards SAPIEN and the CoreValve should be positioned 15-20% and 4 mm below the sewing ring, respectively. Intraprocedural transoesophageal echocardiography is strongly recommended to aid in positioning in cases with stentless valves or for stented valves with radiolucent sewing rings or when the leaflets are noncalcified or regurgitant. Stable guide wire position and coaxial implantation of the THV are essential for accurate positioning. Ventricular pacing should be considered for patients with greater than mild bioprosthetic regurgitation. The Edwards SAPIEN valve is probably best inflated gradually and slowly, as small adjustments can be made during deployment to optimise positioning. Cautious initial deployment of the CoreValve is essential as further positioning of the THV is extremely difficult or even impossible once firm contact has been made with the frame of the surgical valve. Ventricular pacing or breath-hold may also facilitate deployment. Second-generation TAVI systems that are recapturable and repositionable will hopefully reduce the incidence of THV malposition.³⁴

Durability of TAV-in-SAV

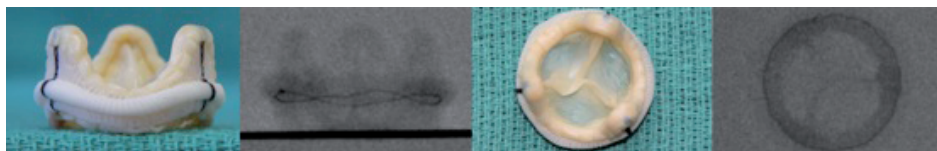
Since TAV-in-SAV is a relatively new procedure, the long-term durability of such approach has to be defined. Anecdotal cases of earlier than expected valve deteriorations have been presented at professional meetings, yet rarely reported in the medical literature.⁴³ The long-term quality and functionality of the implanted catheter-based valve in the setting of TAV-in-SAV will dictate how widely this therapeutic strategy can be offered to patients with surgical bioprosthetic valve deterioration.

Figure 10. Bioprosthetic Heart Valves Gallery

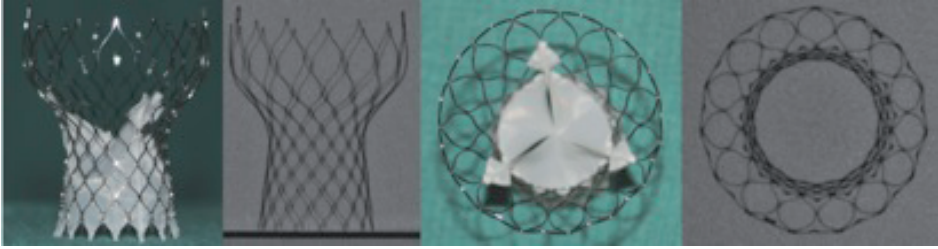
Biocor supra



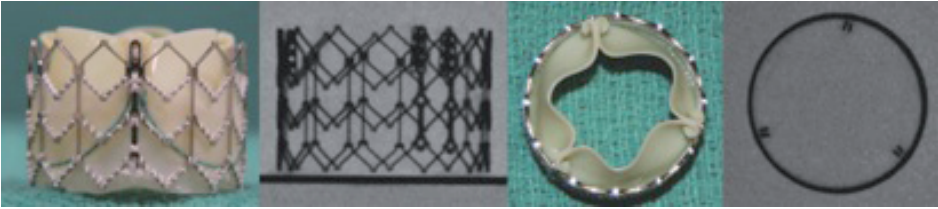
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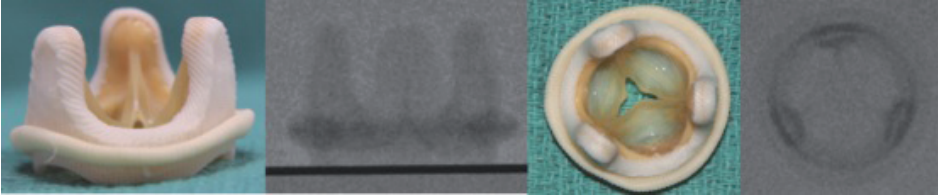
CoreValve



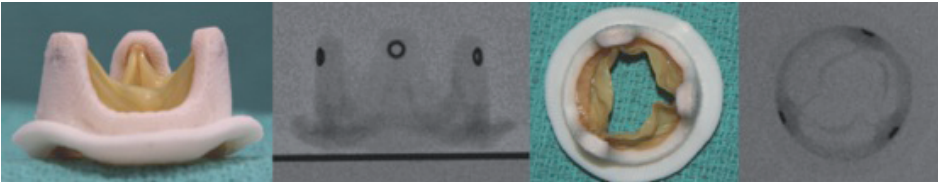
Sapien



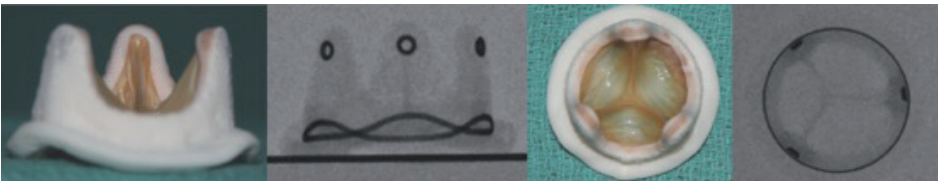
Aspire



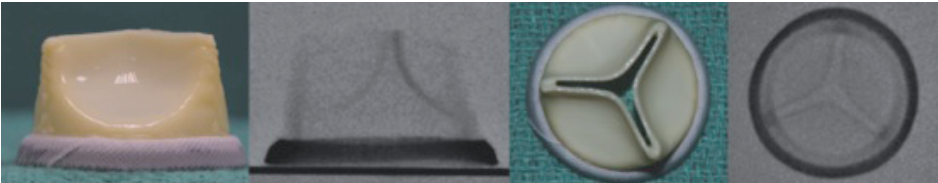
Mosaic



Hancock



Mitroflow



Soprano

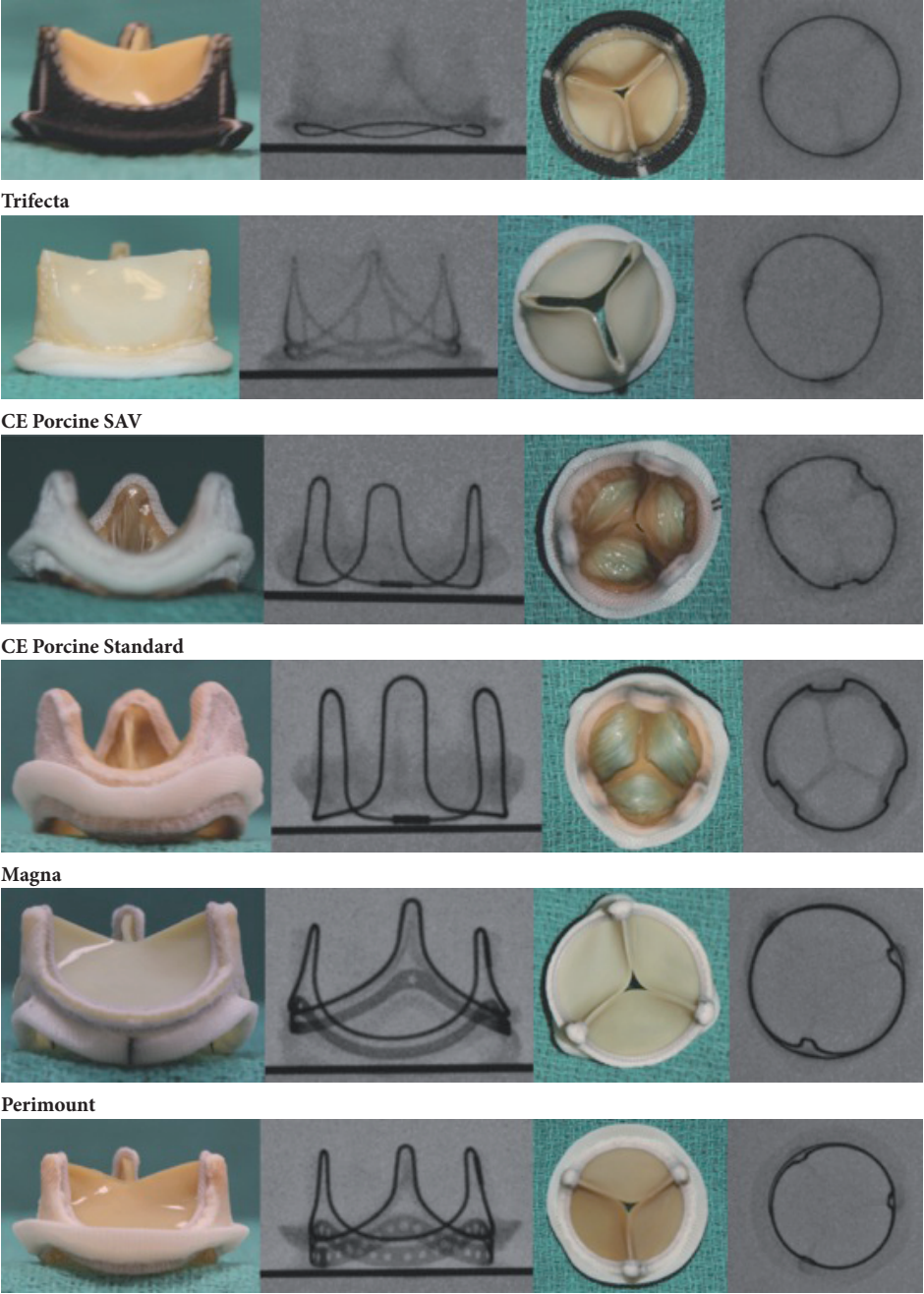


Figure 10. Surgical bioprosthesis valves visualized from the side and the corresponding fluoroscopic image, and from above, with corresponding fluoroscopic image (left to right)

REFERENCES

1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd and Thomas JD. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014.
2. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL and Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33:2451-96.
3. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP and Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg*. 2009;137:82-90.
4. Chan V, Malas T, Lapierre H, Boodhwani M, Lam BK, Rubens FD, Hendry PJ, Masters RG, Goldstein W, Mesana TG and Ruel M. Reoperation of left heart valve bioprostheses according to age at implantation. *Circulation*. 2011;124:S75-80.
5. Ruel M, Chan V, Bedard P, Kulik A, Ressler L, Lam BK, Rubens FD, Goldstein W, Hendry PJ, Masters RG and Mesana TG. Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age. *Circulation*. 2007;116:I294-300.
6. Ruel M, Kulik A, Rubens FD, Bedard P, Masters RG, Pipe AL and Mesana TG. Late incidence and determinants of reoperation in patients with prosthetic heart valves. *Eur J Cardiothorac Surg*. 2004;25:364-70.
7. Vogt PR, Brunner-LaRocca H, Sidler P, Zund G, Truniger K, Lachat M, Turina J and Turina MI. Reoperative surgery for degenerated aortic bioprostheses: predictors for emergency surgery and reoperative mortality. *Eur J Cardiothorac Surg*. 2000;17:134-9.
8. Jamieson WR, Burr LH, Miyagishima RT, Janusz MT, Fradet GJ, Ling H and Lichtenstein SV. Re-operation for bioprosthetic aortic structural failure - risk assessment. *European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery*. 2003;24:873-8.
9. Walther T, Kempfert J, Borger MA, Fassl J, Falk V, Blumenstein J, Dehdashtian M, Schuler G and Mohr FW. Human minimally invasive off-pump valve-in-a-valve implantation. *Ann Thorac Surg*. 2008;85:1072-3.
10. Piazza N, Bleiziffer S, Brockmann G, Hendrick R, Deutsch MA, Opitz A, Mazzitelli D, Tassani-Prell P, Schreiber C and Lange R. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 2). *JACC Cardiovascular interventions*. 2011;4:733-42.
11. Piazza N, Bleiziffer S, Brockmann G, Hendrick R, Deutsch MA, Opitz A, Mazzitelli D, Tassani-Prell P, Schreiber C and Lange R. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 1). *JACC Cardiovascular interventions*. 2011;4:721-32.
12. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, Descoutures F, Hengstenberg C, Moat NE, Bekeredjian R, Napodano M, Testa L, Lefevre T, Guetta V, Nissen H, Hernandez JM, Roy D, Teles RC, Segev A, Dumonteil N, Fiorina C, Gotzmann M, Tchetché D, Abdel-Wahab M, De Marco F, Baumbach A, Laborde JC and Kornowski R. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. *Circulation*. 2012;126:2335-44.

13. Eggebrecht H, Schafer U, Treede H, Boekstegers P, Babin-Ebell J, Ferrari M, Mollmann H, Baumgartner H, Carrel T, Kahlert P, Lange P, Walther T, Erbel R, Mehta RH and Thielmann M. Valve-in-valve transcatheter aortic valve implantation for degenerated bioprosthetic heart valves. *JACC Cardiovascular interventions*. 2011;4:1218-27.
14. Kelly T, Marquez S and Popelar C. In Vitro Testing of Heart Valve Substitutes. In: P. Iaizzo, R. Bianco, A. Hill and J. St Louis, eds. *Heart Valves: From Design to Clinical Implantation* New York: Springer; 2013.
15. Mylotte D, Osnabrugge RL, Martucci G, Lange R, Kappetein AP and Piazza N. Failing surgical bioprosthesis in aortic and mitral position. *EuroIntervention*. 2013;9 Suppl:S77-83.
16. Dunning J, Graham RJ, Thambyrajah J, Stewart MJ, Kendall SW and Hunter S. Stentless vs. stented aortic valve bioprostheses: a prospective randomized controlled trial. *Eur Heart J*. 2007;28:2369-74.
17. Mylotte D, Lange R, Martucci G and Piazza N. Transcatheter heart valve implantation for failing surgical bioprostheses: technical considerations and evidence for valve-in-valve procedures. *Heart*. 2013. 99: 960-7.
18. Chikwe J, Filsoofi F and Carpentier AF. Prosthetic valve selection for middle-aged patients with aortic stenosis. *Nat Rev Cardiol*. 2010;7:711-9.
19. Cohn LH, Collins JJ, Jr., Rizzo RJ, Adams DH, Couper GS and Aranki SE. Twenty-year follow-up of the Hancock modified orifice porcine aortic valve. *Ann Thorac Surg*. 1998;66:S30-4.
20. David TE, Ivanov J, Armstrong S, Feindel CM and Cohen G. Late results of heart valve replacement with the Hancock II bioprosthesis. *J Thorac Cardiovasc Surg*. 2001;121:268-77.
21. Briand M, Pibarot P, Despres JP, Voisine P, Dumesnil JG, Dagenais F and Mathieu P. Metabolic syndrome is associated with faster degeneration of bioprosthetic valves. *Circulation*. 2006;114:I512-7.
22. Roselli EE, Smedira NG and Blackstone EH. Failure modes of the Carpentier-Edwards pericardial bioprosthesis in the aortic position. *J Heart Valve Dis*. 2006;15:421-7; discussion 427-8.
23. Bapat VN, Attia R and Thomas M. Effect of valve design on the stent internal diameter of a bioprosthetic valve: a concept of true internal diameter and its implications for the valve-in-valve procedure. *JACC Cardiovascular interventions*. 2014;7:115-27.
24. Webb JG and Dvir D. Transcatheter aortic valve replacement for bioprosthetic aortic valve failure: the valve-in-valve procedure. *Circulation*. 2013;127:2542-50.
25. Webb JG, Wood DA, Ye J, Gurvitch R, Masson JB, Rodes-Cabau J, Osten M, Horlick E, Wendler O, Dumont E, Carere RG, Wijesinghe N, Nietlispach F, Johnson M, Thompson CR, Moss R, Leipsic J, Munt B, Lichtenstein SV and Cheung A. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation*. 2010;121:1848-57.
26. Latib A, Ielasi A, Montorfano M, Maisano F, Chieffo A, Cioni M, Mussardo M, Bertoldi L, Shannon J, Sacco F, Covello RD, Figini F, Godino C, Grimaldi A, Spagnolo P, Alfieri O and Colombo A. Transcatheter valve-in-valve implantation with the Edwards SAPIEN in patients with bioprosthetic heart valve failure: the Milan experience. *EuroIntervention*. 2012;7:1275-84.
27. Kempfert J, Van Linden A, Linke A, Borger MA, Rastan A, Mukherjee C, Ender J, Schuler G, Mohr FW and Walther T. Transapical off-pump valve-in-valve implantation in patients with degenerated aortic xenografts. *Ann Thorac Surg*. 2010;89:1934-41.
28. Bedogni F, Laudisa ML, Pizzocri S, Tamburino C, Ussia GP, Petronio AS, Napodano M, Ramondo A, Presbitero P, Etti F, Santoro G, Klugman S, De Marco F, Brambilla N and Testa L. Transcatheter valve-in-valve implantation using Corevalve Revalving System for failed surgical aortic bioprostheses. *JACC Cardiovascular interventions*. 2011;4:1228-34.
29. Linke A, Woitek F, Merx MW, Schiefer C, Mobius-Winkler S, Holzhey D, Rastan A, Ender J, Walther T, Kelm M, Mohr FW and Schuler G. Valve-in-valve implantation of Medtronic CoreValve prosthesis in patients with failing bioprosthetic aortic valves. *Circ Cardiovasc Interv*. 2012;5:689-97.

30. Dvir D, Assali A, Vaknin-Assa H, Sagie A, Shapira Y, Porat E and Kornowski R. Transcatheter aortic and mitral valve implantations for failed bioprosthetic heart valves. *J Invasive Cardiol.* 2011;23:377-81.
31. Dvir D, Webb J, Bleiziffer S, Pasic M, Waksman R, Kodali S, Barbanti B, Latib A, Schaefer U, Rodés-Cabau J, Treede H, Piazza N, Hildick-Smith D, Himbert D, Walther T, Hengstenberg C, Nissen H, Bekerédjian R, Presbitero P, Ferrari E, Segev A, de Weger A, Windecker S, Moat N, Napodano M, Wilbring M, Cerillo A, Brecker S, Tchetché D, Lefèvre T, De Marco F, Fiorina C, Petronio A, Teles R, Testa L, Laborde J, Leon M and Kornowski R. Transcatheter Aortic Valve Implantation in Failed Bioprosthetic Surgical Valves: Correlates for Survival from the Valve-in-Valve International Data. *JAMA.* 2014; 312:162-70.
32. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW and Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *EuroIntervention.* 2012;8:782-95.
33. Azadani AN, Jaussaud N, Matthews PB, Ge L, Chuter TA and Tseng EE. Transcatheter aortic valves inadequately relieve stenosis in small degenerated bioprostheses. *Interact Cardiovasc Thorac Surg.* 2010; 11:70-7.
34. Piazza N, Martucci G, Lachapelle K, de Varennes B, Bilodeau L, Buithieu J and Mylotte D. First-in-human experience with the Medtronic CoreValve Evolut R. *EuroIntervention.* 2014;9:1260-3.
35. Binder RK, Wood D, Webb JG and Cheung A. First-in-human valve-in-valve implantation of a 20 mm balloon expandable transcatheter heart valve. *Catheter Cardiovasc Interv.* 2013;82:E929-31.
36. Ben-Gal Y, Finkelstein A, Bruckheimer E, Banai S, Keren G, Kramer A and Uretzky G. Transapical implantation of a melody valve in a degenerated low-diameter prosthetic aortic valve. *Circulation.* 2013; 127:e553-6.
37. Kempfert J, Gírrbach F, Haensig M, Subramanian S, Holzhey DM and Mohr FW. Transapical aortic valve-in-valve-in-valve implantation as a procedural rescue option. *Ann Thorac Surg.* 2013;95:325-8.
38. Jeger RV, Manoharan G and Kaiser CA. First-in-man Portico(R) transcatheter aortic valve-in-valve implantation in a degenerated 19 mm Mitroflow(R) aortic pericardial heart valve. *EuroIntervention.* 2014;9:1368.
39. Kiefer P, Lehmkuhl L, Seeburger J, Vollroth M, Noack T, Schroter T, Mohr FW and Holzhey D. Symetis Acurate aortic valve-in-valve implantation for early degeneration of a Sapien THV prosthesis. *Ann Thorac Surg.* 2013;96:1880.
40. Ribeiro HB, Nombela-Franco L, Urena M, Mok M, Pasian S, Doyle D, Delarochelliere R, Cote M, Laflamme L, Delarochelliere H, Allende R, Dumont E and Rodés-Cabau J. Coronary Obstruction After Transcatheter Aortic Valve Implantation: A Systematic Review. *JACC Cardiovascular interventions.* 2013. 6:452-61.
41. Stortecky S, Wenaweser P and Windecker S. Transcatheter aortic valve implantation and cerebrovascular accidents. *EuroIntervention.* 2012;8 Suppl Q:Q60-9.
42. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd and Thomas JD. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014. 129:2440-92.
43. Seeburger J, Weiss G, Borger MA and Mohr FW. Structural valve deterioration of a Corevalve prosthesis 9 months after implantation. *Eur Heart J.* 2013;34:1607.

**TRANSCATHETER AORTIC
VALVE IMPLANTATION
VERSUS RE-DO SURGERY
FOR FAILING SURGICAL
AORTIC BIOPROSTHESIS: A
MULTI-CENTER PROPENSITY
SCORE ANALYSIS**

Transcatheter Aortic Valve Implantation Versus Re-do Surgery for Failing Surgical Aortic Bioprosthesis: a Multi-Center Propensity Score Analysis

Spaziano M, Mylotte D, Thériault-Lauzier P, De Backer O, Søndergaard L, Bosmans J, Debry N, Modine T, Barbanti M, Tamburino C, Sinning JM, Grube E, Nickenig G, Mellert F, Bleiziffer S, Lange R, de Varennes B, Lachapelle K, Martucci G, Piazza N. *Circ EuroIntervention*. 2017;13:1149-1156.

ABSTRACT

Aims

Transcatheter aortic valve implantation for a failing surgical bioprosthesis (TAV-in-SAV) has become an alternative for patients at high risk for redo surgical aortic valve replacement (redo-SAVR). Comparisons between these approaches are non-existent. This study aimed to compare clinical and echocardiographic outcomes of patients undergoing TAV-in-SAV versus redo-SAVR after accounting for baseline differences by propensity score matching.

Methods and results

Patients from seven centres in Europe and Canada who had undergone either TAV-in-SAV (n=79) or redo-SAVR (n=126) were identified. Significant independent predictors used for propensity scoring were age, NYHA functional class, number of prior cardiac surgeries, urgent procedure, pulmonary hypertension, and COPD grade. Using a calliper range of ± 0.05 , a total of 78 well-matched patient pairs were found. All-cause mortality was similar between groups at 30 days (6.4% redo-SAVR vs. 3.9% TAV-in-SAV; $p=0.49$) and one year (13.1% redo-SAVR vs. 12.3% TAV-in-SAV; $p=0.80$). Both groups also showed similar incidences of stroke (0% redo-SAVR vs. 1.3% TAV-in-SAV; $p=1.0$) and new pacemaker implantation (10.3% redo-SAVR vs. 10.3% TAV-in-SAV; $p=1.0$). The incidence of acute kidney injury requiring dialysis was numerically lower in the TAV-in-SAV group (11.5% redo-SAVR vs. 3.8% TAV-in-SAV; $p=0.13$). The TAV-in-SAV group had a significantly shorter median total hospital stay (12 days redo-SAVR vs. 9 days TAV-in-SAV; $p=0.001$).

Conclusions

Patients with aortic bioprosthesis failure treated with either redo-SAVR or TAV-in-SAV have similar 30-day and one-year clinical outcomes.

Keywords: prior cardiovascular surgery, valve-in-valve, valve restenosis

INTRODUCTION

Transcatheter aortic valve implantation in a failing surgical aortic valve (TAV-in-SAV) was first reported in 2007 in an elderly patient with multiple comorbidities and at extreme risk for redo surgery¹. Since then, numerous small TAV-in-SAV case series have demonstrated good results with this procedure, with 30-day risk of mortality ranging from 0% to 7.4%²⁻⁴.

The historical gold standard treatment for patients with a failing surgical bioprosthesis is redo-SAVR. Although the clinical outcomes of redo-SAVR approach those of the index procedure in low-risk patients, periprocedural mortality rates increase significantly in those at high risk, with in-hospital mortality ranging from 2.3 to 16.4%⁵⁻⁷. This is especially true in the elderly as the odds ratio of mortality for redo-SAVR is 1.49 (1.10-1.97) per decade⁶. TAV-in-SAV is a less invasive procedure that obviates the need for sternotomy and cardiopulmonary bypass, and eliminates the risk of injury to a substernal internal mammary arterial graft in patients with previous coronary artery bypass grafting (CABG).

Recently, a 459-patient TAV-in-SAV registry⁸ reported 30-day and one-year mortality rates of 7.6% and 16.8%, respectively. Of note, moderately elevated post-procedural mean gradients >20 mmHg were reported in 27% of patients. In March 2015, the FDA approved the Medtronic CoreValve® (Medtronic, Minneapolis, MN, USA) for the treatment of a failing surgical bioprosthesis in high/extreme surgical risk patients. In October 2015, the Edwards SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA) received the same approval.

Studies comparing matched patients undergoing redo-SAVR or TAV-in-SAV are currently inexistent. While observational case series suggest similar clinical outcomes between the two approaches, patient characteristics are often dissimilar, making any comparison difficult and possibly futile^{8,9}. Adequately powered prospective randomised trials are unlikely given the sample size requirements in this very specific subgroup of patients¹⁰.

To investigate the comparative clinical effectiveness between TAV-in-SAV and redo-SAVR, we conducted a propensity score-matched analysis across seven international centres. Results from this study could validate the use of TAV-in-SAV as an alternative to redo-SAVR.

METHODS

Patient selection and identification of the study population

Patients were eligible for study inclusion if they had undergone TAV-in-SAV or redo-SAVR for a failing aortic bioprosthesis (stenosis, regurgitation or both) between January 2007 and January 2015 in one of seven centres in Europe and Canada: Antwerp University Hospital, Antwerp, Belgium; Ferrarotto Alessi Hospital, Catania, Italy; German Heart Centre, Munich, Germany; Lille University Health Centre, Lille, France; Rigshospitalet, Copenhagen, Denmark; Royal Victoria Hospital, Montreal, Canada; and Universitätsklinikum Bonn, Bonn,

Germany. All patients were identified by retrospective assessment of institutional databases. The selection of patients for TAV-in-SAV or redo-SAVR was performed at an institutional level, following consideration of the risk profile of each case and Heart Team assessment. For all patients, centres submitted a dedicated case report form detailing patient baseline characteristics, echocardiographic data, procedural information and scheduled clinical follow-up.

The study included all consecutive patients who were potential candidates for either a TAV-in-SAV or redo-SAVR. Patients were excluded if they underwent redo-SAVR for paravalvular leak, valve thrombosis or endocarditis. Concomitant coronary revascularisation performed by either percutaneous or surgical techniques was permitted. Local ethics committees approved the retrospective collection of data, and all subjects gave written informed consent for their intervention.

Data collection and study endpoints

Baseline data were complete for all patients, except logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) and STS scores which were unavailable in 35% of redo-SAVR patients. The primary endpoint was 30-day mortality. Secondary endpoints included one-year mortality, stroke, myocardial infarction, new pacemaker implantation, acute kidney injury requiring dialysis, post-procedural mean gradient, and length of hospital stay. Endpoints were defined according to the updated Valve Academic Research Consortium (VARC) criteria¹¹. Pulmonary hypertension was defined as systolic pulmonary artery pressure above 50 mmHg as estimated by tricuspid regurgitation jet on Doppler echocardiography. Procedure urgency was defined as being performed in a hospitalised patient rather than electively.

Statistical analysis

Baseline clinical and surgical characteristics were compared using Fisher's exact test for categorical variables and the Student's t-test for continuous variables. Propensity scores were derived by including age and sex with pre-treatment variables that were independently associated with treatment selection at $p < 0.10$ in a multivariable model of all variables. Propensity scores among patients undergoing either TAV-in-SAV or redo-SAVR were then matched using a calliper range of ± 0.05 to obtain matched pairs of patients. Replacements were permitted (maximum of four uses) in the redo-SAVR group.

In addition to matching, we also compared redo-SAVR and TAV-in-SAV using the inverse probability of treatment weights technique. Patients with propensity scores below the 2.5th percentile in the TAV-in-SAV group and above the 97.5th percentile in the redo-SAVR group were removed. Next, a weight was attributed to each remaining patient according to the inverse of their propensity score, and comparisons were performed on this weighted and trimmed data set.

Survival at 30 days and one year was plotted using Kaplan-Meier curves and between group differences were calculated using the log-rank test. A p-value <0.05 was considered significant. Statistical analyses were performed with SPSS, Version 23 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

A total of 205 consecutive patients meeting inclusion and exclusion criteria underwent redo-SAVR (n=126) or TAV-in-SAV (n=79) for a failing aortic bioprosthesis during the study period. Patients undergoing TAV-in-SAV were older, more likely to have had multiple prior cardiac surgeries, be in NYHA functional Class III or IV, have higher logistic EuroSCORE and STS scores, and display more comorbidities (**Table 1**).

Standardised differences between groups after trimming and weighting were less than 0.20 (i.e., small) for all variables except atrial fibrillation and number of previous surgeries (**Table 1**).

Propensity score matching

Pre-treatment variables found to be independent predictors of treatment selection and used for propensity scoring were age, NYHA functional class, number of prior cardiac surgeries, urgent procedure, pulmonary hypertension, and chronic obstructive pulmonary disease (COPD) grade (**Table 2**). These variables were all associated with assignment to TAV-in-SAV, with the exception of urgent procedure, which was associated with redo-SAVR.

Propensity score matching generated 78 pairs of patients. Baseline characteristics were similar between groups after propensity matching (**Table 1**). In each pair, redo-SAVR occurred at a median of 421 days before TAV-in-SAV. However, in 28 of 78 pairs, TAV-in-SAV predated redo-SAVR.

The surgical and bioprosthesis characteristics of matched patients are displayed in **Table 3**. The mean delay between index procedure and either redo-SAVR or TAV-in-SAV was 8.2 and 9 years, respectively (p=0.30). This delay was less than three years in 16.4% of the total population, with regurgitation being the most common mode of failure in this “accelerated failure” subgroup. While pure regurgitation was the mode of failure in half the patients in the redo-SAVR group (50.0%), pure stenosis was the most common mode of failure in TAV-in-SAV patients (51.3%). In total, 25 patients in the redo-SAVR group (32%) had coronary artery disease (CAD) necessitating revascularisation. Of these, 21 underwent concomitant CABG at the time of surgery; the other four underwent PCI as conduits for bypass were unavailable. In the TAV-in-SAV group, 33 patients (42%) had CAD necessitating revascularisation (p=0.25 vs. redo-SAVR group). PCI was performed before TAV-in-SAV in 32 patients, and at the time of procedure in one patient. A Carpentier-Edwards (Edwards Lifesciences) was the failing

Table 1 Baseline characteristics: before vs. after PS matching and standardised differences.

Variable	Before PS matching				After PS matching				IPTW	
	Redo-SAVR (n=126)	TAV-in-SAV (n=79)	Diff	p-value	Redo-SAVR (n=78)	TAV-in-SAV (n=78)	Diff	p-value	Diff	p-value
Age	67.6±12.9	78.1±8.0	-0.98	<0.001	77.4±5.0	78.0±8.0	-0.09	0.58	0.19	0.1
Female sex	46 (37)	39 (49)	-0.26	0.08	34 (44)	39 (50)	-0.13	0.52	-0.11	0.4
Logistic EuroSCORE	14.0±12.4	22.0±16.0	-0.56	<0.001	22.1±18.3	22.1±16.0	0.00	0.99	-0.01	0.92
STS score*	4.4±4.4	7.4±4.9	-0.64	<0.001	5.8±4.6	7.2±4.9	-0.29	0.09	-0.07	0.62
More than 1 prior cardiac surgery	7 (6)	11 (14)	-0.29	0.05	9 (12)	10 (13)	-0.04	0.81	0.28	0.03
NYHA										
I	9 (8)	1 (1)	0.30	0.05	1 (1)	1 (1)	0.00	0.16	-0.14	0.32
II	33 (28)	14 (18)	0.21		8 (11)	13 (17)	-0.19		0.01	1
III	53 (45)	42 (54)	-0.22		33 (45)	42 (55)	-0.23		0.06	0.71
IV	22 (19)	21 (27)	-0.22		32 (43)	21 (27)	0.30		-0.04	0.79
Urgent procedure	17 (14)	5 (6)	0.24	0.16	10 (13)	5 (6)	0.22	0.28	0.08	0.55
LVEF (%)	50.6±13.3	50.7±13.4	-0.01	0.96	49.5±13.4	50.7±13.5	-0.09	0.58	0.02	0.87
Atrial arrhythmia (flutter or fibrillation)	39 (31)	27 (34)	-0.07	0.65	29 (37)	27 (35)	0.05	0.87	-0.25	0.04
Diabetes mellitus	15 (12)	16 (20)	-0.23	0.11	12 (15)	15 (19)	-0.10	0.67	-0.02	0.87
Hypertension	80 (64)	57 (72)	-0.19	0.23	57 (73)	56 (72)	0.03	1	-0.11	0.43
Coronary artery disease necessitating revascularisation	34 (27)	34 (43)	-0.34	0.02	25 (32)	33 (42)	-0.21	0.25	-0.02	0.9
Prior CABG	26 (21)	25 (32)	-0.25	0.1	18 (23)	24 (31)	-0.17	0.37	0.08	0.59
Prior stroke	15 (12)	7 (9)	0.10	0.64	9 (12)	7 (9)	0.08	0.79	-0.09	0.55
Peripheral vascular disease	13 (10)	12 (15)	-0.15	0.38	13 (17)	11 (14)	0.07	0.83	-0.14	0.29
COPD	116 (92)	63 (80)	0.36	0.04	70 (90)	62 (80)	0.29	0.15	-0.03	0.86
Grade 1	4 (3)	7 (9)	-0.24		2 (3)	7 (9)	-0.28		0.18	0.18
Grade 2 or more	6 (5)	9 (11)	-0.25		6 (8)	9 (12)	-0.13		-0.11	0.38
Pulmonary hypertension	13 (10)	24 (30)	-0.51	0.001	28 (36)	24 (31)	0.11	0.61	-0.05	0.77
eGFR (ml/min/1.73 m ²)	70.2±22.8	59.7±18.0	0.51	<0.001	59.3±20.7	59.7±18.2	-0.02	0.89	-0.1	0.37

Values are mean±SD or n (%).

* STS score was available for 80 patients in the redo-SAVR group before PS matching and 51 patients after PS matching. CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; Diff: standardised difference; eGFR: glomerular filtration rate estimated by the MDRD formula; EuroSCORE: European System for Cardiac Operative Risk Evaluation; IPTW: inverse probability treatment weighting after trimming of 2.5% of tails; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association (functional class); PS: propensity score; SAVR: surgical aortic valve replacement; STS: Society of Thoracic Surgeons; TAV-in-SAV: transcatheter aortic valve in surgical aortic valve

bioprosthesis in 19 patients of the redo-SAVR group (24.4%) and 34 patients of the TAV-in-SAV group (43.6%). Other valves were found less frequently. Types and sizes of surgical bioprostheses or transcatheter heart valves (THV) used in both groups are also displayed in **Table 3**. Among patients undergoing TAV-in-SAV, self-expanding and balloon-expandable THV were used in similar proportions, and transfemoral access was chosen in 53.8% of patients. Conversion to open surgery did not occur in any of the TAV-in-SAV patients, and requirement for a second THV during the procedure occurred in four (5.1%) cases.

Clinical outcomes

Table 4 describes clinical outcomes at 30 days and one year for both groups before and after propensity score matching. Time-to-event curves comparing both treatment modalities after matching are depicted in **Figure 1**. Thirty-day follow-up was complete in 99.4%, and 88.5% at one year. Thirty-day Kaplan-Meier mortality was 2.5% higher in the redo-SAVR group compared to the TAV-in-SAV group, but this difference did not reach statistical significance (6.4 vs. 3.9%, respectively; $p=0.49$). One-year mortality was similar between groups (13.1 redo-SAVR vs. 12.3% TAV-in-SAV; $p=0.80$). Similar results were found when using inverse probability of treatment weights (**Table 5**), when stratified by failure mechanism and failing prosthesis size. There was no difference in 30-day mortality between patients who underwent TAV-in-SAV with the Edwards THV compared to those who underwent TAV-in-SAV with the Medtronic CoreValve THV (3.1 vs. 4.3%, respectively; $p=0.77$).

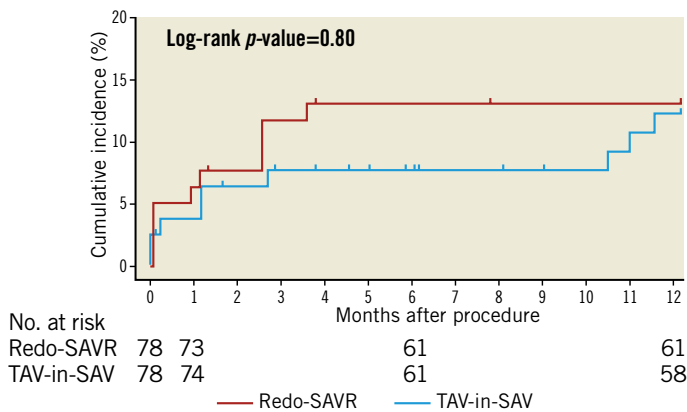


Figure 1 Cumulative incidence of all-cause mortality. Cumulative incidence (%) of all-cause one-year mortality in redo-SAVR (red line) and TAV-in-SAV (blue line). There was no difference in one-year mortality between groups.

Table 2 Independent predictors of treatment assignment.

Variable	OR	<i>p</i> -value
Age (per 1-year increment)	1.128	<0.0001
NYHA class (per 1 class increment)	1.553	0.06
Number of prior surgeries (per surgery)	4.704	0.008
Urgent procedure	0.218	0.02
Pulmonary hypertension	2.059	0.1
COPD grade (per 1 grade increment)	1.469	0.1

Odds ratios (OR) values above 1 indicate association with TAV-in-SAV. COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association

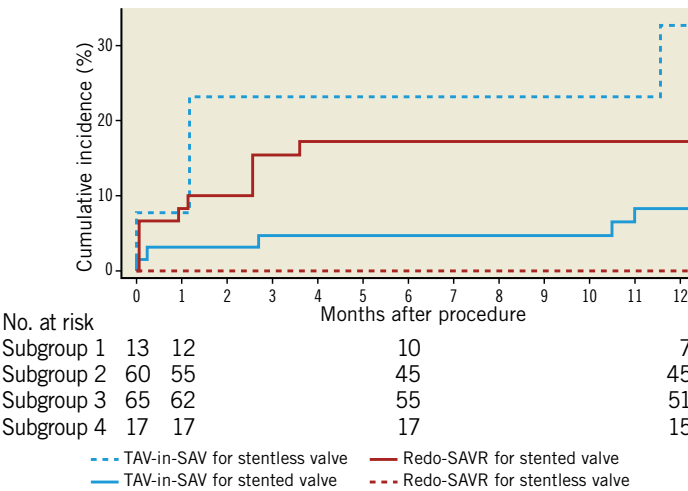


Figure 2 Cumulative incidence of all-cause mortality stratified by failing bioprosthesis type. Cumulative incidence (%) of all-cause one-year mortality in TAV-in-SAV for failing stentless valve (group 1, dashed blue line), redo-SAVR for failing stented valve (group 2, solid red line), TAV-in-SAV for failing stented valve (group 3, solid blue line), and redo-SAVR for failing stentless valve (group 4, dashed red line). There was a statistically significant difference in one-year mortality between groups 1 and 4.

Secondary outcome measures

Propensity-matched groups did not differ with respect to the following clinical outcomes: stroke, myocardial infarction and new pacemaker implantation. Patients with a failing stentless bioprosthesis had a higher rate of new pacemaker implantation compared to those with a stented bioprosthesis, regardless of treatment modality (23.3 vs. 6.4%; $p=0.01$). There was three times more renal failure requiring dialysis in the redo-SAVR group compared to the TAV-in-SAV group; however, this difference did not reach statistical significance (11.5% vs. 3.8%, respectively; $p=0.13$). Median total hospital length of stay was three days shorter in the TAV-in-SAV than in the redo-SAVR group (9 vs. 12 days, $p=0.001$) (**Table 4**). Similar results were found when using inverse probability of treatment weights (**Table 5**).

Table 3 Procedural and bioprosthesis characteristics of PS-matched patients.

Variable		Redo-SAVR (n=78)	TAV-in-SAV (n=78)	p-value
Time since last SAVR (years)		8.2±5.1	9.0±4.3	0.3
Type of failing bioprosthesis	Stented	60 (78)	65 (83)	0.68
	Stentless	17 (22)	13 (17)	
Label size of failing bioprosthesis	≤21 mm	32 (41)	18 (23)	<0.0001
	>21 mm and <25 mm	14 (18)	40 (51)	
	≥25 mm	19 (24)	17 (22)	
	Unknown	13 (17)	3 (4)	
Mechanism of failure	Stenosis	24 (31)	40 (51)	0.001
	Regurgitation	39 (50)	17 (22)	
	Mixed	15 (19)	21 (27)	
Centre	Munich	23 (30)	33 (42)	0.1
	Copenhagen	19 (24)	11 (14)	
	Bonn	16 (21)	11 (14)	
	Lille	7 (9)	6 (8)	
	Montreal	8 (10)	4 (5)	
	Catania	4 (5)	7 (9)	
	Antwerp	1 (1)	6 (8)	
Type of bioprosthesis used for redo-SAVR	Stented	77 (99)		
	Stentless	1 (1)		
Label size	≤21 mm	48 (62)		
	>21 mm and <25 mm	16 (21)		
	≥25 mm	15 (19)		
THV type	CoreValve		46 (59)	
	Edwards (SAPIEN/XT/ SAPIEN 3)		32 (41)	
THV size	23		45 (58)	
	26		26 (33)	
	29		4 (5)	
	31		3 (4)	
THV access site	Transfemoral		42 (54)	
	Transapical		24 (31)	
	Other		12 (15)	
Conversion to open surgery			0 (0)	
Requirement for a second THV			4 (5)	

Echocardiographic outcomes

At 30 days, redo-SAVR was associated with a lower mean gradient compared to TAV-in-SAV (14.3 mmHg vs. 18.1 mmHg, $p=0.01$). This difference was due to a significantly higher mean gradient in the Edwards TAV-in-SAV group (21.3 ± 7.2 mmHg) compared to patients

Table 4 Thirty-day and one-year outcomes before and after PS matching.

Variable	Before PS matching			After PS matching		
	Redo-SAVR (n=126)	TAV-in-SAV (n=79)	p-value	Redo-SAVR (n=78)	TAV- in-SAV (n=78)	OR or coefficient (95% CI) p-value
Thirty-day outcomes						
Death	6 (4.8)	3 (3.8)	1	5 (6.4)	3 (3.9)	0.58 (0.13-2.53) 0.49
Stroke	2 (1.6)	1 (1.3)	1	0 (0)	1 (1)	3.04 (0.12-75.75) 1
Myocardial infarction	2 (1.6)	1 (1.3)	1	0 (0)	1 (2)	3.04 (0.12-75.75) 0.49
Renal failure requiring dialysis	8 (6.3)	3 (3.8)	0.54	9 (12)	3 (4)	0.31 (0.08-1.18) 0.13
New pacemaker implantation	11 (8.7)	9 (11.4)	0.63	8 (10)	8 (10)	1.00 (0.36-2.81) 1
Mean gradient (mmHg)	14.2±5.9	18.1±7.4	0.002	14.3±6.2	18.1±7.4	+3.78 (0.95-6.60) 0.01
Mean gradient greater than 20 mmHg	9 (16.4)	20 (34.5)	0.03	7 (17)	21 (36)	3.74 (1.48-9.41) 0.04
Total hospital length of stay (median [IQR])	12 (8-18.5)	9 (6.75-13)	0.002	12 (8-24)	9 (7-13)	-9.38 (-14.84, -3.92) 0.001
One-year mortality	15 (12.2)	10 (13.5)	0.82	10 (13.1)	9 (12.3)	0.89 (0.34-2.32) 0.80

Values are mean±SD or n (%) unless specified otherwise. IQR: interquartile range; PS: propensity score; SAVR: surgical aortic valve replacement; TAV-in-SAV: transcatheter aortic valve in surgical aortic valve

in the CoreValve TAV-in-SAV group (15.4 ± 6.7 mmHg) and the redo-SAVR group (14.3 ± 6.2 mmHg) (**Figure 3A**). This difference between devices was found regardless of failing device inner diameter (**Figure 3B**). Furthermore, post-procedural transaortic gradients >20 mmHg were more than twice as likely in the Edwards TAV-in-SAV group (51.9%) compared to the CoreValve TAV-in-SAV and redo-SAVR groups (22.6 and 17.1%, respectively). **Figure 3C** displays mean post-procedural gradients stratified according to the type of failing bioprosthesis. Independent predictors of higher post-procedural gradients were a failing stented bioprosthesis (increase of 2.5 mmHg; $p=0.02$), treatment with an Edwards THV (increase of 4.7 mmHg compared to redo-SAVR and 4.3 mmHg compared to CoreValve; both $p<0.01$), and lower EuroSCORE (increase of 0.31 mmHg per 5% decrease in EuroSCORE; $p=0.02$).

DISCUSSION

The major findings of this propensity-matched comparison of redo-SAVR and TAV-in-SAV for failing aortic bioprostheses are as follows: 1) redo-SAVR and TAV-in-SAV for a failing bioprosthesis showed similar rates of 30-day and one-year mortality; 2) total hospital length of stay was shorter with TAV-in-SAV than redo-SAVR; 3) mean post-procedural gradients were higher with Edwards TAV-in-SAV compared to redo-SAVR and CoreValve TAV-in-SAV; and 4) failing stentless bioprostheses were associated with a higher rate of new pacemaker implantation and a lower mean post-procedural gradient, regardless of treatment modality. Mortality rates of 3.9% at 30 days for TAV-in-SAV are nearly two times lower than those reported in other studies^{3,12}. The Valve-in-Valve registry reported a 30-day mortality rate of 7.6% in patients with a similar risk profile⁸. This may be due to site selection bias, as we included only high-volume centres in the present study. While smaller valve sizes and valve stenosis were shown to be associated with higher mortality rates in the Valve-in-Valve registry, this was not found to be the case in our study.

With respect to the surgical group, the 6.4% and 13.1% mortality rates at 30 days and one year, respectively, are comparable to those reported in the surgical literature. Jones et al reported a 30-day mortality rate of 6.4% in an all-comers series⁶. Eitz et al reported 30-day and one-year mortality rates of 16.4% and 23%, respectively, in a cohort of 71 octogenarians⁵. However, comparisons to this last series may be inappropriate because patients with emergent indications such as endocarditis and thrombosis were excluded from our study.

The higher mortality rates with TAV-in-SAV in patients with a failing stentless bioprosthesis should be treated with circumspection as they are based on only four events in a small subgroup. Only one death occurred in the first 30 days, indicating that mortality may be due to patient characteristics more than procedural failure.

Table 5 Thirty-day and one-year outcome comparisons of TAV-in-SAV vs. redo-SAVR (trimmed groups, inverse probability of treatment weights).

Variable	OR or coefficient (95% CI)	<i>p</i> -value
Thirty-day outcomes		
Death	0.98 (0.12-8.40)	0.99
Stroke	2.18 (0.13-35.70)	0.59
Myocardial infarction	2.51 (0.15-41.20)	0.52
Renal failure requiring dialysis	1.21 (0.24-6.11)	0.82
New pacemaker implantation	0.99 (0.31-3.15)	0.99
Mean gradient (mmHg)	+5.37 (2.49-8.26)	<0.001
Mean gradient greater than 20 mmHg	6.70 (1.37-32.70)	0.02
Total hospital length of stay (days)	-4.59 (-10.15, -0.97)	0.11
One-year mortality	0.74 (0.24-2.31)	0.61

Odds ratios and continuous coefficients use redo-SAVR as reference group. SAVR: surgical aortic valve replacement; TAV-in SAV: transcatheter aortic valve in surgical aortic valve

Values are mean±SD or n (%). PS: propensity score; SAVR: surgical aortic valve replacement; TAV-in-SAV: transcatheter aortic valve in surgical aortic valve; THV: transcatheter heart valve

The main advantage of stentless bioprostheses over stented valves seems to be the superior haemodynamic profile achieved after the procedure with lower mean gradients. This is due to the increased space in the aortic root of patients with stentless valves.

Redo-SAVR also allows increased space in the aortic root compared to TAV-in-SAV. However, the CoreValve bioprosthesis, with its supra-annular leaflet position, yielded similar post-procedural gradients to redo-SAVR, while the Edwards THV (intra-annular leaflets) produced higher gradients, regardless of failing device size¹³. The CoreValve device may be better suited to tackle TAV-in-SAV but, in our study, higher mean gradients did not seem to translate into midterm clinical events.

There was no difference between TAV-in-SAV and redo-SAVR with respect to other clinical outcomes. The rate of renal failure requiring dialysis was numerically higher in the redo-SAVR group, but statistical significance was not found, possibly because of lack of power. The similar outcomes regarding pacemakers (something which is different from the literature concerning procedures performed on the native aortic valve) may be due to the more extensive debridement involving the ventricular septum in redo-SAVR (thereby increasing the pacemaker rate in that group) and the relative “shielding” of the septum by the failing prosthesis stent for TAV-in-SAV (thereby decreasing the pacemaker rate in that group). The relatively high rate of new pacemaker implantation in the stentless bioprosthesis group undergoing TAV-in-SAV may be related to baseline conduction disturbances, the absence of “shielding”, and deeper than usual implantation in these challenging cases. As reported in previous comparisons between TAVR and SAVR, less invasive approaches are associated

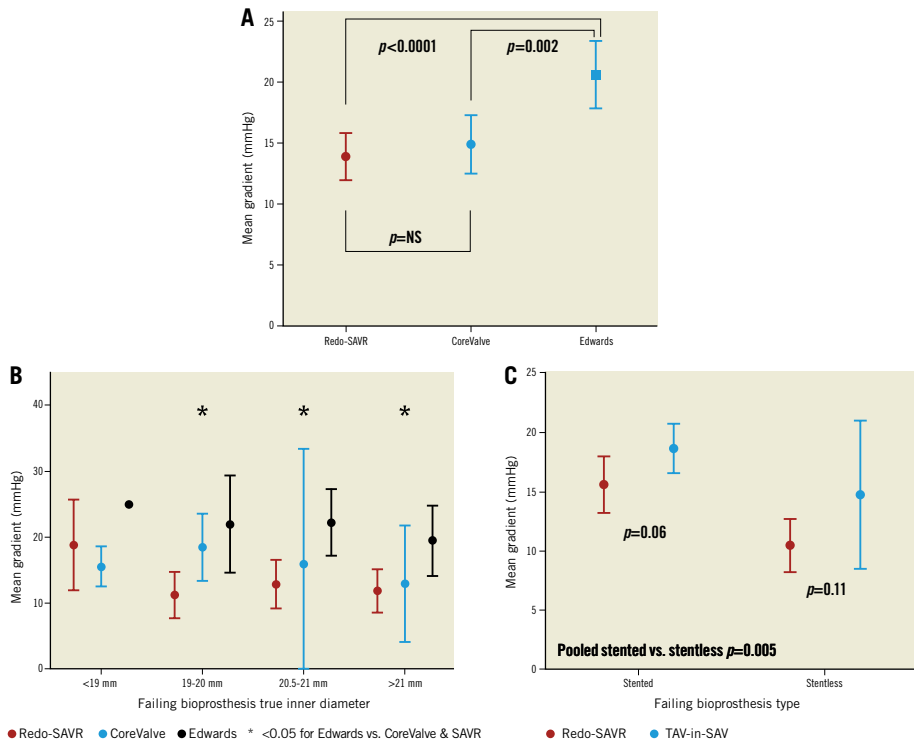


Figure 3 In-hospital mean gradient by treatment type. A) Post-procedural mean aortic gradient for patients in the redo-SAVR group (red circle), CoreValve TAV-in-SAV group (blue circle), and Edwards TAV-in-SAV group (blue square). Error bars represent 95% confidence interval. B) In-hospital mean gradient stratified by failing bioprosthesis true inner diameter and replacement device. P-values are for comparisons between Edwards (black) and redo-SAVR grouped with CoreValve (red and blue) for each size. Error bars represent 95% confidence interval. Only one case was performed with the Edwards device for the smallest size (<19 mm). C) In-hospital mean gradient stratified by failing bioprosthesis type. Post-procedural mean aortic gradient for patients with a failing stented bioprosthesis (left) and a failing stentless bioprosthesis (right). P-values are for comparisons between redo-SAVR (red) and TAV-in-SAV (blue). Error bars represent 95% confidence interval. The difference in gradients for pooled stented vs. stentless bioprostheses was statistically significant ($p=0.005$).

with shorter durations of hospital stay¹⁴. Total duration of hospital stay was similar to those reported in the PARTNER A trial.

LIMITATIONS

The present study has limitations inherent to all retrospective analyses. First, reasons for treatment allocation cannot be fully resolved, despite attempts for propensity matching. The large residual standardised differences after PS matching are a possible marker of residual

confounding. Certain baseline characteristics, such as failing bioprosthesis size and mechanism of failure, were dissimilar. Both of these are proven to be related to better outcomes in TAV-in-SAV. On the other hand, STS scores may appear to favour redo-SAVR. In this context, the direction and magnitude of bias cannot be determined. Matching for bioprosthesis would have been ideal, but impractical because the number of matched pairs would decrease. Smaller valves were treated more often by redo-SAVR because there are fewer transcatheter devices available for small surgical valves (for example, for a 19 mm Carpentier-Edwards SAV, only the Edwards SAPIEN 20 mm is recommended). Including more patients from more centres would not, in our view, modify the proportions of small surgical valves treated by redo-SAVR or TAV-in-SAV. With respect to revascularisation, groups differ because PCI was undertaken before the procedure in the TAV-in-SAV group, rather than during the procedure, as in redo-SAVR. Sites decided to perform PCI before TAV-in-SAV or CABG during redo-SAVR based on different criteria and did not report this in the same manner. Therefore, adjustment for this variable could not be performed. This retrospective trial used data that were not audited, and the collected haemodynamic data were not core laboratory adjudicated. STS scores were not available for a significant proportion of surgical patients. However, most of the elements that make up the STS score were not missing and fairly well balanced after matching. We preferred not to calculate missing STS scores with the data at hand, as these calculated “*post hoc*” values would be biased by the use of a calculator version that does not match the date of the procedure, giving artefactually low values¹⁵. In addition, the logistic EuroSCORE was almost identical between groups after matching. Follow-up was limited to one year, limiting the long-term assessment of haemodynamic findings. However, results up to one year are the current standard in studies focused on the elderly (mean age >77 years in each group) undergoing this type of procedure. Large randomised controlled trials would palliate most of these limitations. Realistically, as these are relatively infrequent procedures, we may never see an adequately powered randomised trial.

CONCLUSIONS

Patients with aortic bioprosthesis failure treated with either redo-SAVR or TAV-in-SAV have similar 30-day and one-year clinical outcomes.

IMPACT ON DAILY PRACTICE

Patients with a failing aortic bioprosthesis at high risk for redo surgery have similar outcomes whether they undergo TAV-in-SAV or redo-SAVR.

CONFLICT OF INTEREST STATEMENT

D. Mylotte, L. Søndergaard, J. Bosmans, T. Modine, J-M. Sinning, E. Grube, G. Nickenig, F. Mellert, S. Bleiziffer, R. Lange, G. Martucci, and N. Piazza report being proctor and/or consultant for Medtronic. O. De Backer, L. Søndergaard, and N. Piazza report being proctor and/or consultant for St. Jude Medical. L. Søndergaard, T. Modine, J-M. Sinning, E. Grube, G. Nickenig, and F. Mellert report being proctor and/or consultant for Boston Scientific. L. Søndergaard, M. Barbanti, J-M. Sinning, G. Nickenig, and F. Mellert report being proctor and/or consultant for Edwards Lifesciences. T. Modine reports being proctor and/or consultant for General Electric. The other authors have no conflicts of interest to declare.

ABBREVIATIONS

COPD	chronic obstructive pulmonary disease
eGFR	estimated glomerular filtration rate
EuroSCORE	European System for Cardiac Operative Risk Evaluation
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PS	propensity score
SAVR	surgical aortic valve replacement
STS	Society of Thoracic Surgeons
TAV-in-SAV	transcatheter aortic valve in surgical aortic valve
THV	transcatheter heart valve
VARC	Valve Academic Research Consortium

REFERENCES

1. Wenaweser P, Buellesfeld L, Gerckens U, Grube E. Percutaneous aortic valve replacement for severe aortic regurgitation in degenerated bioprosthesis: the first valve in valve procedure using the Corevalve Revalving system. *Catheter Cardiovasc Interv.* 2007;70:760-4.
2. Duncan A, Davies S, Di Mario C, Moat N. Valve-in-valve transcatheter aortic valve implantation for failing surgical aortic stentless bioprosthetic valves: A single-center experience. *J Thorac Cardiovasc Surg.* 2015;150:91-8.
3. Stahli BE, Reinthaler M, Nguyen-Kim TD, Gebhard C, Tasnady H, Grünenfelder J, Falk V, Corti R, Frauenfelder T, Lüscher TF, Maier W, Mullen MJ, Landmesser U. Transcatheter aortic valve-in-valve implantation: clinical outcome as defined by VARC-2 and postprocedural valve dysfunction according to the primary mode of bioprosthesis failure. *J Invasive Cardiol.* 2014;26:542-7.
4. Subban V, Savage M, Crowhurst J, Poon K, Incani A, Aroney C, Tesar P, Clarke A, Raffel C, Murdoch D, Platts D, Burstow D, Saireddy R, Bett N, Walters DL. Transcatheter valve-in-valve replacement of degenerated bioprosthetic aortic valves: a single Australian Centre experience. *Cardiovasc Revasc Med.* 2014;15:388-92.
5. Eitz T, Fritzsche D, Kleikamp G, Zittermann A, Horstkotte D, Körfer R. Reoperation of the aortic valve in octogenarians. *Ann Thorac Surg.* 2006;82:1385-90.
6. Jones JM, O'Kane H, Gladstone DJ, Sarsam MA, Campalaini G, MacGowan SW, Cleland J, Cran GW. Repeat heart valve surgery: risk factors for operative mortality. *J Thorac Cardiovasc Surg.* 2001;122:913-8.
7. Pechlivanidis K, Onorati F, Petrilli G, Santini F, Milano A, Torre S, Calzaferri D, Mazzucco A, Faggian G. In which patients is transcatheter aortic valve replacement potentially better indicated than surgery for redo aortic valve disease? Long-term results of a 10-year surgical experience. *J Thorac Cardiovasc Surg.* 2014;148:500-8. e1.
8. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, Barbanti M, Latib A, Schaefer U, Rodés-Cabau J, Treede H, Piazza N, Hildick-Smith D, Himbert D, Walther T, Hengstenberg C, Nissen H, Bekerredjian R, Presbitero P, Ferrari E, Segev A, de Weger A, Windecker S, Moat NE, Napodano M, Wilbring M, Cerillo AG, Brecker S, Tchetché D, Lefèvre T, De Marco F, Fiorina C, Petronio AS, Teles RC, Testa L, Laborde JC, Leon MB, Kornowski R; Valve-in-Valve International Data Registry Investigators. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA.* 2014;312:162-70.
9. Christiansen S, Schmid M, Autschbach R. Perioperative risk of redo aortic valve replacement. *Ann Thorac Cardiovasc Surg.* 2009;15:105-10.
10. Lange R, Piazza N. Transcatheter aortic valve-in-surgical aortic valve implantation: current status and future perspectives. *Eur J Cardiothorac Surg.* 2013;44:403-6.
11. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol.* 2012;60:1438-54.
12. Wilbring M, Tugtekin SM, Alexiou K, Simonis G, Matschke K, Kappert U. Transapical transcatheter aortic valve implantation vs conventional aortic valve replacement in high-risk patients with previous cardiac surgery: a propensity-score analysis. *Eur J Cardiothorac Surg.* 2013;44:42-7.
13. Dvir D, Webb JG. Transcatheter aortic valve-in-valve implantation for patients with degenerative surgical bioprosthetic valves. *Circ J.* 2015;79:695-703.

14. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187-98.
15. Jin R, Furnary AP, Fine SC, Blackstone EH, Grunkemeier GL. Using Society of Thoracic Surgeons risk models for risk-adjusting cardiac surgery results. *Ann Thorac Surg.* 2010;89:677-82.

TRANSCATHETER AORTIC VALVE REPLACEMENT IN BICUSPID AORTIC VALVE DISEASE

13

Transcatheter aortic valve replacement in bicuspid aortic valve disease

Mylotte D, Lefevre T, Søndergaard L, Watanabe Y, Modine T, Dvir D, Bosmans J, Tchetché D, Kornowski R, Sinning JM, Thériault-Lauzier P, O'Sullivan CJ, Barbanti M, Debry N, Buithieu J, Codner P, Dorfmeister M, Martucci G, Nickenig G, Wenaweser P, Tamburino C, Grube E, Webb JG, Windecker S, Lange R, Piazza N. J Am Coll Cardiol. 2014;64:2330-9.

ABSTRACT

Background

Limited information exists describing the results of transcatheter aortic valve (TAV) replacement in patients with bicuspid aortic valve (BAV) disease (TAV-in-BAV).

Objectives

This study sought to evaluate clinical outcomes of a large cohort of patients undergoing TAV-in-BAV.

Methods

We retrospectively collected baseline characteristics, procedural data, and clinical follow-up findings from 12 centers in Europe and Canada that had performed TAV-in-BAV.

Results

A total of 139 patients underwent TAV-in-BAV with the balloon-expandable transcatheter heart valve (THV) ($n = 48$) or self-expandable THV ($n = 91$) systems. Patient mean age and Society of Thoracic Surgeons predicted risk of mortality scores were 78.0 ± 8.9 years and $4.9 \pm 3.4\%$, respectively. BAV stenosis occurred in 65.5%, regurgitation in 0.7%, and mixed disease in 33.8% of patients. Incidence of type 0 BAV was 26.7%; type 1 BAV was 68.3%; and type 2 BAV was 5.0%. Multislice computed tomography (MSCT)-based TAV sizing was used in 63.5% of patients (77.1% balloon-expandable THV vs. 56.0% self-expandable THV, $p = 0.02$). Procedural mortality was 3.6%, with TAV embolization in 2.2% and conversion to surgery in 2.2%. The mean aortic gradient decreased from 48.7 ± 16.5 mm Hg to 11.4 ± 9.9 mm Hg ($p < 0.0001$). Post-implantation aortic regurgitation (AR) grade ≥ 2 occurred in 28.4% (19.6% balloon-expandable THV vs. 32.2% self-expandable THV, $p = 0.11$) but was prevalent in only 17.4% when MSCT-based TAV sizing was performed (16.7% balloon-expandable THV vs. 17.6% self-expandable THV, $p = 0.99$). MSCT sizing was associated with reduced AR on multivariate analysis (odds ratio [OR]: 0.19, 95% confidence intervals [CI]: 0.08 to 0.45; $p < 0.0001$). Thirty-day device safety, success, and efficacy were noted in 79.1%, 89.9%, and 84.9% of patients, respectively. One-year mortality was 17.5%. Major vascular complications were associated with increased 1-year mortality (OR: 5.66, 95% CI: 1.21 to 26.43; $p = 0.03$).

Conclusions

TAV-in-BAV is feasible with encouraging short- and intermediate-term clinical outcomes. Importantly, a high incidence of post-implantation AR is observed, which appears to be mitigated by MSCT-based TAV sizing. Given the suboptimal echocardiographic results, further study is required to evaluate long-term efficacy.

Keywords: aortic stenosis, aortic valve replacement, bicuspid aortic valve, transcatheter aortic valve implantation, transcatheter aortic valve replacement

Bicuspid aortic valve (BAV) is a heritable disease affecting 0.5% to 2% of the general population, with a strong male predilection (1–3). BAV stenosis and/or regurgitation is the most common indication for surgical aortic valve replacement (SAVR) in patients <70 years of age. Nonetheless, a recent study that examined surgically excised aortic valves observed that one-fifth of patients older than 80 years of age had underlying bicuspid pathology; echocardiography had identified only two-thirds of these patients as having bicuspid morphology (4). BAV has been excluded from the landmark clinical trials involving transcatheter AVR (TAVR) (5,6). Theoretically, abnormal cusp fusion, pronounced asymmetry of the valve orifice and annulus, heavily calcified and fibrotic leaflets, and calcified raphe (**Figure 1**) could have adverse effects on the expansion of transcatheter aortic valves (TAV), ultimately leading to paravalvular aortic regurgitation (AR) and poor hemodynamic function (7–9). The small number of published case reports and series describing the feasibility of TAV implantation in BAV stenosis (TAV-in-BAV) have been limited in their demonstration of safety and efficacy (10–16). Given the possibility that there are a significant number of elderly patients with BAV stenosis currently undergoing TAVR and that there is a shift toward treating younger patients with TAVR, a better understanding of the clinical outcomes of patients subjected to TAV-in-BAV is necessary (17,18).

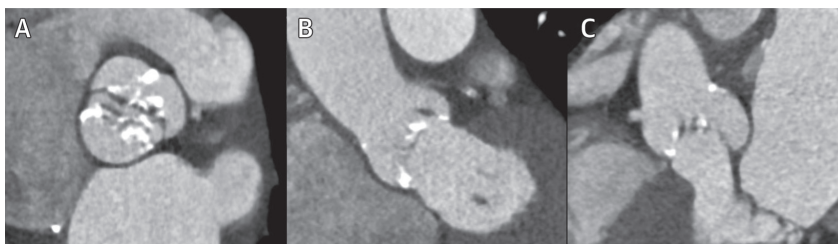


FIGURE 1 Bicuspid Aortic Valve Stenosis

Multislice computed tomography of a type 1 (left-right) bicuspid aortic valve. Axial (A), sagittal (B), and coronal (C) images demonstrate the asymmetrical nature of the bicuspid aortic root.

This multicenter study sought to assess the safety and efficacy of TAV-in-BAV in a large group of patients. More specifically, we sought to assess hemodynamic, echocardiographic, and clinical outcomes, along with the association between BAV morphology and TAV prosthesis type on these aforementioned outcomes.

METHODS

Participating centers and patients

The TAV-in-BAV registry, a multinational collaboration of interventional cardiologists and cardiac surgeons from high-volume TAVR centers, collected data from patients who underwent TAV-in-BAV from 12 participating centers in Europe and Canada (Online Table 1). Data

have been prospectively collected since October 2013. Patient selection for TAV-in- BAV was performed at an institutional level, following consideration of the risk profile of each case and discussions by the Heart Team. In each case, centers submitted a dedicated case report form detailing patient baseline characteristics, echocardiographic and/or multislice computed tomographic (MSCT) data, procedural information, and scheduled clinical follow-up.

Bicuspid aortic valve

BAV was defined as a spectrum of abnormal aortic valve morphology consisting of 2 functional cusps with less than 3 zones of parallel apposition between cusps (19). BAV classification was assigned according to the number and spatial orientation of the raphe (**Figure 2**). Type 0, commonly referred to as “pure BAV,” has 2 normally developed cusps, sinuses, and commissures and no raphe. Type 1 has 3 anlagen, 2 underdeveloped, and 1 fully developed cusps, 1 underdeveloped commissure, 2 fully developed commissures, and 1 raphe whose orientation in relation to the sinuses defined subcategorization (left-right; right-non; and left-non). Type 2 has 3 anlagen, 2 underdeveloped cusps, 1 fully developed cusp, 2 underdeveloped commissures, 1 fully developed commissure, and 2 raphe (19). Consistent with findings by prior publications, cases of commissural fusion with a raphe <3 mm long were not considered to represent BAV (20). All participating sites retrospectively confirmed the diagnosis and classification of BAV using multimodal imaging: transthoracic and transesophageal echocardiography (TEE) and MSCT. When both TEE and MSCT were performed, cases were excluded if the diagnosis of BAV was not consistent or remained speculative.

Endpoints and definitions

Procedural, 30-day mortality and other major clinical endpoints were defined according to the updated Valve Academic Research Consortium (VARC) criteria (21). Of particular interest were the composite clinical endpoints of valve efficacy, safety, and success (21). Post-implant AR represented an important nonclinical endpoint (22). Regurgitation was defined as the sum of transvalvular and paravalvular regurgitation following prosthesis implantation and removal of the stiff guidewire. At each institution, the severity of regurgitation was qualitatively assessed and graded using TEE according to established guidelines (23,24). Regurgitation was categorized as paravalvular, transvalvular, or mixed and was classified as none (0), trace (I), mild (II), moderate (III), or severe (IV) (23,24).

The dimensions of the aortic valve annulus were measured using TEE or MSCT. TAV sizing was thus defined as either TEE- or MSCT-based. The ellipticity ratio was determined using the formula “long/short-axis” in patients who underwent MSCT analysis. The cover index describes the amount of transcatheter heart valve (THV) oversizing relative to native aortic annulus and was defined by the formula: $\left(\frac{\text{prosthesis diameter} - \text{annulus diameter}}{\text{prosthesis diameter}}\right) \times 100$ (25,26).

TABLE 1 Baseline Characteristics

Characteristic	All Patients (n = 139)	Sapien (n = 48)	CoreValve (n = 91)	p Value
Age, yrs	78.0 ± 8.9	77.6 ± 9.7	78.2 ± 8.4	0.71
Males	78 (56.1)	30 (62.5)	48 (52.7)	0.29
BMI, kg/m ²	25.7 ± 5.8	26.5 ± 6.9	25.3 ± 5.2	0.25
Diabetes mellitus	34 (24.5)	14 (29.2)	20 (22.0)	0.41
NYHA functional class	3.0 ± 0.6	3.0 ± 0.5	2.9 ± 0.6	0.33
NYHA functional class III/IV	114 (82.0)	44 (91.7)	70 (76.9)	0.04
Previous MI	26 (18.7)	9 (18.8)	17 (18.7)	0.99
Previous PCI	30 (21.6)	9 (18.8)	21 (23.1)	0.67
Previous CABG	14 (10.1)	5 (10.4)	9 (9.9)	0.99
Peripheral vascular disease	17 (12.2)	6 (12.5)	11 (12.1)	0.99
Previous stroke	8 (5.8)	4 (8.3)	4 (4.4)	0.45
Atrial fibrillation	34 (24.5)	7 (14.6)	27 (29.7)	0.06
Pulmonary hypertension*	34 (24.5)	10 (20.8)	24 (26.4)	0.68
eGFR, ml/min	61.0 ± 25.4	61.2 ± 21.2	60.9 ± 27.2	0.95
eGFR, ≤60 ml/min	70 (50.4)	23 (47.9)	47 (51.6)	0.74
STS PROM	4.9 ± 3.4	5.0 ± 3.9	4.8 ± 3.1	0.96
Logistic EuroSCORE	14.8 ± 10.6	15.3 ± 10.7	14.5 ± 10.7	0.68
EuroSCORE II	4.6 ± 3.6	5.3 ± 4.0	4.3 ± 3.4	0.12
Echocardiography				
Aortic valve mean gradient, mm Hg	48.7 ± 16.5	49.9 ± 15.5	48.1 ± 17.1	0.54
Aortic valve area, cm ²	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.006
Estimated annulus diameter, mm	23.2 ± 2.3	24.2 ± 2.4	23.2 ± 3.7	0.09
LV ejection fraction, %	50.4 ± 14.6	50.9 ± 14.1	50.1 ± 14.9	0.76
LV ejection fraction, ≤40%	41 (29.5)	13 (27.1)	28 (30.8)	0.70
MSCT aortic annulus dimensions†				
Mean diameter, mm	24.5 ± 3.4	24.0 ± 2.2	24.7 ± 3.9	0.25
Long diameter, mm	27.6 ± 2.8	27.0 ± 2.7	28.0 ± 2.8	0.09
Short diameter, mm	22.2 ± 2.5	21.6 ± 2.3	22.7 ± 2.5	0.04
Ellipticity ratio	1.25 ± 0.12	1.26 ± 0.12	1.24 ± 0.12	0.44

Values are mean ± SD or n (%). p Values represent comparisons between the balloon-expandable and self-expandable valve prostheses.

* Pulmonary artery systolic pressure ≥60 mm Hg.

† Total of 88 patients underwent MSCT analysis.

BMI = body mass index; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; LV = left ventricle; MI = myocardial infarction; MSCT = multislice computed tomography; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PROM = predicted risk of mortality; STS = Society of Thoracic Surgeons.

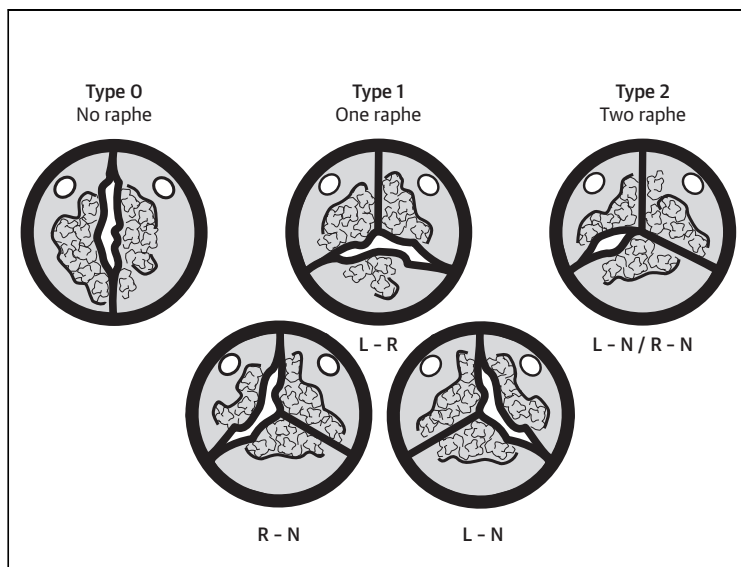


FIGURE 2 Classification of BAV

Classification of BAV according to the description of Sievers et al. (19). BAV = bicuspid aortic valve; L = left coronary cusp; N = non coronary cusp; R = right coronary cusp.

Statistics

Continuous variables are presented as mean \pm SD, medians, and ranges and were compared using Student *t* test, Mann-Whitney test, or paired *t* test for repeated measures. Categorical variables are presented as frequencies and percentages and were compared using the chi-square or Fisher exact test. Rates of 1-year mortality were shown using Kaplan-Meier curves, and between-group differences were analyzed with the log-rank test. Logistic regression was performed with the entire cohort to identify possible predictors of 1-year survival and post-implantation AR. All variables that could plausibly be associated with these outcomes were evaluated in a univariate approach, and then factors with a *p* value of <0.08 in the univariate analysis were combined in a multivariate logistic regression model. A *p* value of <0.05 was considered significant. Analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, New York).

RESULTS

Patients

A total of 139 elderly patients underwent TAV-in-BAV across 12 participating centers between April 2005 and January 2014. Isolated stenoses occurred in 91 patients (65.5%), isolated

regurgitation in 1 patient (0.7%), and mixed disease in 47 patients (33.8%). The baseline demographics of the study patients are outlined in **Table 1**. The mean age was 78.0 ± 8.9 years, and the mean Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM) score was $4.9 \pm 3.4\%$.

Bicuspid morphology

Evaluation of the morphology of the aortic valve was performed using TEE in all patients. MSCT was performed for the purpose of sizing the TAV in 88 cases (63.3%). Among these patients, the annuli were elliptical with an average ellipticity ratio of 1.25 ± 0.12 . The BAV type was definitively established in 120 patients (86.3%) and remained uncertain in 19 patients (13.7%), despite multimodal imaging. Among patients with a confirmed BAV type (**Table 2**), 32 patients (26.7%) were type 0, 82 (68.3%) were type 1 (left-right: $n = 60$; right-non: $n = 15$; and left-non: $n = 7$), and 6 (5.0%) were type 2. Diameter of the aortic sinuses (mean: 34.7 ± 3.3 mm; range: 29 to 41 mm), root (mean: 32.7 ± 5.8 mm; range: 22 to 41 mm), and ascending aorta (mean: 35.9 ± 6.1 mm; range: 25 to 46 mm) indicated that no patient had significant ascending aortopathy.

Procedures

Table 3 outlines the procedural characteristics and results of the TAV-in-BAV procedures. A balloon-expandable THV (SapienXT, Edwards Lifesciences, Inc., Irvine, California) (**Figure 3**) and self-expandable THV (CoreValve, Medtronic, Inc., Minneapolis, Minnesota) (**Figure 4**) were used in 48 patients (34.5%) and 91 patients (65.5%), respectively. Transfemoral vascular access was performed in 78.5% of cases, and pre-implantation balloon aortic valvuloplasty was performed in 98.6% of cases. A TAV was subsequently implanted in 137 cases (98.6%). Of 2 patients who did not receive a TAV, 1 case had severe aortic incompetence and fatal cardiogenic shock following balloon valvuloplasty (balloon-to-annulus ratio: 0.9), and in 1 case, the balloon-expandable valve failed to cross the native aortic valve. The mean diameter of the transcatheter valve was $27.8 \pm$

TABLE 2 Bicuspid Aortic Valve Type

Valve Type	All Patients (n = 120)	Sapien (n = 40)	CoreValve (n = 80)	p Value
Type 0	32 (26.7)	8 (20.0)	24 (30.0)	0.28
Type 1	82 (68.3)	31 (77.5)	51 (63.8)	0.15
LR	60 (50.0)	26 (65.0)	34 (42.5)	
RN	15 (12.5)	2 (5.0)	13 (16.3)	
LN	7 (5.8)	3 (7.5)	4 (5.0)	
Type 2				
LR/RN	6 (5.0)	1 (2.5)	5 (6.2)	0.66

Values are n (%). Classification of bicuspid aortic valve morphology according to Sievers et al. (19).

LN = left - non; LR = left - right; RN = right - non.

2.2 mm and was significantly smaller in patients receiving the balloon-expandable valve than in those receiving the self-expandable THV (26.3 ± 2.2 mm vs. 28.5 ± 1.8 mm, respectively; $p = 0.0002$). Similarly, the cover index was significantly smaller in patients treated with the balloon-expandable THV ($8.9 \pm 5.7\%$ vs $16.3 \pm 9.8\%$, respectively; $p < 0.0001$). Post-implantation balloon dilation was required in 25 cases (18.1%; balloon-expandable THV $n = 5$; self-expandable THV $n = 20$), and there were 3 (2.2%) episodes of TAV embolization (balloon-expandable THV $n = 2$; self-expandable THV: $n = 1$). A second TAV was implanted in 5 patients (3.6%; balloon-expandable THV $n = 1$; self-expandable THV $n = 4$), and 3 cases (2.2%) were converted to SAVR (balloon-expandable THV $n = 2$; self-expandable THV $n = 1$). SAVR was required for 1 annular rupture, 1 balloon-expandable THV embolization, and 1 self-expandable THV malposition. Procedural mortality occurred in 5 patients (3.5%) and was attributed to cardiac tamponade resulting from guidewire perforation of the left ventricle ($n = 2$), major vascular complication, annular rupture, and the case of severe AR following balloon aortic valvuloplasty, as described previously.

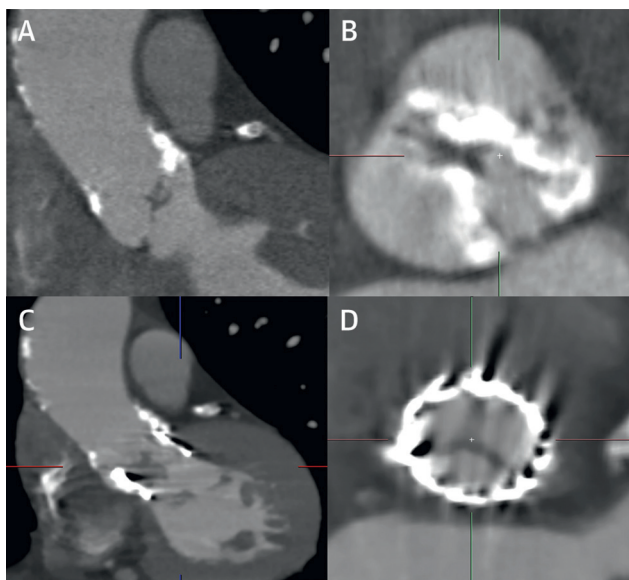


FIGURE 3 Newer Generation Balloon-Expandable TAV-in-BAV

TAV-in-BAV with a newer generation 29-mm balloon-expandable THV (Sapien XT, Edwards Lifesciences). (A and B) Multislice computed tomography of bicuspid aortic valve stenosis (type 1, RN). (C and D) Same patient after implantation with the newer generation balloon-expandable valve. RN = right - non; TAV-in-BAV = transcatheter aortic valve in bicuspid aortic valve; THV = transcatheter heart valve.

TABLE 3 Procedural Information and Outcomes

Characteristic	All Patients (n = 139)	Sapien (n = 48)	CoreValve (n = 91)	p Value
TAV size, mm	27.8 ± 2.2	26.3 ± 2.2	28.5 ± 1.8	0.0002
23 mm	10 (7.2)	10 (20.8)	–	–
26 mm	50 (36.0)	23 (47.9)	27 (29.7)	0.04
29 mm	59 (42.4)	15 (31.3)	44 (48.4)	0.07
31 mm	20 (14.4)	–	20 (22.0)	–
MSCT cover index, %	13.2 ± 9.1	8.9 ± 5.7	16.3 ± 9.8	<0.0001
MSCT-based TAV sizing	88 (63.3)	37 (77.1)	51 (56.0)	0.02
Vascular access				
Femoral	109 (78.5)	30 (62.5)	79 (86.8)	0.002
Subclavian	5 (3.6)	–	5 (5.5)	–
Apical	12 (8.6)	12 (25.0)	–	–
Aortic	12 (8.6)	6 (12.5)	6 (6.6)	–
Carotid	1 (0.7)	–	1 (1.1)	–
General anesthesia	85 (61.1)	33 (68.8)	52 (57.1)	0.20
Balloon predilation	137 (98.6)	51 (100.0)	89 (97.8)	0.54
Predilation balloon size, mm	22.5 ± 2.1	21.9 ± 2.2	22.9 ± 2.0	0.008
Balloon postdilation*	25 (18.1)	5 (10.6)	20 (22.2)	0.11
Postdilation balloon size, mm*	26.5 ± 2.3	24.7 ± 2.5	26.8 ± 2.1	0.07
TAV malposition*	9 (6.5)	2 (4.3)	7 (7.8)	0.72
TAV embolization*	3 (2.2)	2 (4.3)	1 (1.1)	0.27
Need for 2nd TAV*	5 (3.6)	1 (2.1)	4 (4.4)	0.66
Tamponade	5 (3.6)	0	5 (5.7)	0.16
Aortic root rupture	1 (0.7)	1 (2.1)	0	–
Conversion to SAVR	3 (2.2)	2 (4.2)	1 (1.1)	0.30
Postimplantation echocardiography				
Aortic regurgitation, grade (1–4)*	1.1 ± 0.9	1.0 ± 0.9	1.1 ± 0.9	0.53
≥Grade 2	38 (28.4)	9 (19.6)	29 (32.2)	0.11
≥Grade 3	8 (6.0)	3 (6.5)	5 (5.5)	0.99
Aortic valve gradient, mm Hg*	11.4 ± 9.9	11.7 ± 8.7	11.3 ± 10.4	0.82
Aortic valve area, cm ² *	1.7 ± 0.5	1.6 ± 0.4	1.7 ± 0.5	0.23
Contrast media, ml	174 ± 88	176 ± 118	172 ± 81.5	0.17
Fluoroscopy duration, min	20 (14–28)	14 (9–25)	20 (15–29)	0.004

Values are mean ± SD, n (%), or median (interquartile range). p values represent comparisons between the Edwards Sapien and Medtronic CoreValve prostheses.

* Refers to 137 patients who received a TAV.

MSCT = multislice computed tomography; SAVR = surgical aortic valve replacement; TAV = transcatheter aortic valve.

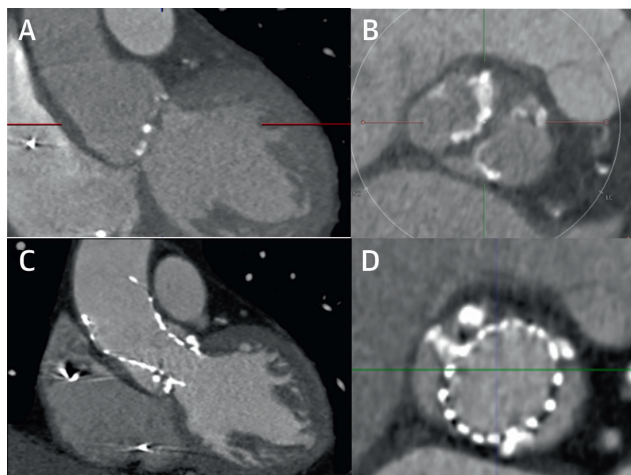


FIGURE 4 Self-Expandable TAV-in-BAV

TAV-in-BAV with a 29-mm self-expandable THV (CoreValve; Medtronic). (**A and B**) Multislice computed tomography of bicuspid aortic valve stenosis (type 1, LN). (**C and D**) Same patient with the self-expandable valve. LN = left - non; other abbreviations as in **Figure 3**.

Clinical outcomes

The median duration of hospital stay was 8 (interquartile range: 5 to 11) days (**Table 4**). The 30-day rates of death, myocardial infarction, and stroke were 5.0%, 2.2%, and 2.2%, respectively. Any instance of bleeding occurred in 37 patients (26.6%), life-threatening bleeding occurred in 10 patients (7.2%), and major vascular complications occurred in 9 patients (6.5%). Overall, 110 patients (79.1%) met the combined safety endpoint, and device success was observed in 125 patients (89.9%). At 30 days, the combined efficacy endpoint was achieved in 118 patients (84.9%).

Follow-up was available for all patients. At the time of data lock, 136 patients (97.8%) and 129 patients (92.8%) had reached 6- and 12-month follow-up examinations, respectively. The Kaplan-Meier survival curve is shown in the **Central Illustration**. There were 13 deaths (9.6%) at 6 months and 21 (17.5%) at 12 months; causes of death between 30 days and 1 year ($n = 16$) were congestive cardiac failure ($n = 6$), cancer ($n = 3$), unknown ($n = 3$), gastrointestinal hemorrhage ($n = 1$), stroke ($n = 1$), lung disease ($n = 1$), and a road traffic accident ($n = 1$). On multivariate analysis (**Table 5**), major vascular complications were associated with increased 1-year mortality (odds ratio [OR]: 5.66; 95% confidence interval [CI]: 1.21 to 26.43; $p = 0.03$). At 1 year, 60.4%, 30.2%, and 9.4% of patients were assessed at New York Heart Association (NYHA) functional class I, II, or III, respectively.

Post-procedural echocardiography

Among the 137 patients who received a TAV, the mean aortic valve gradient decreased from 48.7 ± 16.5 mm Hg at baseline to 11.4 ± 9.9 mm Hg at 30 days ($p < 0.0001$), whereas the

TABLE 4 Clinical Outcomes

Characteristic	All patients (n = 139)	Sapien (n = 48)	CoreValve (n = 91)	p Value
Hospital stay, days	8 (5, 11)	7 (4, 12)	8 (6, 11)	0.38
Mortality				
Procedural	5 (3.6)	1 (2.1)	4 (4.9)	0.66
At 30 days	7 (5.0)	3 (6.3)	4 (4.9)	0.69
At 6 months*	13 (9.6)	7 (14.6)	6 (6.6)	0.12
At 1 year†	21 (17.5)	10 (20.8)	11 (12.5)	0.12
Myocardial infarction	3 (2.2)	0	3 (3.3)	0.55
Periprocedural	3 (2.2)	0	3 (3.3)	–
Spontaneous	0	0	0	–
Stroke	3 (2.2)	1 (2.1)	2 (2.2)	0.99
Disabling	2 (1.4)	1 (2.1)	1 (1.1)	–
Non disabling	1 (0.8)	0	1 (1.1)	–
Bleeding	37 (26.6)	8 (16.7)	29 (31.9)	0.07
Minor	18 (12.9)	2 (4.2)	16 (17.6)	–
Major	9 (6.5)	4 (8.3)	5 (5.5)	–
Life-threatening	10 (7.2)	2 (4.2)	8 (8.8)	–
Acute kidney injury (stage 3)	3 (2.2)	1 (2.1)	2 (2.0)	0.99
Vascular complications	30 (21.6)	6 (12.5)	24 (26.4)	0.08
Minor	21 (15.1)	2 (4.2)	19 (20.9)	–
Major	9 (6.5)	4 (8.3)	5 (5.5)	–
New pacemaker	32 (23.2)	8 (16.7)	24 (26.7)	0.21
Device success	125 (89.9)	43 (89.6)	82 (90.1)	0.99
Combined safety endpoint	110 (79.1)	39 (82.2)	71 (78.0)	0.83
Combined efficacy endpoint	118 (84.9)	42 (87.5)	76 (84.5)	0.81

mean aortic valve area increased from $0.6 \pm 0.2 \text{ cm}^2$ at baseline to $1.7 \pm 0.5 \text{ cm}^2$ at 30 days ($p < 0.0001$). Post-implantation AR grade ≥ 2 (paravalvular in 92% of cases) was present in 38 patients (28.4%) at 30 days. When only those patients with MSCT-based TAV sizing were considered, the incidence of AR grade ≥ 2 was 17.4%. On multivariate analysis, MSCT-based TAV sizing was independently associated with a reduction in the incidence of post-implantation AR grade ≥ 2 (OR: 0.19; 95% CI: 0.08 to 0.45; $p < 0.0001$) (**Table 6**). Male sex (OR: 4.29; 95% CI: 1.63 to 10.79; $p = 0.003$) was the only independent predictor of increased AR grade ≥ 2 . AR grade ≥ 2 occurred in 13.3% of BAV type 0 patients, 34.2% of type 1, and 16.6% of type 2 (type 0 vs. type 1: $p = 0.03$).

TABLE 5 Predictors of 1-Year Survival

Characteristic	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
Age	1.06	0.99–1.13	0.10			
Males	1.15	0.45–3.95	0.77			
STS PROM	1.06	0.94–1.19	0.38			
Mean aortic gradient	1.00	0.97–1.03	0.94			
Aortic valve area	0.08	0.01–1.50	0.09			
LV ejection fraction <40%	1.14	0.42–3.08	0.80			
Annulus size	1.03	0.88–1.19	0.74			
TAV size	0.94	0.77–1.16	0.59			
MSCT-based TAV sizing	1.32	0.49–3.55	0.58			
Bicuspid type 1	1.29	0.45–3.69	0.63			
CoreValve	0.44	0.17–1.15	0.08	0.38	0.14–1.04	0.06
Year of procedure	0.91	0.67–1.22	0.51			
Diabetes	0.53	0.14–1.93	0.33			
NYHA functional class II/III	2.57	0.56–11.85	0.23			
Pulmonary hypertension	1.85	0.67–5.11	0.24			
eGFR <60	1.44	0.56–3.69	0.45			
TAV malposition	4.29	0.89–20.80	0.07	5.05	0.93–27.31	0.06
TAV embolization	5.30	0.32–88.27	0.25			
Requirement for 2nd TAV	2.63	0.23–30.35	0.44			
Major vascular complications	1.12	1.40–26.81	0.02	5.66	1.21–26.42	0.03
New pacemaker	0.73	0.23–2.36	0.61			
AR grade ≥ 2	1.55	0.56–4.32	0.40			

AR = aortic regurgitation; CI = confidence interval; other abbreviations as in **Table 1**.

Prosthesis choice

Baseline characteristics among patients treated with the balloon-expandable THV were similar to those of patients who received the self-expandable THV, although NYHA functional class III or IV was more common in the balloon-expandable valve cohort ($p = 0.04$). MSCT-based TAV sizing was also performed more frequently in the balloon-expandable THV cohort (56.0% vs. 77.1%, respectively; $p = 0.02$), and the transfemoral approach was more common among self-expandable valve patients ($p = 0.002$). There was a trend toward an increased incidence of post-implantation AR grade ≥ 2 among the self-expandable valve-treated patients (19.6% vs. 32.2%, respectively; $p = 0.11$). When patients undergoing MSCT-based TAV sizing were considered, the incidence of AR grade ≥ 2 was similar between the 2 prostheses (6 of 37 [16.7%] vs. 9 of 50 [17.6%], respectively; $p = 0.99$). The choice of TAV was not associated with post-implantation AR in multivariate analysis. There were no significant differences in

TABLE 6 Predictors of Aortic Regurgitation Grade ≥ 2

Characteristic	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
Age	0.95	0.96–1.03	0.63			
Males	3.50	1.50–8.20	0.004	4.29	1.63–10.79	0.003
STS PROM	0.85	0.75–1.04	0.05	0.88	0.75–1.04	0.13
Mean aortic gradient	0.99	0.97–1.02	0.61			
Aortic valve area	3.20	0.34–29.86	0.31			
LV ejection fraction <40%	1.40	0.62–3.14	0.41			
Annulus size	0.93	0.82–1.04	0.20			
TAV size	1.10	0.92–1.31	0.31			
MSCT-based TAV sizing	0.23	0.10–0.51	<0.0001	0.19	0.08–0.45	<0.0001
Bicuspid type 1	2.14	0.82–5.56	0.11			
CoreValve	1.93	0.82–4.54	0.13			
Year of procedure	0.78	0.60–1.03	0.08			

Abbreviations as in **Tables 1 and 5**.

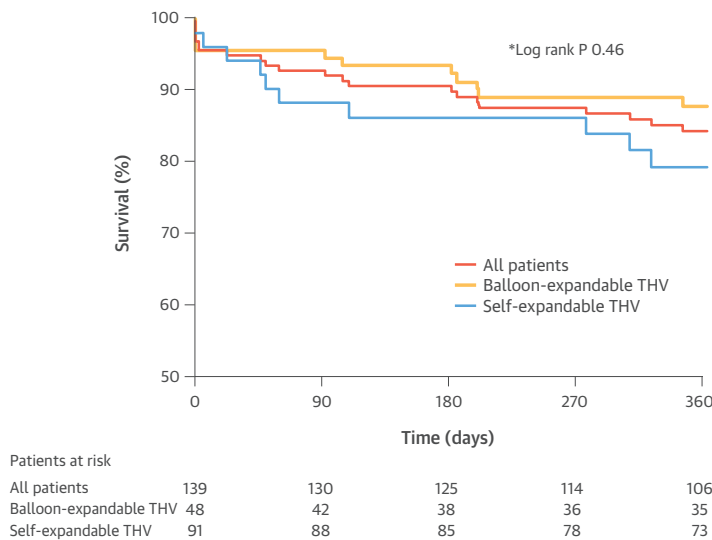
procedural outcomes between patients receiving the two types of valves. At 12 months, death occurred in 10 patients who received the balloon-expandable valve (20.8%) and in 11 self-expandable valve recipients (12.5%; log-rank: $p = 0.46$) (**Central Illustration**).

Values are n (%). Totals of 136* and 129† patients who reached 6-month or 1-year follow-up examination, respectively.

SAVR = surgical aortic valve replacement.

DISCUSSION

This is the first large multicenter analysis of TAV implantation in patients with significant BAV stenosis or regurgitation. We observed a 30-day mortality rate of 5%, a 30-day stroke rate of 2%, and a device success rate of 90%. One-year mortality was 17.5%, and the patients were NYHA functional class I or II. These results suggest that TAV-in-BAV is feasible and associated with encouraging short- and intermediate-term clinical outcomes. The current analysis, however, demonstrated a high incidence of post-implantation AR grade ≥ 2 (28.4%), although this was reduced to 17% in those with MSCT-based TAV sizing.



Mylotte, D. et al. J Am Coll Cardiol. 2014; 64(22):2330–9.

Kaplan-Meier survival curve of patients undergoing transcatheter aortic valve in bicuspid aortic valve with the balloon-expandable THV (blue line) or self-expandable valve (orange line) prostheses. The p value is the log-rank comparison between the 2 valves. THV = transcatheter heart valve.

Procedural safety and efficacy

Treatment of BAV disease with TAV technology is considered an off-label indication. Surgically excised bicuspid valves typically demonstrate leaflet fusion (raphe) and extensive nodular calcification. The histo-architectural distribution of calcific deposits in BAV leaflets is different from that of stenotic tricuspid valves (27). Extensive calcium deposition in the body of BAV leaflets and asymmetrical nature of the bicuspid aortic root could impair TAVR outcomes (19,28). Anecdotally, registry participants suggested that guidewire crossing and THV positioning were more difficult with bicuspid than tricuspid aortic valve stenosis. Nevertheless, the acute procedural results were acceptable, with acute TAV embolization occurring in 2.2%, conversion to SAVR in 2.2%, and encouraging 30-day rates of VARC-defined device success (89.9%), safety (79.1%), and efficacy (84.9%). These results are comparable to those reported for TAVR in tricuspid aortic stenosis (5,6,29–32).

Traditionally, TAVR has been reserved for patients at excessive or high risk for surgery (STS PROM >10%). More recently, it has been recognized that current risk models are ill equipped to accurately gauge risk among TAVR recipients (33). TAVR technology is therefore being applied to patients at lower predicted risk, following discussions by the institutional heart team. In our study, the expected 30-day mortality (STS PROM) was 4.9%, indicating an intermediate-risk cohort. We observed remarkable similarities between expected and observed (5.0%) 30-day mortality rates. Mortality continued to accrue, however, increasing

to 17.5% at 1 year. By comparison, Piazza et al. (34) performed a propensity-matched analysis comparing TAVR to SAVR among 205 intermediate-risk patient pairs (STS PROM 3% to 8%) with severe tricuspid aortic valve stenosis. They reported mortality in the TAVR and SAVR cohorts of 7.8 and 7.1%, respectively, at 30-days and 16.5 and 16.9%, respectively, at 1 year. One-year outcomes in the current study compare favorably to those reported for other TAV-in-BAV cohorts (11,15). The 1-year outcomes probably reflect the advanced age, heavy burden of comorbidities, and other adverse features inherent in TAVR cohorts that are not captured by current risk prediction models (33). The high rates of post-implantation AR also may have influenced 1-year mortality (22).

Post-implantation AR

In the current analysis, AR grade ≥ 2 occurred in 28.4% of patients. This rate is consistent with that reported in smaller TAV-in-BAV series (13–15) and compares poorly with reported rates ($<20\%$) of AR following TAV for tricuspid aortic valve stenosis (30,35,36). Notably, the incidence of AR grade ≥ 2 was 17.4% when only patients who underwent MSCT-based sizing were considered and was similar between balloon- and self-expanding prostheses (16.7% vs. 17.6%, respectively; $p = 0.99$). Consistent with prior studies (37,38), MSCT-based TAV sizing was associated with reduced paravalvular regurgitation and should be considered a mandatory element of patient screening for TAV-in-BAV. Nevertheless, MSCT-based TAV sizing is unlikely to represent a panacea for post-implantation AR in BAV because the unique anatomic features of BAV pathology appear to present a challenge for first-generation TAVI systems. The TAV frame may be unable to expand completely and appose to the native annulus in the presence of pronounced annular ellipticity (mean ellipticity ratio: 1.25 ± 0.12), heavy calcification, and calcified raphe. The latter may have contributed to the increased rate of post-implantation AR observed in patients with BAV type 1 compared with those with type 0 (34.2 vs. 13.3%, respectively; $p = 0.03$). Aortic root dilation and/or angulation, as well as concomitant native aortic valve incompetence, may further impede accurate TAV positioning and contribute to the risk of paravalvular regurgitation. Given the strong association between post-procedural AR and both short- and long-term mortality (22,35), the high incidence of AR observed in BAV patients is disconcerting, and the suboptimal echocardiographic outcomes mandate further longer term follow-up to ascertain the clinical implications of aortic incompetence in BAV cohorts.

Comparison with SAVR

Comparisons between current study outcomes and those of historical surgical series of patients undergoing isolated SAVR for BAV disease are challenging. Most surgical series included younger and lower-risk patients who do not reflect the complexities of the current cohort (39,40). Furthermore, such comparisons are also likely to be confounded by considerable selection bias, whereas in our study, each case was discussed by a dedicated heart team whose members recommended TAV-in-BAV rather than SAVR. Surgery, however, should remain

the treatment of choice for BAV disease, especially in low-risk patients or in the presence of aortic root dilation. Ultimately, a randomized comparison between TAV-in-BAV and SAVR will be required to prove equivalent safety and long-term efficacy.

Choice of prosthesis

BAV morphology presents potential advantages and disadvantages for balloon- and self-expanding TAV systems. The balloon-expandable valve exerts greater radial force and may circularize the native annulus, obliterating potential sites of paravalvular AR. Calcified nodules or raphe, however, may impair complete prosthesis expansion, thereby necessitating post-implantation balloon dilation or, potentially, resulting in residual paravalvular leakage. The self-expanding THV could have greater propensity to such paravalvular regurgitation given the reduced radial strength relative to balloon-expandable systems. The greater compliance of self-expanding prostheses and the supra-annular position of the leaflets could, however, mitigate the unequal circular stress at the level of the annulus and potentially improve long-term hemodynamic outcomes. In our study, clinical outcomes among patients treated with balloon expandable TAV were similar to those observed in patients treated with the self-expanding prostheses. We observed a trend toward increased rates of post-implantation AR grade ≥ 2 with the self-expandable THV; however, the considerably lower use of MSCT-based TAV sizing in the self-expandable THV cohort might have accounted for this difference. Subgroup analysis of patients undergoing MSCT-based TAV sizing demonstrated no significant between-group differences in the rates of post-implantation AR. Further study is required to evaluate the comparative effectiveness of the balloon-expandable and self-expandable valve systems in patients with BAV disease.

Currently unproven emerging TAV technology with dedicated sealing cuffs (Sapien 3 [Edwards Lifesciences]), repositionable systems (CoreValve Evolut R [Medtronic], Portico [St. Jude Medical, Minneapolis, Minnesota], or Lotus [Boston Scientific, Natick, Massachusetts]) may have the potential to reduce post-implantation AR (41–44).

Study limitations

The study findings should be interpreted in light of the study design. This predominantly retrospective voluntary registry of TAV-in-BAV cases necessitates cautious interpretation, and definitive conclusions should be avoided. The exact indication for proceeding with TAV-in-BAV rather than SAVR was not available for each patient, although all cases were reviewed by the institutional heart team. Adverse events and post-implantation AR, which may be operator and laboratory dependent, were adjudicated by the participating centers rather than by a core laboratory. Information about the depth of implantation and invasive hemodynamic data, such as the AR index, were not available in this study. The cover index and annular ellipticity were not entered into the multivariate regression because MSCT data were only available in 64% of patients.

CONCLUSIONS

TAV-in-BAV is feasible, with encouraging short-and intermediate-term clinical outcomes. A high incidence of post-implantation aortic regurgitation is observed following TAV-in-BAV. The incidence of post-implantation paravalvular leak is moderated by MSCT-based TAV sizing, which should be considered mandatory for TAV-in-BAV. Longer-term follow-up of a larger cohort of patients is required to more completely assess the efficacy and durability of TAV implantation in patients with bicuspid disease.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: TAVR of bicuspid aortic valves is associated with high rates of grade ≥ 2 post-implantation aortic regurgitation.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Sizing of the prosthesis based on measurements obtained by multislice computed tomography can reduce the likelihood of developing post-implantation aortic regurgitation in patients with bicuspid aortic valves undergoing TAVR.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether later generation TAVR devices reduce the risk of aortic regurgitation after TAVR in patients with bicuspid aortic valves.

ABBREVIATIONS AND ACRONYMS

BAV	= bicuspid aortic valve
CI	= confidence interval
MSCT	= multislice computed tomography
NYHA	= New York Heart Association
OR	= odds ratio
SAVR	= surgical aortic valve replacement
STS PROM	= Society of Thoracic Surgeons predicted risk of mortality
TAV-in-BAV	= transcatheter aortic valve in bicuspid aortic valve
TAVR	= transcatheter aortic valve replacement
TEE	= transesophageal echocardiography
THV	= transcatheter heart valve
VARC	= Valve Academic Research Consortium

APPENDIX

For a supplemental table, please see the online version of this article.

REFERENCES

1. Steinberger J, Moller JH, Berry JM, Sinaiko AR. Echocardiographic diagnosis of heart disease in apparently healthy adolescents. *Pediatrics* 2000; 105:815–8.
2. Sabet HY, Edwards WD, Tazelaar HD, Daly RC. Congenitally bicuspid aortic valves: a surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases. *Mayo Clin Proc* 1999;74:14–26.
3. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol* 2010;55:2789–800.
4. Roberts WC, Janning KG, Ko JM, Filardo G, Matter GJ. Frequency of congenitally bicuspid aortic valves in patients ≥ 80 years of age undergoing aortic valve replacement for aortic stenosis (with or without aortic regurgitation) and implications for transcatheter aortic valve implantation. *Am J Cardiol* 2012; 109:1632–6.
5. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607.
6. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364: 2187–98.
7. Zegdi R, Blanchard D, Azarine A, Folliguet T, Fabiani JN. Elliptical shape of a SAPIEN XT prosthesis deployed in a patient with bicuspid aortic valve stenosis. *J Heart Valve Dis* 2012;21:764–6.
8. Zegdi R, Ciobotaru V, Noghin M, et al. Is it reasonable to treat all calcified stenotic aortic valves with a valved stent? Results from a human anatomic study in adults. *J Am Coll Cardiol* 2008;51:579–84.
9. Mahadevia R, Barker AJ, Schnell S, et al. Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. *Circulation* 2014;129: 673–82.
10. Delgado V, Tops LF, Schuijff JD, et al. Successful deployment of a transcatheter aortic valve in bicuspid aortic stenosis: role of imaging with multislice computed tomography. *Circ Cardiovasc Imaging* 2009;2: e12–3.
11. Chiam PT, Chao VT, Tan SY, et al. Percutaneous transcatheter heart valve implantation in a bicuspid aortic valve. *J Am Coll Cardiol Interv* 2010; 3:559–61.
12. Wijesinghe N, Ye J, Rodes-Cabau J, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. *J Am Coll Cardiol Interv* 2010;3:1122–5.
13. Hayashida K, Bouvier E, Lefevre T, et al. Transcatheter aortic valve implantation for patients with severe bicuspid aortic valve stenosis. *Circ Cardiovasc Interv* 2013;6:284–91.
14. Bauer T, Linke A, Sievert H, et al. Comparison of the effectiveness of transcatheter aortic valve implantation in patients with stenotic bicuspid versus tricuspid aortic valves (from the German TAVI Registry). *Am J Cardiol* 2014;113:518–21.
15. Costopoulos C, Latib A, Maisano F, et al. Comparison of results of transcatheter aortic valve implantation in patients with severely stenotic bicuspid versus tricuspid or nonbicuspid valves. *Am J Cardiol* 2014;113:1390–3.
16. Himbert D, Pontnau F, Messika-Zeitoun D, et al. Feasibility and outcomes of transcatheter aortic valve implantation in high-risk patients with stenotic bicuspid aortic valves. *Am J Cardiol* 2012; 110:877–83.
17. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2011;59:280–7.
18. Mylotte D, Osnabrugge RL, Windecker S, et al. Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. *J Am Coll Cardiol* 2013;62:210–9.
19. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg* 2007;133:1226–33.

20. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation* 2005;111:920–5.
21. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *EuroIntervention* 2012;8:782–95.
22. Kodali SK, Williams MR, Smith CR, et al. Two--year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686–95.
23. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J J Thorac Cardiovasc Surg* 2014;148:e1–e132.
24. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. *J Am Soc Echo-cardiogr* 2009;22:975–1014.
25. Detaint D, Lepage L, Himbert D, et al. Determinants of significant paravalvular regurgitation after transcatheter aortic valve: implantation impact of device and annulus discongruence. *J Am Coll Cardiol Intv* 2009;2:821–7.
26. Mylotte D, Dorfmeister M, Elhmidi Y, et al. Erroneous measurement of the aortic annular diameter using 2-dimensional echocardiography resulting in inappropriate corevalve size selection: a retrospective comparison with multislice computed tomography. *J Am Coll Cardiol Intv* 2014;7:652–61.
27. Isner JM, Chokshi SK, DeFranco A, Braimen J, Slovenkai GA. Contrasting histoarchitecture of calcified leaflets from stenotic bicuspid versus stenotic tricuspid aortic valves. *J Am Coll Cardiol* 1990;15:1104–8.
28. Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. *JAMA* 2011;306:1104–12.
29. Makkar RR, Jilaihawi H, Chakravarty T, et al. Determinants and outcomes of acute transcatheter valve-in-valve therapy or embolization: a study of multiple valve implants in the U.S. PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve). *J Am Coll Cardiol* 2013;62:418–30.
30. Gilard M, Eltchaninoff H, Iung B, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012;366: 1705–15.
31. Roy DA, Schaefer U, Guetta V, et al. Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. *J Am Coll Cardiol* 2013;61:1577–84.
32. Ussia GP, Barbanti M, Petronio AS, et al. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. *Eur Heart J* 2012;33:969–76.
33. Piazza N, Wenaweser P, van Gameren M, et al. Relationship between the logistic EuroSCORE and the Society of Thoracic Surgeons predicted risk of mortality score in patients implanted with the CoreValve ReValving system—a Bern-Rotterdam study. *Am Heart J* 2010;159:323–9.

34. Piazza N, Kalesan B, van Mieghem N, et al. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. *J Am Coll Cardiol Interv* 2013;6: 443–51.
35. Genereux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. *J Am Coll Cardiol* 2013;61:1125–36.
36. Abdel-Wahab M, Mehilli J, Frerker C, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. *JAMA* 2014;311:1503–14.
37. Willson AB, Webb JG, Labounty TM, et al. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. *J Am Coll Cardiol* 2012;59:1287–94.
38. Jilaihawi H, Kashif M, Fontana G, et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. *J Am Coll Cardiol* 2012;59: 1275–86.
39. Girdauskas E, Disha K, Secknus M, Borger M, Kuntze T. Increased risk of late aortic events after isolated aortic valve replacement in patients with bicuspid aortic valve insufficiency versus stenosis. *J Cardio-vasc Surg (Torino)* 2013; 54:653–9.
40. Girdauskas E, Disha K, Raisin HH, Secknus MA, Borger MA, Kuntze T. Risk of late aortic events after an isolated aortic valve replacement for bicuspid aortic valve stenosis with concomitant ascending aortic dilation. *Eur J Cardiothorac Surg* 2012;42:832–7.
41. Binder RK, Rodes-Cabau J, Wood DA, Webb JG. Edwards SAPIEN 3 valve. *Euro-Intervention* 2012;8 Suppl:Q83–7.
42. Piazza N, Martucci G, Lachapelle K, et al. First-in-human experience with the Medtronic CoreValve Evolut R. *EuroIntervention* 2014;9: 1260–3.
43. Meredith IT, Worthley SG, Whitbourn RJ, et al. Transfemoral aortic valve replacement with the repositionable Lotus Valve System in high surgical risk patients: the REPRISE I study. *Euro-Intervention* 2014;9:1264–70.
44. Manoharan G, Spence MS, Rodes-Cabau J, Webb JG. St Jude Medical Portico valve. *Euro-Intervention* 2012;8 Suppl:Q97–101.

NOVEL TAVI SYSTEMS

14

First-in-human experience with the Medtronic CoreValve Evolut R

Piazza N, Martucci G, Lachapelle K, de Varennes B, Bilodeau L, Buithieu J, Mylotte D.
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ABSTRACT

Objectives

The purpose of this study was to assess the feasibility and safety of transcarotid transcatheter aortic valve replacement (TAVR).

Background

Many candidates for TAVR have challenging vascular anatomy that precludes transfemoral access. Transcarotid arterial access may be an option for such patients.

Methods

The French Transcarotid TAVR Registry is a voluntary database that prospectively collected patient demographics, procedural characteristics, and clinical outcomes among patients undergoing transcarotid TAVR. Outcomes are reported according to the updated Valve Academic Research Consortium criteria.

Results

Among 96 patients undergoing transcarotid TAVR at 3 French sites (2009 to 2013), the mean age and Society of Thoracic Surgeons predicted risk of mortality were 79.4 ± 9.2 years and $7.1 \pm 4.1\%$, respectively. Successful carotid artery access was achieved in all patients. The Medtronic CoreValve (Medtronic, Inc., Minneapolis, Minnesota) ($n = 89$; 92.7%) and Edwards SAPIEN valves (Edwards Lifesciences, Irvine, California) ($n = 7$; 7.3%) were used. Procedural complications included: valve embolization (3.1%), requirement for a second valve (3.1%), and tamponade (4.2%). There were no major bleeds or major vascular complications related to the access site. There were 3 (3.1%) procedural deaths and 6 (6.3%) deaths at 30 days. The 1-year mortality rate was 16.7%. There were 3 (3.1%) cases of Valve Academic Research Consortium–defined in-hospital stroke ($n = 0$) or transient ischemic attack (TIA) ($n = 3$). None of these patients achieved the criteria for stroke and none manifested new ischemic lesions on cerebral computed tomography or magnetic resonance imaging. At 30 days, a further 3 TIAs were observed, giving an overall stroke/TIA rate of 6.3%.

Conclusions

Transcarotid vascular access for TAVR is feasible and is associated with encouraging short- and medium-term clinical outcomes. Prospective studies are required to ascertain if transcarotid TAVR yields equivalent results to other nonfemoral vascular access routes.

Keywords: aortic stenosis, carotid vascular access, transcatheter aortic valve replacement

Substantive peripheral vascular disease and small-caliber iliofemoral vasculature renders transfemoral transcatheter aortic valve replacement (TAVR) challenging or impossible in up to one-quarter of TAVR candidates (1–3). In such cases, a variety of alternate vascular access routes have been described: transapical (4), transaxillary (5), direct aortic (6), and transcaval (7). Each of these alternative strategies may be undesirable in certain clinical and anatomical situations, and each may be associated with adverse clinical consequences, including greater invasiveness, post-procedural pain, delayed mobility and patient discharge, and perhaps, increased mortality in the case of the transapical route (8). Transcarotid vascular access for the purposes of TAVR has been suggested as an access route with the potential to mitigate some of the disadvantages of other nonfemoral approaches (9). Manipulation of the carotid arteries and insertion of large-bore sheaths for the delivery of transcatheter heart valves (THVs), however, could potentially increase the risk of stroke. Importantly, there remain few published data describing the safety and efficacy of this approach.

We sought to address this knowledge gap by describing the procedural and clinical outcomes of a large cohort of consecutive patients undergoing transcarotid TAVR.

METHODS

Patients

The French Transcarotid TAVR registry is a collaborative initiative developed by interventional cardiologists and cardiac surgeons performing transcarotid TAVR. This voluntary database has prospectively collected consecutive patient data from 3 participating centers (Hôpital Cardiologique, Lille; Hôpital Louis Pradel, Lyon; and Hôpital Henri Mondor, Paris) since April 2009, including patient demographics, clinical and procedural characteristics, and clinical outcomes.

At each participating institution, patients with severe aortic stenosis considered by the institutional Heart Team to be at high or excessive surgical risk were considered for TAVR. In all cases, multimodal vascular access assessment was performed to determine the optimal vascular access route for TAVR. Nonfemoral vascular access was considered in patients with iliofemoral or descending aortic anatomy at high risk for vascular complications who would potentially benefit from TAVR. In April 2009, the first transcarotid TAVR was performed using the Medtronic CoreValve (Medtronic, Inc., Minneapolis, Minnesota) in a patient without traditional vascular access options (9). Subsequently, experience with this technique has increased, and in some centers, transcarotid vascular access has become the default access of choice when transfemoral TAVR is not possible (10). All patients provided written informed consent for the intervention.

Pre-procedural screening.

TAVR candidates underwent anatomic assessment with contrast angiography or, more recently, multislice computed tomography. Patients with small-caliber (≤ 6 mm), heavily calcified, severely tortuous, or stenotic iliofemoral anatomy or those with significant descending aortic pathology were considered to be candidates for transcatheter aortic valve replacement (TAVR). The dimensions of the carotid, subclavian, and vertebral arteries were carefully assessed using multislice computed tomography and Doppler ultrasonography. Patients with evidence of significant ($\geq 50\%$) common or internal carotid artery stenosis, with plaque considered to be at high risk of embolization, or with congenital variants of the aortic arch (e.g., Bovine arch) were not considered for transcatheter aortic valve replacement. A common carotid artery minimal luminal diameter threshold of ≥ 7.0 mm was considered appropriate for transcatheter aortic valve replacement vascular access. Prior ipsilateral carotid artery intervention, contralateral carotid artery occlusion, or stenosis/occlusion of the vertebral arteries were also considered to be contraindications to transcatheter aortic valve replacement.

The arterial circle of Willis serves as a potential collateral pathway that maintains cerebral perfusion in cases of diminished afferent blood supply through the internal carotid arteries. Cerebral magnetic resonance angiography (MRA) can accurately delineate the components of the circle of Willis and determine the adequacy of collateral blood flow (11,12). In all cases, screening cerebral MRA was performed and interpreted by neuroimaging specialists to evaluate collateral cerebral blood flow, and patients with suspected inadequate collateral flow were excluded. In cases with equivocal cerebral MRA, transcranial echo Doppler was also performed in an attempt to further identify patients with the potential for cerebral hypoperfusion.

Procedures.

The participating institutions adopted a standardized procedural technique, in which the left common carotid artery was preferentially selected for all TAVR devices. The left side provides superior coaxial alignment between the aortic root and the transcatheter heart valve (THV) during deployment, and affords simpler cardiac catheterization and operating room configuration. All patients received a loading dose of aspirin (300 mg) and clopidogrel (300 mg), prophylactic antibiotics, and had central venous access for insertion of a temporary pacing wire. Control angiography during the procedure necessitated insertion of a 6-F vascular access sheath via the radial or femoral arteries. Intra-operatively, cerebral perfusion was continually monitored using cerebral oximetry with near-infrared spectrometry (Equanox 7600, Nonin Medical Inc., North Plymouth, Minnesota). The proximal left common carotid artery was exposed via a small incision 2 cm above the left clavicle (**Figure 1**).

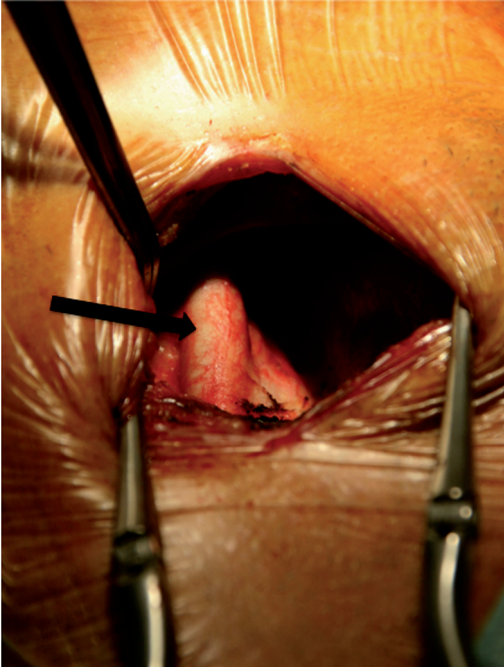


FIGURE 1 Exposure of the Left Common Carotid Artery
Exposure of the left common carotid artery (**black arrow**) for transcatheter aortic valve replacement.

The carotid artery was carefully dissected to avoid injury to the vagus nerve, which was retracted from the immediate surgical field. Vascular clamps were used to achieve proximal and distal control of the carotid artery, and percutaneous access was then achieved by insertion of a 5-F vascular access sheath. The stenotic aortic valve was then crossed in the usual fashion, using a straight-tip guide wire and a Judkin's right or Amplatz left 1 diagnostic catheter. A pre-shaped Amplatz Super stiff guide wire was then positioned in the apex of the left ventricle, and a 14-F sheath was inserted for the purposes of performing balloon aortic valvuloplasty. Thereafter, sequential dilation of the carotid artery was performed in selected cases with 16- and 18-F dilators, and an 18-F vascular access sheath (CoreValve cases, Cook Medical, Bloomington, Indiana) or the Edwards e-sheath (Edwards Lifesciences, Irvine, California) were then carefully advanced into the ascending aorta (**Figure 2**).

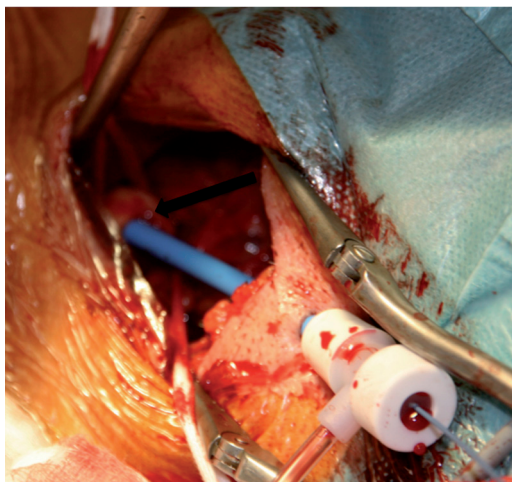


FIGURE 2 Insertion of the Vascular Access Sheath

The 14-F vascular access sheath in situ in the left common carotid artery (**black arrow**). Note the vascular access sheath is stabilized through a 1-cm incision cranial to the carotid dissection field.

Intravenous heparin was administered to maintain an activated clotting time ≥ 250 s. Standard TAVR implantation techniques were followed as previously described (9,13). After valve deployment, the 18-F sheath was carefully retracted, and vascular clamps were used to minimize blood loss while the arterial access site was surgically repaired using 6/0 Prolene suture (**Figure 3**). A control angiogram was performed to assess artery patency, and patients were then transferred to the intensive care unit for overnight monitoring.

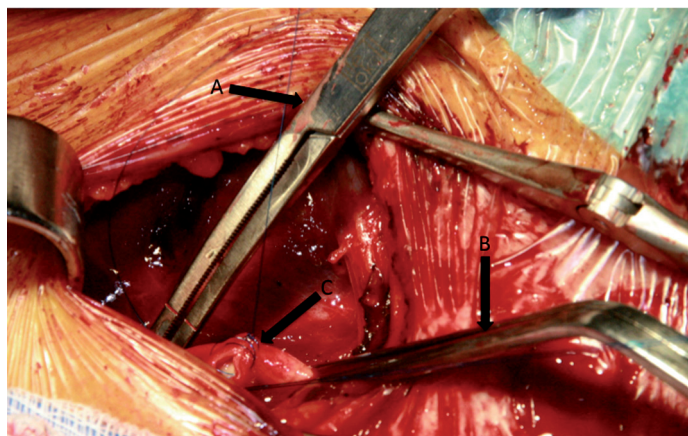


FIGURE 3 Vascular Closure

Proximal (**A**) and distal (**B**) vascular clamps are used to control access site bleeding during surgical closure of the left common carotid arteriotomy (**C**).

Clinical endpoints and follow-up.

Procedural, 30-day, and 1-year major clinical endpoints were defined according to the updated Valve Academic Research Consortium criteria (14). Stroke was of particular interest, and was defined as an acute episode of a focal or global neurological deficit and a change in the level of consciousness; hemiplegia, hemiparesis, numbness, or unilateral sensory loss; aphasia or dysphasia; hemianopia; amaurosis fugax; or other neurological signs or symptoms consistent with stroke (14). Stroke diagnosis required input from a stroke physician and/or diagnostic neuroimaging. Nonfocal global encephalopathy was not defined as stroke without neuroimaging evidence of cerebral infarction (14). The duration of symptoms and/or the demonstration of an ischemic or hemorrhagic lesion on neuroimaging further defined stroke (≥ 24 h; positive imaging) or transient ischemic attack (TIA) (< 24 h; negative imaging). Stroke was further classified as ischemic, hemorrhagic, or undetermined. Finally, stroke was categorized as disabling or nondisabling, the former being determined by a modified Rankin score of 2 or more at 90 days and an increase in at least 1 modified Rankin score category from an individual's pre-stroke baseline (15).

Statistical analysis.

Continuous variables are presented as mean \pm SD or median and range, and repeated measures were compared using a paired Student *t* test. Categorical variables are presented as frequencies and percentages. The 1-year rate of death is shown using a Kaplan-Meier curve. Analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, New York).

RESULTS

A total of 96 elderly patients underwent transcatheter aortic valve replacement (TAVR) across 3 participating sites between April 2009 and December 2013. The mean age and Society of Thoracic Surgeons predicted risk of mortality score of the transcatheter aortic valve replacement patients was 79.4 ± 9.2 years and $7.1 \pm 4.1\%$, respectively (**Table 1**). Most patients (92.7%) described New York Heart Association functional class III or IV, and one-fifth had previously had cardiac surgery.

TABLE 1 Baseline Characteristics of Transcatheter Aortic Valve Replacement Patients (N = 96)

Age, yrs	79.4 ± 9.2
Female	38 (39.6)
Logistic EuroScore	21.7 ± 12.9
EuroScore II	7.2 ± 5.8
STS PROM	7.1 ± 4.1
NYHA functional class III or IV	89 (92.7)
Diabetes mellitus	31 (32.3)
Coronary artery disease	54 (56.3)
Prior myocardial infarction	16 (16.7)
Prior coronary artery bypass grafting	18 (18.8)
Prior stroke or TIA	10 (10.4)
Atrial fibrillation	39 (40.6)
Prior cardiac surgery	21 (21.9)
Permanent pacemaker	13 (13.5)
Pulmonary hypertension*	11 (11.5)
Peripheral arterial disease prohibiting TAVR	96 (100)
Aortic valve area, mm ²	0.8 ± 0.3
Aortic valve mean gradient, mm Hg	45.7 ± 13.7
Left ventricular ejection fraction, %	50.5 ± 16.7

Values are mean ± SD or n (%).

* Pulmonary artery systolic pressure >60 mm Hg.

NYHA = New York Heart Association; STS PROM = Society of Thoracic Surgeons predicted risk of mortality; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

Successful carotid artery vascular access was achieved in all patients. The majority of cases were performed under general anesthesia (98.9%) using the left common carotid artery (88.5%) (**Table 2**). The Medtronic CoreValve and Edwards SAPIEN THV were implanted in 89 (92.7%) and 7 (7.3%) patients, respectively. Procedural complications included: THV embolization (n = 3, 3.1%), implantation of a second THV (n = 3, 3.1%), and cardiac tamponade due to left ventricular wire perforation (n = 4; 4.2%). There were 4 (4.2%) cases of both major bleeding and major vascular complications; none involved the carotid vascular access site (**Table 3**). Conversion to SAVR was not performed in any case. Post-implantation hemodynamics demonstrated a significant reduction in transvalvular mean gradient from 45.7 ± 13.7 mm Hg to 5.7 ± 3.9 mm Hg ($p < 0.0001$) and an increase in effective orifice area from 0.8 ± 0.3 cm² to 1.9 ± 0.4 cm² ($p < 0.0001$). More than mild post-implantation aortic regurgitation was observed in 20 (21.5%) patients.

TABLE 2 Procedural Characteristics of Transcatheter TAVR Patients (N = 96)

General anesthesia	95 (98.9)
Left carotid vascular access	85 (88.5)
Pre-implant balloon valvuloplasty	93 (96.9)
Pre-implant valvuloplasty balloon size, mm	23.4 ± 1.9
Post-implant valvuloplasty	9 (9.4)
Medtronic CoreValve	89 (92.7)
Edwards SAPIEN	7 (7.3)
23 mm	2 (2.1)
26 mm	25 (26.0)
29 mm	53 (55.2)
31 mm	16 (16.7)
THV embolization	3 (3.1)
Procedural valve-in-valve	3 (3.1)
Tamponade	4 (4.2)
Conversion to SAVR	0 (0.0)
Mean gradient, mm Hg	5.7 ± 3.9
Estimated orifice area, cm ²	1.9 ± 0.4
Aortic regurgitation*	
Grade 0	31 (33.3)
Grade 1	42 (45.2)
Grade 2	17 (18.3)
Grade 3	3 (3.1)
Grade 4	0 (0.0)

Values are n (%) or mean ± SD.

* Data available in 93 patients.

SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve.

There were 3 (3.1%) procedural deaths: 1 case of left main coronary artery occlusion, and 2 patients who experienced cardiac tamponade. At 30 days, there were an additional 3 deaths (aspiration pneumonia and multiorgan failure; spontaneous ventricular fibrillation; and gastrointestinal hemorrhage), resulting in a 30-day mortality rate of 6.3%. The median duration of hospital stay was 11 days (inter-quartile range: 9 to 15 days). Long-term follow-up was available in all patients: median follow-up 360 days (interquartile range: 265 to 606 days). The 1-year mortality rate was 16.7% (**Figure 4**).

TABLE 3 Clinical Outcomes of Transcatheter Aortic Valve Replacement Patients (N = 96)

Mortality	
Procedural	3 (3.1)
30-day	6 (6.3)
1-year	16 (16.7)
Bleeding	
Minor	34 (37.4)
Major	4 (4.2)
Life-threatening	4 (4.2)
Vascular complications	
Minor	4 (4.2)
Major	4 (4.2)
Myocardial infarction	1 (1.0)
Acute kidney injury (grade 3)	7 (7.3)
New pacemaker*	22 (26.5)
Hospital stay, days	11 (9–15)
Composite endpoints	
Device success	86 (89.9)
Early safety	89 (92.7)
Clinical efficacy	89 (92.7)

Values are n (%) or median (interquartile range).

* A total of 22 of 83 patients required new pacemaker.

TAVR = transcatheter aortic valve replacement.

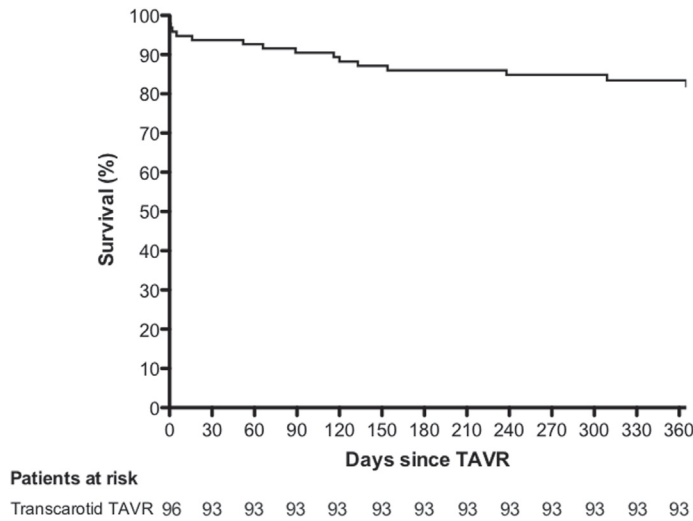


FIGURE 4 1-Year Mortality After Transcatheter TAVR

Kaplan-Meier survival curve of patients undergoing transcatheter transcatheter aortic valve replacement (TAVR).

There were 3 (3.1%) cases of Valve Academic Research Consortium–defined in-hospital stroke ($n = 0$) or TIA ($n = 3$) (**Table 4**). All patients underwent computed tomographic or magnetic resonance neuroimaging and were assessed by a consultant neurologist. Two TIAs were noted immediately post-operatively and 1 on post-operative day 1. These events were localized as ipsilateral ($n = 1$) or contralateral ($n = 2$) to the carotid vascular access site. Clinical features of the events included hemiparesis ($n = 2$) and aphasia ($n = 1$); however, neuroimaging did not show new ischemic lesions in any case. Pre-operatively, all patients were prescribed dual antiplatelet therapy, and all received intraprocedural heparin. Two additional cases of transient nonfocal global encephalopathy with normal neuroimaging were not defined as stroke/TIA. At 30 days, a further 3 TIAs were observed (1 ipsilateral, 2 contralateral), thus yielding an overall event rate of (6.3%). In-hospital atrial fibrillation occurred in each of these additional cases, and the events occurred despite treatment with aspirin and oral anticoagulation. Clinical localization relative to the carotid vascular access site was ipsilateral in 1 case and contralateral in 2 cases. Neuroimaging did not demonstrate any new ischemic lesions in any of these patients. Two further neurological events were noted during long-term follow-up: an ischemic stroke causing aphasia and visual field defect on day 51, and a hemorrhagic stroke on day 409.

TABLE 4 Stroke and TIA in Transcatheter TAVR Patients (N = 96)

In-hospital stroke or TIA	3 (3.1)
TIA	3 (3.1)
Stroke	0 (0)
Ipsilateral localization	1 (33)
Hemorrhagic stroke	0 (0)
In-hospital atrial fibrillation	1 (33)
CHA ₂ DS ₂ -VASc score*	3.8 ± 0.8
Aortic valve pre-dilation	3 (100)
THV post-dilation	1 (33)
30-day stroke or TIA	6 (6.3)
TIA	6 (100)
Stroke	0 (0)
Ipsilateral localization	2 (33)
Hemorrhagic stroke	0 (0)
In-hospital atrial fibrillation	4 (67)
Discharge anticoagulation	4 (67)
Discharge dual antiplatelet therapy	2 (33)

Values are n (%).

* CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) score (24).

TIA = transient ischemic attack; other abbreviations as in **Table 2**.

DISCUSSION

This study provides information on the largest cohort of patients undergoing transcatheter vascular access for TAVR. The salient findings from this study are: transcatheter TAVR is technically feasible in appropriately selected patients; carotid vascular access site complications are rare; and the 30-day rate of stroke or TIA was 6.3%, although all of these ischemic events were transient in nature.

Initially approved TAVR systems in the United States required vascular access sheaths with 18- to 24-F inner diameter. Such large-bore catheters are problematic for the 25% to 30% of patients with peripheral arterial disease and, in particular, for elderly females with small iliofemoral anatomy (3,16). The sheath to femoral artery ratio is considered to be the most powerful predictor of TAVR-related vascular complications (3), and using this measurement almost one-quarter of TAVR candidates require an alternate vascular access route (1,2). A variety of alternative access solutions have been described (4–6), each with specific advantages and disadvantages. Most recently, transcaval TAVR has produced encouraging short-term outcomes (7). It is likely that the proportion of patients undergoing TAVR using alternate vascular access routes will fall due to advances in transcatheter technology (some current devices

are now 14- to 16-F) (17,18); however, these technologies are not yet available worldwide, and patients with severe peripheral arterial disease will remain a considerable challenge for transfemoral access regardless of sheath size.

Transcarotid TAVR with a self-expanding prosthesis was first performed in Lille in 2009 (9). The technique has subsequently been adopted by several European and U.S. centers (9,13,19,20) and has been performed with both self- and balloon-expandable prostheses (13). The surgical approach to the carotid artery is relatively uncomplicated due to its superficial location, and operative experience with the carotid arteries is widely available among cardiovascular surgeons. For the purposes of TAVR, the left common carotid is preferentially chosen, as it allows superior coaxial alignment of the THV with the aortic annulus (**Figure 5**). We prefer to perform transcarotid TAVR under general anesthesia, although regional anesthesia has been successfully performed (19). Important procedural differences from other access routes include routine sequential dilation of the artery (10- to 16-F dilators) and insertion of the 18-F sheath at the time of THV deployment (after balloon valvuloplasty). In the current series, we did not experience major vascular complications or major bleeding related to the vascular access site. There were no access-related deaths.

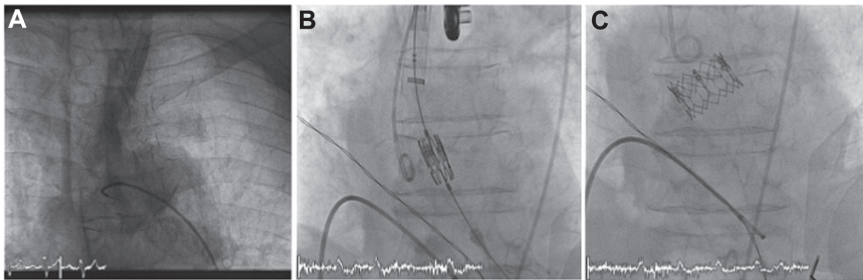


FIGURE 5 Transcarotid TAVR

Transcarotid transcatheter aortic valve replacement (TAVR). (**A**) Selective angiography of the left common carotid artery, (**B**) positioning, and (**C**) deployment of a 29-mm Edwards Sapien XT valve.

At 30 days, 6 patients (6.3%) had evidence of transient cerebral ischemia. Significantly, none of these events met the criteria for stroke, and neuroimaging did not demonstrate new ischemic lesions in any case. These data compare favorably with stroke rates reported in other alternate access series, where the rate of stroke is higher than that observed in transfemoral cohorts (18,21). Webb et al. (18) reported a 30-day stroke rate of 5.6% among patients undergoing contemporary transaortic or transapical TAVR with the SAPIEN 3 valve (Edwards Lifesciences), whereas a stroke rate of 4.3% was described for alternate-access CoreValve implantation in the Advance registry (21). It is intriguing that 4 of 6 TIAs were clinically located contralateral to the site of vascular access. This suggests that there may be several potential stroke mechanisms during transcarotid TAVR: 1) embolization of carotid artery plaque due to arterial puncture and instrumentation; 2) access site trauma providing a nidus for thrombosis

with subsequent embolization; 3) inadequate collateral perfusion through the circle of Willis; and 4) embolization of debris during balloon valvuloplasty or THV implantation. The low rate of stroke observed in this study may be attributed to careful patient selection (common carotid artery minimal lumen diameter ≥ 7.0 mm), mandatory pre-treatment with dual antiplatelet agents, and adequate intraoperative anticoagulation (activated clotting time >250 s). We also limited the duration of antegrade ischemia by placing the large bore introducer sheath only when necessary. Nevertheless, there remains the potential to further reduce the risk of cerebral ischemia by limiting THV post-dilation (22), using embolic protection devices (23), and by further refining the anatomical selection criteria for transcatheter TAVR. A total of 4 of 6 episodes of TIA were located to the right cerebral hemisphere in patients that underwent TAVR using the left common carotid artery. Although we believe this observation is due to the play of chance, we must acknowledge that there is a possibility that embolization from the aortic valve may preferentially access the cerebral vasculature via the right common carotid artery, and therefore, using the right common carotid artery for transcatheter TAVR could be associated with a reduced risk of stroke. More study is required into the mechanism of stroke with this technique.

The observed 30-day mortality rate (6.3%) was relatively high compared with contemporary series. However, this patient cohort was unsuitable for transfemoral TAVR, and thus the mean Society of Thoracic Surgeons predicted risk of mortality score of 7.1% may underestimate the true risk features of this group. Furthermore, this series includes all patients undergoing transcatheter TAVR since 2009, and the complication rates probably reflect our learning curve with TAVR and this technique using first-generation TAVR devices.

Ultimately, we believe that transcatheter TAVR should be considered as an alternative to transapical, transaortic, transcaval, or trans-subclavian procedures. Because there exists limited comparative data between alternate access routes, a patient-centric individualized approach to vascular access should be undertaken by the institutional Heart Team. Transcatheter TAVR may have particular benefits over procedures requiring thoracotomy or sternotomy in patients with advanced lung disease or prior sternotomy, where recovery from surgery could be protracted. Similarly, transcatheter TAVR is technically less challenging than the transcaval approach. Longer-term follow-up is, however, required to demonstrate the efficacy of this approach.

Study limitations.

The study findings should be interpreted in light of the study design. This prospective study included a small number of patients at selected high-volume TAVR centers, and the results demand cautious interpretation. It is possible that the true rate of neurological events has been underestimated, as systematic evaluation by a neurologist was not performed prior to and following TAVR. We were, however, very focused on neurological outcomes, and there was a low threshold for neurologist evaluation and/or neuroimaging.

CONCLUSIONS

Transcarotid vascular access for TAVR is feasible and is associated with encouraging short- and medium-term clinical outcomes. Prospective studies with longer-term follow-up are required to ascertain if transcarotid TAVR yields equivalent safety and efficacy to other nonfemoral vascular access routes.

PERSPECTIVES

WHAT IS KNOWN? A significant proportion of patients undergoing TAVR are not suitable for transfemoral vascular access. In such cases, a range of vascular alternate access routes have been described, including the transapical, transaortic, trans-subclavian, and transcaval approaches. Transcarotid vascular access has been previously described and may be a minimally invasive and more straightforward technique compared with the aforementioned approaches; however, little information is available describing the performance and outcomes associated with this strategy.

WHAT IS NEW? This study describes the largest cohort of patients undergoing transcarotid TAVR to date. It demonstrates that carotid vascular access for the purposes of TAVR is feasible and safe. This approach safely facilitated the implantation of both self- and balloon-expandable THVs. Importantly, no patient in this series experienced a stroke; however, a 30-day rate of TIA of 6.3% was observed.

WHAT IS NEXT? The results of this study suggest that transcarotid TAVR should be considered a reasonable vascular access route in patients who are not suitable for a transfemoral approach. Indeed, this technique may have specific advantages over the more invasive transapical or transaortic strategies in certain patient cohorts. Larger series with extended follow-up are required to definitively prove the safety and efficacy of this technique.

ABBREVIATIONS AND ACRONYMS

- MRA = magnetic resonance angiography
- TAVR = transcatheter aortic valve replacement
- THV = transcatheter heart valve

REFERENCES

1. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014; 370:1790–8.
2. Reardon MJ, Adams DH, Coselli JS, et al. Self-expanding transcatheter aortic valve replacement using alternative access sites in symptomatic patients with severe aortic stenosis deemed extreme risk of surgery. *J Thorac Cardiovasc Surg* 2014; 148:2869–76.
3. Hayashida K, Lefevre T, Chevalier B, et al. Transfemoral aortic valve implantation new criteria to predict vascular complications. *J Am Coll Cardiol Interv* 2011;4:851–8.
4. Walther T, Simon P, Dewey T, et al. Transapical minimally invasive aortic valve implantation: multi-center experience. *Circulation* 2007;116: I240–5.
5. Petronio AS, De Carlo M, Bedogni F, et al. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. *Circ Cardiovasc Interv* 2010;3: 359–66.
6. Bauernschmitt R, Schreiber C, Bleiziffer S, et al. Transcatheter aortic valve implantation through the ascending aorta: an alternative option for no-access patients. *Heart Surg Forum* 2009;12:E63–4.
7. Greenbaum AB, O'Neill WW, Paone G, et al. Caval-aortic access to allow transcatheter aortic valve replacement in otherwise ineligible patients: initial human experience. *J Am Coll Cardiol* 2014; 63: 2795–804.
8. Blackstone EH, Suri RM, Rajeswaran J, et al. Propensity-matched comparisons of clinical outcomes after transapical or transfemoral transcatheter aortic valve replacement: a Placement of Aortic Transcatheter Valves (PARTNER)-I Trial Substudy. *Circulation* 2015;131:1989–2000.
9. Modine T, Lemesle G, Azzaoui R, Sudre A. Aortic valve implantation with the CoreValve ReValving System via left carotid artery access: first case report. *J Thorac Cardiovasc Surg* 2010; 140:928–9.
10. Modine T, Sudre A, Delhaye C, et al. Trans-cutaneous aortic valve implantation using the left carotid access: feasibility and early clinical outcomes. *Ann Thorac Surg* 2012;93:1489–94.
11. Hartkamp MJ, van Der Grond J, van Everdingen KJ, Hillen B, Mali WP. Circle of Willis collateral flow investigated by magnetic resonance angiography. *Stroke* 1999;30:2671–8.
12. Hendrikse J, Rutgers DR, Klijn CJ, Eikelboom BC, van der Grond J. Effect of carotid endarterectomy on primary collateral blood flow in patients with severe carotid artery lesions. *Stroke* 2003;34:1650–4.
13. Modine T, Sudre A, Amr G, Delhaye C, Koussa M. Implantation of a Sapien XT aortic bioprosthesis through the left carotid artery. *J Card Surg* 2014;29:337–9.
14. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *EuroIntervention* 2012;8:782–95.
15. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604–7.
16. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607.
17. Piazza N, Martucci G, Lachapelle K, et al. First-in-human experience with the Medtronic Core-Valve Evolut R. *EuroIntervention* 2014;9:1260–3.
18. Webb J, Gerosa G, Lefevre T, et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. *J Am Coll Cardiol* 2014;64:2235–43.
19. Daly MJ, Blair PH, Modine T, et al. Carotid-access transcatheter aortic valve replacement in a patient with a previous mitral valve replacement. *J Card Surg* 2015;30:256–9.

20. Guyton RA, Block PC, Thourani VH, Lerakis S, Babaliaros V. Carotid artery access for transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2013;82:E583–6.
21. Linke A, Wenaweser P, Gerckens U, et al. Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. *Eur Heart J* 2014; 35:2672–84.
22. Hahn RT, Pibarot P, Webb J, et al. Outcomes with post-dilation following transcatheter aortic valve replacement: the PARTNER I trial (placement of aortic transcatheter valve). *J Am Coll Cardiol Intv* 2014;7:781–9.
23. Naber CK, Ghanem A, Abizaid AA, et al. First-in-man use of a novel embolic protection device for patients undergoing transcatheter aortic valve implantation. *EuroIntervention* 2012;8:43–50.
24. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* 2010;137:263–72.

TRANSCAROTID TAVI

15

Transcarotid Transcatheter Aortic Valve Replacement: Feasibility and Safety.

Mylotte D, Sudre A, Teiger E, Obadia JF, Spence M, Khamis H, Delhayé C, Koussa M, Debry N, Piazza N, Modine, T.

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ABSTRACT

The CoreValve Evolut R with EnVeo R delivery catheter is a novel transcatheter heart valve (THV) system with enhanced features that have the potential to improve the safety of transcatheter aortic valve implantation (TAVI). The newly designed delivery catheter is 14 Fr-equivalent and thus expands the option of transfemoral TAVI to a greater proportion of patients. Most importantly, the EnVeo R delivery catheter allows the valve to be recaptured and repositioned during deployment, thus minimising the consequences of THV malposition. Furthermore, the nitinol frame of the CoreValve Evolut R has been redesigned for superior interaction, consistent radial force and optimised cover index across the sizing range, and conformability with the native annulus, thereby hypothetically reducing stress on the left bundle branch. Although large series with long-term follow-up are required to demonstrate the safety and efficacy of this device, we present the first human experience with the Evolut R system.

INTRODUCTION

The emergence of second-generation transcatheter aortic valve implantation (TAVI) systems is timely, as this technology is being evaluated in lower-risk patients. Extending the remit of TAVI to lower-risk patients necessitates more flexible, user-friendly and safer devices. Among the TAVI physician's "wish list" are smaller calibre and more flexible delivery catheters with the ability to recapture, reposition, or remove the transcatheter heart valve (THV) from the body if necessary. The newly designed CoreValve Evolut R™ (Medtronic, Minneapolis, MN, USA) is a low-profile system that encompasses these important requirements. Herein, we describe the technical features of this novel system and describe the first-in-human experience with this device.

COREVALVE EVOLUT R TRANSCATHETER HEART VALVE

The CoreValve Evolut R represents a significant step in the evolution of the Medtronic CoreValve family of THVs. The design features of prior iterations have been described elsewhere¹, and the Evolut R retains many of the characteristics of its predecessors: a radiopaque self-expanding nitinol support frame, supra-annular trileaflet porcine pericardial leaflets, and porcine pericardium fabric skirt. As before, the Evolut R will be available in 23, 26, 29 and 31 mm sizes.

The cell geometry and frame of the Evolut R have been redesigned to optimise frame interaction with the native anatomy, to improve conformability to the aortic annulus and



Figure 1 The CoreValve Evolut R. The CoreValve Evolut R has been redesigned to provide more consistent radial force across the sizing range with modified cell geometry to improve conformability to the aortic annulus. The new valve release mechanism has a paddle design to prevent hang-ups and the porcine pericardial leaflets are treated with alpha-amino oleic acid (AOA®) to retard mineralisation.

reduce paravalvular leak (**Figure 1**). The inflow has more consistent radial force across the sizing spectrum, and the outflow has been shortened and reshaped to provide improved alignment between valve housing and the native sinus, which is expected to reduce stress on the left bundle branch. The EnVeo R catheter valve release mechanism now features a paddle design in place of the previously used tabs, thereby allowing a more consistent release from the delivery catheter. Finally, the valve leaflets are now routinely treated with alpha-amino oleic acid (AOA[®]) to impede calcium deposition.

ENVEO R™ DELIVERY CATHETER WITH INLINE™ SHEATH

The new EnVeo R delivery catheter (Medtronic, Minneapolis, MN, USA) features a complete redesign of the AccuTrak system (Medtronic) that is currently employed for CoreValve and CoreValve Evolut (Medtronic) implantation (**Figure 2**). The EnVeo R catheter with InLine sheath (Medtronic) allows the valve to be delivered without the requirement for a separate introducer sheath. As a 14 Fr-equivalent delivery system (true 18 Fr outer diameter) the EnVeo R system represents a 4 Fr reduction in profile compared to the currently used 18 Fr introducer sheaths (approximately 22 Fr outer diameter). Alternatively, the EnVeo R catheter can be introduced through an 18 Fr introducer sheath, if required. The EnVeo R catheter also features a new ergonomic handle that affords more comfortable and stable hand positioning during valve deployment, and an independent mechanism for catheter tip retrieval after implantation. The new system also provides stable and accurate valve deployment by engineering the delivery capsule to be retracted (or advanced) in increments equal to the distance that the deployment wheel is turned (i.e., 1:1 valve deployment). Most importantly, the novel laser-cut nitinol-reinforced capsule provides the ability to resheath or recapture the partially deployed THV (up to 80% of maximal deployment) in order to reposition or retrieve the implant.

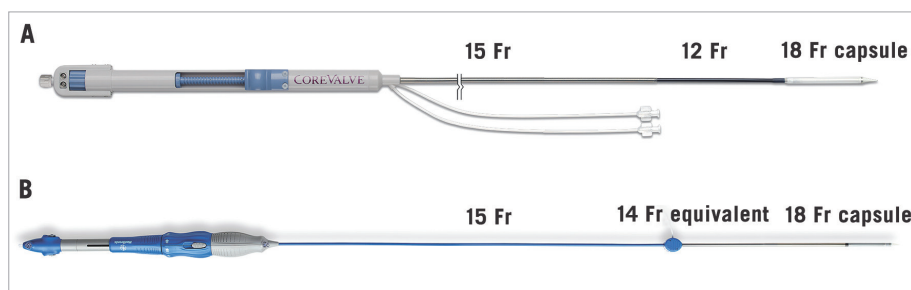


Figure 2 The EnVeo R delivery system. The AccuTrak delivery system (A) has been replaced by the EnVeo R delivery catheter with InLine sheath technology (B). The new system is now a 14 Fr-equivalent system that can deliver the transcatheter heart valve without the requirement for a separate introducer sheath. The modified valve capsule now allows the valve to be fully recaptured and repositioned during deployment.

CLINICAL APPLICATIONS

In the PARTNER trial (cohorts A and B), implantation of a second THV due to malposition or severe aortic incompetence occurred in 2.47% of cases and is even more common when THVs are used to treat degenerated surgical bioprostheses^{2,3}. Considering the litany of complications associated with THV malposition (mitral valve injury, severe paravalvular leak, conduction abnormalities, THV embolisation) and the independent association with increased one-year cardiovascular mortality³, the capacity to recapture and reposition or remove a malpositioned THV is of considerable importance. The ability to recapture a partially deployed THV also allows the operator to attempt more challenging anatomy, knowing that the system can be retrieved if suboptimal results are encountered. On a cautionary note, attempts to optimise THV implantation by repeatedly recapturing and repositioning the THV could potentially increase the risk of embolic events and could represent a downside to recapturable TAVI systems⁴. Further study is required to assess this important issue.

Compared to their predecessors, the EnVeo R catheter and InLine sheath represent a significant reduction in the profile of the delivery system. The Evolut R 14 Fr-equivalent system compares favourably to the expanded diameter of the 14-16 Fr eSheath and the 18 Fr sheath used by the Edwards SAPIEN 3 and CENTERA systems (Edwards Lifesciences, Irvine, CA, USA), respectively. Given that major vascular complications are associated with considerable morbidity and mortality⁴, and that the ratio of the outer diameter of the delivery sheath to the femoral artery (SFAR) is a strong predictor of these complications⁵, the 4 Fr reduction in sheath size is likely to extend the potential and safety of transfemoral TAVI. Applying the SFAR ratio to the EnVeo R system, transfemoral TAVI can be safely performed in patients with iliofemoral diameters as small as 5.4 mm. Indeed, if the 20% oversizing ratio between the introducer sheath (18 Fr: outer diameter 7.2 mm) and the minimal femoral artery diameter (6 mm) is maintained, then femoral anatomy as small as 5 mm could be navigated with the EnVeo R delivery catheter.

FIRST HUMAN EXPERIENCE

The first-in-human experience with the 23 mm CoreValve Evolut R system took place at the McGill University Health Centre in Montreal, Quebec, Canada, in September 2013. The recipient was a 70-year-old female with progressive dyspnoea (NYHA III) due to severely stenotic degenerated aortic bioprosthetic valve (mean gradient 41 mmHg; effective orifice area: 0.61 cm²). The Heart Team considered her too high risk for redo aortic valve surgery as she had previously undergone two coronary artery bypass surgeries and had multiple comorbid medical conditions (Society of Thoracic Surgeons mortality risk score: 7.9%). The degenerated aortic bioprosthesis (19 mm Carpentier Edwards Perimount Magna Ease) had an internal stent diameter of 16.5 mm on multislice computed tomography (**Figure 3A** and **Figure 3B**).

The 23 mm Evolut R is suitable for native annuli between 18 and 20 mm in diameter; however, smaller diameter degenerated surgical bioprostheses have been successfully treated⁶. The CoreValve Evolut R was successfully implanted via the right femoral artery using the EnVeo R delivery catheter and InLine sheath (**Figure 3C - Figure 3E**) (**Moving image 1**). In this case, it was not necessary to recapture the Evolut R during deployment. Post implantation, the peak-to-peak and mean transaortic valve gradients were gratifyingly low: 6 mmHg by invasive pressure recording and 8 mmHg by echocardiography, respectively (**Figure 3F**). It is likely that the supra-annular position of the CoreValve Evolut R leaflets accounted for this low post-procedural gradient. There was no central or paravalvular aortic regurgitation.

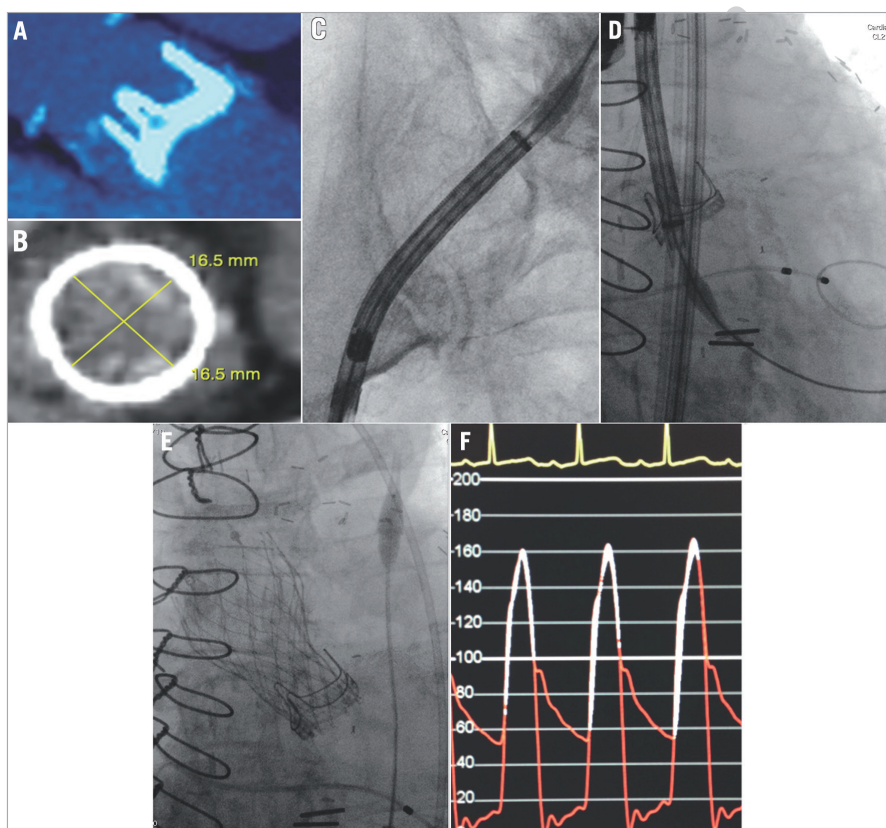


Figure 3 CoreValve Evolut R: first-in-human experience. The first-in-human CoreValve Evolut R was implanted inside a 19 mm Carpentier Edwards Perimount Magna Ease (manufacturer labelled internal stent diameter 17.5 mm) (A). The internal stent diameter of the degenerated aortic bioprosthesis was 16.5 mm on multislice computed tomography (B). The EnVeo R delivery system was advanced through the tortuous calcified iliofemoral anatomy (C), and the CoreValve Evolut R was positioned appropriately. The final position of the Evolut R was acceptable (E), and the post-implantation transvalvular gradient decreased from 41 mmHg to 6 mmHg (F).

LIMITATIONS

Herein, we describe the first human experience with the CoreValve Evolut R. Although this device has been specifically designed to improve procedural outcomes, demonstration of device safety and clinical efficacy requires verification. For example, the potential to reduce the repeated attempts to position the THV optimally could potentially increase the risk of embolic events. To this end, the results of the ongoing CoreValve Evolut R Clinical Study (ClinicalTrials.gov Identifier: NCT01876420) are eagerly awaited.

CONCLUSIONS

The CoreValve Evolut R is a low-profile THV system that will extend the possibility of transfemoral TAVI to more patients. Coupled with the ability to recapture and reposition the THV, the CoreValve Evolut R has the potential to improve the accuracy and safety of TAVI procedures.

IMPACT ON DAILY PRACTICE

The redesigned CoreValve Evolut R system should impact daily clinical practice in several ways. First, the 4 Fr reduction in the diameter of the EnVeo R delivery catheter should extend the possibility of transfemoral TAVI to a greater proportion of patients. It is possible that patients with minimal femoral artery diameters as small as 5 mm could become transfemoral TAVI candidates. Second, the new delivery system allows one to one release or recapture of the THV, thereby providing for more stable valve implantation. Most importantly, the ability to recapture and reposition the CoreValve Evolut R during deployment is expected to improve the safety of TAVI. This important feature will potentially reduce THV malposition, embolisation, and the requirement for implantation of multiple THVs.

CONFLICT OF INTEREST STATEMENT

N. Piazza is a consultant for Medtronic. G. Martucci is a proctor for Medtronic. The other authors have no conflicts of interest to declare.

REFERENCES

1. Sinning JM, Werner N, Nickenig G, Grube E. Medtronic CoreValve Evolut valve. *EuroIntervention*. 2012;8:Q94-6.
2. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, Descoutures F, Hengstenberg C, Moat NE, Bekerredjian R, Napodano M, Testa L, Lefevre T, Guetta V, Nissen H, Hernandez JM, Roy D, Teles RC, Segev A, Dumonteil N, Fiorina C, Gotzmann M, Tchetché D, Abdel-Wahab M, De Marco F, Baumbach A, Laborde JC, Kornowski R. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. *Circulation*. 2012;126:2335-44.
3. Makkar RR, Jilaihawi H, Chakravarty T, Fontana GP, Kapadia S, Babaliaros V, Cheng W, Thourani VH, Bavaria J, Svensson L, Kodali S, Shiota T, Siegel R, Tuzcu EM, Xu K, Hahn RT, Herrmann HC, Reisman M, Whisenant B, Lim S, Beohar N, Mack M, Teirstein P, Rihal C, Douglas PS, Blackstone E, Pichard A, Webb JG, Leon MB. Determinants and outcomes of acute transcatheter valve-in-valve therapy or embolization: a study of multiple valve implants in the U.S. PARTNER trial (Placement of AoRTic TraNscatheterER Valve Trial Edwards SAPIEN Transcatheter Heart Valve). *J Am Coll Cardiol*. 2013;62:418-30.
4. Kahlert P, Al-Rashid F, Dottger P, Mori K, Plicht B, Wendt D, Bergmann L, Kottenberg E, Schlamann M, Mummel P, Holle D, Thielmann M, Jakob HG, Konorza T, Heusch G, Erbel R, Eggebrecht H. Cerebral embolization during transcatheter aortic valve implantation: a transcranial Doppler study. *Circulation*. 2012;126:1245-55.
5. Hayashida K, Lefevre T, Chevalier B, Hovasse T, Romano M, Garot P, Mylotte D, Uribe J, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B, Morice MC. Transfemoral aortic valve implantation new criteria to predict vascular complications. *JACC Cardiovasc Interv*. 2011;4:851-8.
6. Zavalloni D, De Benedictis M, Pagnotta P, Scrocca I, Presbitero P. New CoreValve Evolut 23mm technology for treatment of degenerated bioprosthesis. *Heart Lung Circ*. 2014;23:183-5

TRANSCATHETER HEART VALVE FAILURE

IV

Chapter 16 Transcatheter heart valve failure: a systematic review

Mylotte D, Andalib A, Thériault-Lauzier P, Dorfmeister M, Girgis M, Alharbi W, Chetrit M, Galatas C, Mamane S, Sebag I, Buithieu J, Bilodeau L, de Varennes B, Lachapelle K, Lange R, Martucci G, Virmani R, Piazza N.
Eur Heart J. 2015; 36:1306-27.

TAVI FAILURE: A SYSTEMATIC REVIEW

16

Transcatheter heart valve failure: a systematic review

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ABSTRACT

Aims

A comprehensive description of transcatheter heart valve (THV) failure has not been performed. We undertook a systematic review to investigate the aetiology, diagnosis, management, and outcomes of THV failure.

Methods and results

The systematic review was performed in accordance with the PRISMA guidelines using EMBASE, MEDLINE, and Scopus. Between December 2002 and March 2014, 70 publications reported 87 individual cases of transcatheter aortic valve implantation (TAVI) failure. Similar to surgical bioprosthetic heart valve failure, we observed cases of prosthetic valve endocarditis (PVE) ($n = 34$), structural valve failure ($n = 13$), and THV thrombosis ($n = 15$). The microbiological profile of THV PVE was similar to surgical PVE, though one-quarter had satellite mitral valve endocarditis, and surgical intervention was required in 40% (75% survival). Structural valve failure occurred most frequently due to leaflet calcification and was predominantly treated by redo-THV (60%). Transcatheter heart valve thrombosis occurred at a mean 9 ± 7 months post-implantation and was successfully treated by prolonged anticoagulation in three-quarters of cases. Two novel causes of THV failure were identified: late THV embolization ($n = 18$); and THV compression ($n = 7$) following cardiopulmonary resuscitation (CPR). These failure modes have not been reported in the surgical literature. Potential risk factors for late THV embolization include low prosthesis implantation, THV undersizing/underexpansion, bicuspid, and non-calcified anatomy. Transcatheter heart valve embolization mandated surgery in 80% of patients. Transcatheter heart valve compression was noted at post-mortem in most cases

Conclusion

Transcatheter heart valves are susceptible to failure modes typical to those of surgical bioprostheses and unique to their specific design. Transcatheter heart valve compression and late embolization represent complications previously unreported in the surgical literature.

Keywords: Aortic stenosis, Transcatheter aortic valve implantation, Transcatheter heart valve failure, Prosthetic valve endocarditis, Heart valve failure

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a rapidly proliferating technology with the potential to become the dominant treatment strategy for aortic valve stenosis in patients at excessive- or high-operative risk.¹ Improving procedural safety and promising medium-term clinical efficacy have encouraged the application of transcatheter heart valve (THV) technology to lower risk cohorts.²⁻⁵ In this context, understanding the modes of THV failure and demonstrating valve durability and long-term clinical efficacy are of vital importance.

It is estimated that ~200 000 patients worldwide undergo surgical aortic valve replacement (SAVR) annually.⁶ Bioprosthetic surgical heart valves are the most frequently implanted prostheses, especially in older patients, despite the potential for these valves to fail.⁷ A variety of failure modes have been described for surgical bioprostheses, including infective endocarditis (IE), thrombosis, and structural valve failure (SVF) (degeneration of bioprosthetic tissue or stent de-formation). Surgical bioprosthetic failure has been clearly described and quantified,^{8,9} while in contrast, a systematic description of THV failure has not been performed.

We sought to describe the clinical characteristics, failure modes, and outcomes of THV failure by performing a systematic review of the published literature addressing this important subject.

METHODS

This systematic review was performed in accordance with the PRISMA guidelines.¹⁰ We conducted an independent review of citations from EMBASE, Google Scholar, MEDLINE, and Scopus between December 2002 and March 2014. All published studies in English reporting patient-level data on THV failure were identified. Two authors (D.M. and A.A.) screened the title and/or abstract for suitability, and then examined, in detail, all potentially suitable manuscripts to finalise eligibility. Uncertainties were resolved by discussion with another reviewer (N.P.). Each publication was reviewed and in cases of duplication, only the most complete report was included. The citation lists of included articles were examined for further relevant publications. The following combined keywords were used: transcatheter aortic valve or THV or percutaneous valve and IE, abscess, complication, embolization, migration, malposition, valve failure, restenosis, cardiopulmonary resuscitation (CPR), chest compression, deformation, thrombosis, occlusion, and explant.

Published studies meeting the following criteria were included in the study: (i) case reports and series detailing individual causes of post-procedural TAVI failure; (ii) large registries and randomized controlled trials detailing specific incidences of TAVI failure, where sufficient patient-level detail is provided (failure mode, and/or presentation, and/or diagnosis, management, and outcome). Studies describing only an incidence of TAVI failure without specific case detail were excluded.

Definitions

Prosthetic valve endocarditis (PVE) was defined according to the updated Valve Academic Research Consortium (VARC) criteria,¹¹ and was classified as possible or definite according to the modified Duke criteria.¹² Transcatheter heart valve embolization represents an SVF occurring when the forces acting on the valve frame overcome the strength of the valve's attachment to the native aortic annulus.¹³ Late THV embolization may be defined as valve migration after a successful TAVI procedure where further THV-related intervention is not envisaged. Transcatheter heart valve SVF was defined according to the updated VARC criteria:¹¹ valve-related dysfunction demonstrated by a mean aortic valve gradient ≥ 20 mmHg, an effective orifice area of ≤ 0.9 (BSA ≥ 1.6 cm²) to 1.1 cm² (BSA ≤ 1.6 cm²) and/or a Doppler velocity index ≤ 0.35 , and/or moderate or severe prosthetic valve regurgitation (regurgitant volume ≥ 30 mL, regurgitant fraction $\geq 30\%$, effective regurgitant orifice area ≥ 0.10 cm²), or the requirement for a repeat procedure (TAVI or SAVR). We defined THV compression as distortion of the valve on non-invasive imaging or at autopsy, potentially impairing valve function or necessitating further intervention. Compression had to be temporally related to chest wall trauma or CPR. Transcatheter heart valve thrombosis was defined according to the updated VARC criteria:¹¹ non-infective thrombus attached to the valve leaflets or frame that impedes blood flow, valve function, or is sufficiently large to require treatment.

Statistics

Categorical variables were reported as number (%), and continuous variables were reported as mean and SD or median and interquartile range, according to distribution. Analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The initial literature search identified a total of 2400 publications (*Figure 1*). Removal of non-pertinent studies and duplicates by title screening yielded 82 potentially relevant articles that were examined in detail. Finally, 70 publications fulfilled our study inclusion and exclusion criteria, and reported 87 individual cases of THV failure (*Figure 2*). All studies discussed single case reports or small series and the baseline characteristics of these patients were typical of On average, late THV embolization occurred 43 ± 41 days (range: 4 h to 370 days) after the index procedure. Valve embolization was retrograde into the left ventricular outflow tract (LVOT) in 16 (89%) cases and anterograde into the aorta in 2 (11%).

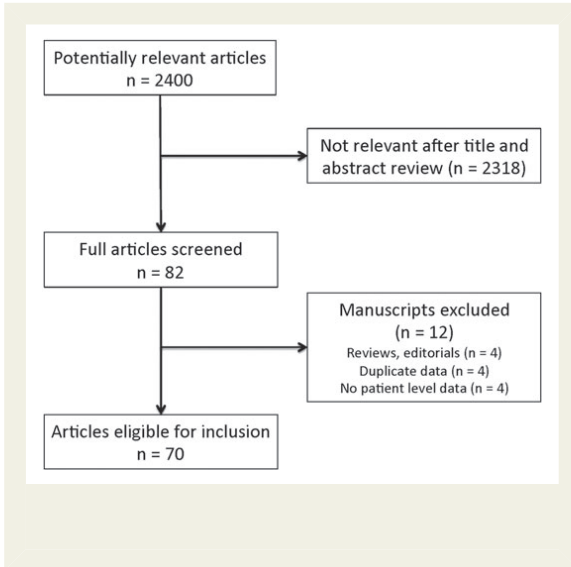


Figure 1 Electronic literature search. Summary of the literature search results.

Transcatheter heart valve-prosthetic valve endocarditis

A total of 26 publications, describing 34 cases of THV PVE were identified (*Table 1*).^{17–42} Among these patients, the median age was 83 (77, 85) years and most ($n = 20$, 59%) presented risk factors predisposing to PVE: diabetes mellitus ($n = 10$), chronic kidney disease ($n = 12$), immunosuppression ($n = 2$), and recurrent infections ($n = 4$). Several factors may have con-

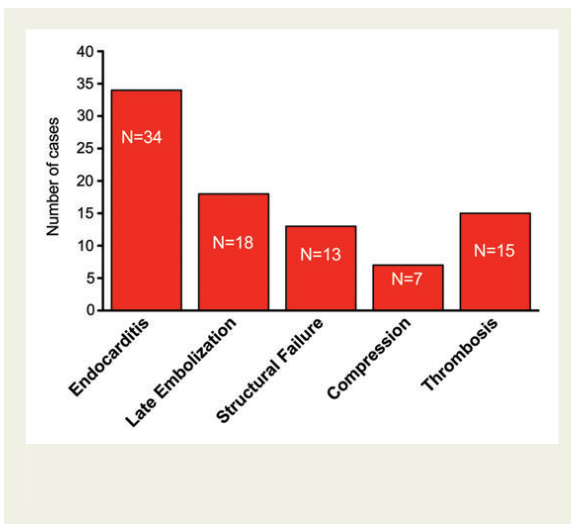


Figure 2 Transcatheter heart valve failure. Aetiology of transcatheter heart valve failure in this systematic review, the elderly high-risk cohorts undergoing TAVI in previously reported^{14–16} large registries.

tributed to the development of PVE, including suboptimal THV positioning causing injury to the anterior mitral valve leaflet,^{17,18,40} failure to administer antibiotic prophylaxis prior to TAVI ($n = 1$) or dental ($n = 3$) procedures.

There were 29 (85%) cases of definite and 5 (15%) cases of possible PVE according to the modified Duke criteria. The median time to IE diagnosis was 6 (3, 12) months, with early (<60 days), intermediate (60 days to 1 year), and late (>1 year) IE classified in 6 (18%), 21 (62%), and 7 (20%) patients, respectively. Cases of PVE were noted with both the Edwards SAPIEN (Edwards Lifesciences Inc., Irvine, CA, USA) ($n = 20$, 59%) and Medtronic CoreValve (Medtronic Inc., Minneapolis, MN, USA) ($n = 14$, 41%) prostheses. Similar numbers of PVE cases were observed with transfemoral and transapical vascular access (both $n = 12$). A total of 27 patients had positive blood cultures with a microbiological profile typical to that previously documented in surgical bioprosthetic PVE: *Enterococcus* species ($n = 10$), coagulase-negative *Staphylococci* ($n = 5$), *Staphylococcus aureus* ($n = 3$), *Streptococcus* species ($n = 5$), and *Histoplasma capsulatum* ($n = 1$). Three patients were culture negative and blood cultures were not performed in two cases. Echocardiography demonstrated mobile vegetations or abscess formation in 18 patients, progressive THV stenosis/regurgitation in 3 cases, and was reportedly normal in 3 patients. Abscess formation was described in 8 cases: aortic root ($n = 3$), aortic sinus ($n = 2$), annular ($n = 1$), and paravalvular ($n = 2$). Interestingly, ‘bridging’ endocarditis between the aortic THV and a satellite infection on the mitral valve was noted in 8 (24%) patients.

Treatment options for PVE include targeted antibiotic therapy or surgical intervention. In the current series, 20 (59%) patients were treated medically (7 died in-hospital, 13 discharged home [1 death at 3 months with sepsis, 6 alive at 1 year, 6 further outcome unknown]), and 14 (41%) underwent surgical intervention (3 died, 9 discharged home, 2 outcome unknown). Surgical intervention consisted of THV retrieval and SAVR ($n = 13$), with concomitant aortic root replacement ($n = 2$), mitral or tricuspid repair/replacement ($n = 5$).

Discussion: prosthetic valve endocarditis

The incidence of surgical PVE is estimated at 0.3–1.2% per patient-year.¹² To date, the incidence of early THV PVE has been reported to be between 0.3 and 3.4%.^{5,28,43} Amongst 180 consecutive TAVI recipients (median follow-up 319 days), Puls *et al.* observed five cases of PVE, thus yielding an incidence rate of 3.4% at 1-year.²⁸ Direct comparisons between these rates may be misleading given the complexity of patients undergoing TAVI and heterogeneity in reporting styles. In the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A), PVE occurred at a similar rate in the surgical and transcatheter groups (1.5 and 1.0%, respectively, $P = 0.61$).⁵ The incidence of PVE may also be influenced by patient risk profile and behaviour: diabetes mellitus, oral hygiene, and adherence to antibiotic prophylaxis.⁴⁴ Physician behaviour, and in particular adherence to recommendations regarding antibiotic

Table 1 Infective Endocarditis

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Wong <i>et al.</i> ¹⁷	88-year-old male, STS 11.1%; IE risks: Dental procedure 6 weeks earlier; no endocarditis prophylaxis; CKD	26 mm Edwards SAPIEN	Low implant with the THV abutting the anterior mitral valve leaflet; repeated PID; final moderate PVL	11 months Definite IE	Presentation: Fever. Blood culture: <i>Streptococcus angiosus</i> . Imaging: Mild-moderate PVL; ruptured anterior mitral valve leaflet aneurysm (13 × 8 mm) contiguous with THV causing severe MR. Treatment: THV retrieval and SAVR; repair of mitral valve perforation with bovine pericardium. Note: Pathology confirmed THV endocarditis. Outcome: Discharged day 38
Comoglio <i>et al.</i> ¹⁸	66-year-old male; EF 60%. IE risks: Myelodysplasia	Transfemoral; 29 mm CoreValve	PID for moderate PVL; final mild-moderate PVL; post-TAVI ventricular arrhythmias; ICD implant	3 months Definite IE	Presentation: Progressive malaise; fever and rigours. Blood culture: <i>Corynebacterium</i> . Imaging: Possible posterior aortic annulus. Pseudoaneurysm; moderate AR; anterior mitral valve leaflet perforation and severe MR. Treatment: THV retrieval and SAVR; repair of mitral valve perforation with bovine pericardial patch. Note: Small THV vegetations on cusps. THV 5 cm into LVOT abutting anterior mitral valve leaflet. Outcome: Discharged day 7
Carnero-Alcazar <i>et al.</i> ¹⁹	83-year-old female; low EF. IE risks: Recurrent urinary tract infections; CKD	Transapical; 23 mm Edwards SAPIEN	Uneventful	3 months Definite IE	Presentation: Acute CHF; fever. Blood culture: <i>Enterococcus faecalis</i> . Imaging: 1.9 cm vegetation on aortic side of THV leaflet. Treatment: Antibiotic therapy; declined for surgery. Note: Autopsy confirmed vegetation occluding valve orifice and an LVOT to right atrium fistula. Outcome: Multiple peripheral emboli and refractory heart failure; died day 14

Table 1 Infective Endocarditis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Santos <i>et al.</i> ²⁰	91-year-old male. IE risks: CKD	Transapical; 23 mm Edwards SAPIEN	Uneventful; no PVL	Index hospitalization Definite IE	Presentation: Fever. Blood culture: <i>Candida albicans</i> . Imaging: Mild PVL; mild AS (PG/MG 20/10 mmHg). No vegetations seen. Treatment: Antifungal therapy. Note: Autopsy showed large polypous friable vegetations completely occupying a pericardial cusp and extending along aortomitral continuity. Outcome: Deceased day 54
Gotzmann <i>et al.</i> ²¹	81-year-old male; LES 39.7%; low EF. IE risks: CKD	Transfemoral; 29 mm CoreValve	Uneventful; mild PVL	19 months Definite IE	Presentation: CHF; fever. Blood culture: <i>Staphylococcus lugdunensis</i> . Imaging: PVL; large (8 × 16 mm) mobile vegetation on the THV frame with fistulae to right and left atria. Treatment: Antibiotic therapy; declined for surgery. Outcome: Deceased day 13
Head <i>et al.</i> ²²	78-year-old male; STS 10.3%. IE risks: N/A	Edwards SAPIEN	N/A	12 months Definite IE	Presentation: Fever (6 months post-TAVI). Blood culture: Negative. Imaging: Extensive large vegetations on THV. Treatment: THV retrieval and SAVR. Note: Large vegetations on left and right commissures extending into LVOT. THV culture positive for <i>Histoplasma capsulatum</i> . Outcome: Discharged day 10

Table 1 Infective Endocarditis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Chrissoheris <i>et al.</i> ²³	84-year-old male; LES 23.5%; AVA 0.7 cm ² ; MG 64 mmHg; IE risks: Recrimping of THV; chronic pancreatitis	Transfemoral; 29 mm CoreValve	Difficult THV positioning requiring recrimping of THV twice; mild-moderate PVL	2.5 months Possible IE	Presentation: Sepsis syndrome. Blood culture: <i>Staphylococcus epidermidis</i> . Imaging: No clear evidence of IE. Treatment: Antibiotics for 4 weeks. Outcome: Well at 12-month follow-up
Rafiq <i>et al.</i> ²⁴	64-year-old female; IE risks: Myasthenia gravis on immunosuppression; no pre-TAVI antibiotic prophylaxis	CoreValve	Uneventful; IE prophylaxis	2 months Possible IE	Presentation: Fever, malaise. Blood culture: <i>Moraxella nonliquefaciens</i> . Imaging: Echo-free space within wall of ascending aorta at level of THV. No vegetations visualized. Treatment: Antibiotic therapy. Outcome: Well at 3-year follow-up
Castiglioni <i>et al.</i> ²⁵	73-year-old male; LES 6.6%; AVA 0.9 cm ² ; MG 78 mmHg; EF 60%. IE risks: Dental procedure two months earlier without antibiotic prophylaxis	Transfemoral; 26 mm Edwards SAPIEN	Uneventful; mild PVL	12 months Definite IE	Presentation: Routine follow-up echocardiogram. Blood culture: Negative. Imaging: Severe PVL; THV dehiscence; abscess between right and non-coronary aortic cusps. Treatment: THV retrieval and SAVR. Note: No vegetations evident but abscess identified. Outcome: Well at 6-month follow-up
Garcia-Pardo <i>et al.</i> ²⁶	81-year-old male; LES 29%; low EF IE risks: Colonoscopy without antibiotic prophylaxis 2 months earlier; DM; CKD	29 mm CoreValve	Uneventful; moderate AR	6 months Definite IE	Presentation: Malaise; fever; sepsis syndrome. Blood culture: <i>Staphylococcus aureus</i> . Imaging: 0.8 cm vegetation on THV. Treatment: Antibiotic therapy. Outcome: Discharged well

Table 1 Infective Endocarditis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Huan Loh <i>et al.</i> ²⁷	85-year-old male; LES 26%; STS 6.4%; AVA 0.8 cm ² ; MG 40 mmHg; EF 40%. IE risks: Chronic urinary retention; DM	29 mm CoreValve	Uneventful	9 months Definite IE	Presentation: Weight loss; malaise; fever (4 months post-TAVI). Blood culture: <i>Enterococcus faecium</i> . Imaging: Vegetation on THV leaflets. Normal THV function. Treatment: Antibiotic therapy. Outcome: Discharged well.

Table 1 Infective Endocarditis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Puls <i>et al.</i> ²⁸	Case 1. 80-year-old male; LES 30%; MVR; low EF;	Transfemoral; 29 mm CoreValve.	Uneventful.	7 months	Presentation: Acute congestive heart failure; fever.
	IE risks: MRSA	Transapical; 23 mm Edwards	Uneventful; moderate PVL.	Definite IE	Blood culture: Methicillin-resistant <i>Staphylococcus aureus</i> .
	Colonisation; DM;	SAPIEN.	Uneventful; trace PVL after PID.	10 months	Imaging: Dynamic PVL; diffuse aortic root thickening; suggestive of aortic root abscess.
	CKD; MVR.	Transapical; 23 mm Edwards	Uneventful; moderate PVL;	Definite IE	Treatment: Antibiotic therapy.
	Case 2.	SAPIEN.	post-TAVI AKI	5 months	Outcome: Deceased day 18.
	81-year-old female;	Transfemoral; 23 mm Edwards	Uneventful	Definite IE	Presentation: Fever.
	LES 48%; severely reduced EF.	SAPIEN.	with haemodialysis.	IE	Blood culture: <i>Enterococcus faecalis</i> .
	IE risks: Reactivation of pulmonary tuberculosis; DM.	Transapical; 23 mm Edwards	Uneventful	23 months	Imaging: Mobile vegetation attached to THV stent; moderate PVL.
	Case 3.	SAPIEN		Possible IE	Treatment: Antibiotic therapy.
	80-year-old female; LES 41%.				Outcome: Discharged day 42.
	Case 4.				Presentation: Rigours.
	85-year-old male; LES 23%.				Blood culture: <i>Enterococcus faecalis</i> .
	IE risks: Recurrent UTI; post-TAVI AKI with haemodialysis.				Imaging: Large vegetation on THV cusp; moderate transvalvular AR.
	Case 5.				Treatment: Antibiotic therapy.
	91-year-old female; LES 25%. IE risks: N/A				Outcome: Deceased at 3 months from septicæmia.
					Presentation: Fever.
					Blood culture: <i>Streptococcus gordonii</i> .
					Imaging: No vegetation; mild PVL.
					Treatment: Antibiotic therapy.
					Outcome: Discharged well

Table 1 Infective Endocarditis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Seeburger <i>et al.</i> ²⁹	82-year-old male. IE risks: N/A	Transfemoral; 26 mm CoreValve within a 23 mm St. Jude Epic	N/A	9 months Definite IE	Presentation: Recurrence of AS symptoms. Blood cultures: Not performed. Imaging: Severe AS (PG 95 mmHg; EOA 0.6 cm ²). Treatment: THV and SAVR retrieval, redo SAVR, and root replacement. Note: Histopathology detected IE. Outcome: N/A
Citro <i>et al.</i> ³⁰	72-year-old female; LES 39.7%. IE risks: Liver cirrhosis	Transfemoral; 23 mm Edwards SAPIEN within a St. Jude n. 21 Biocore	Uneventful; no PVL	5 months Definite IE	Presentation: Fever. Blood culture: <i>Staphylococcus epidermidis</i> . Imaging: Anterior PVL; right coronary sinus abscess; mitroaortic intervalvular fibrosa fistula into LV Treatment: Antibiotic therapy. Outcome: Deceased day 14
Orban <i>et al.</i> ³¹	70-year-old male; LES 33.1%; low EF. IE risks: Haemodialysis with failed renal transplant; DM	CoreValve	N/A	12 months Definite IE	Presentation: Right forearm ischaemia due to infected embolic occlusion of brachial artery; Spondylodiscitis. Blood culture: <i>Staphylococcus epidermidis</i> . Imaging: 3-cm mass within the THV lumen; non-coronary cusp paravalvular abscess. Treatment: TV retrieval and SAVR. Note: Large leaflet vegetations colonized by multiresistant coagulase-negative <i>Staphylococcus</i> spp. Outcome: Discharged day 14
Zytowski <i>et al.</i> ³²	84-year-old male. IE risks: N/A	Transapical; Edwards SAPIEN XT	N/A	4 months Definite IE	Presentation: N/A Blood culture: <i>Enterococcus durans</i> . Treatment: THV retrieval and SAVR. Note: Annulus destruction with abscess. Outcome: N/A

Table 1 Infective Endocarditis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Loeser <i>et al.</i> ³³	Case 1. 84-year-old female. IE risks: N/A	Transapical; Edwards SAPIEN.	N/A N/A	14 days Definite IE 3 days	Presentation: N/A Blood culture: Methicillin-resistant <i>Staphylococcus aureus</i> . Treatment: N/A
	Case 2. 84-year-old female. IE risks: N/A	Transapical; Edwards SAPIEN.		Definite IE	Note: Neutrophilic infiltration of THV and MRSA colonization. Outcome: Deceased. Presentation: N/A Blood culture: N/A Treatment: N/A
					Note: Acute endocarditis and pericarditis with THV Neutrophilic infiltration. Outcome: Deceased
Wilbring <i>et al.</i> ³⁴	76-year-old male; LES 61.1%. IE risks: N/A	Transapical; 23 mm Edwards SAPIEN within a 23 mm Medtronic Hancock II Ultra	Uneventful	4 years Definite IE	Presentation: Fever. Blood culture: Negative. Imaging: Large aortic root abscess with covered rupture of aortic base; perforation to tricuspid annulus and large tricuspid valve vegetation. Treatment: THV and SAVR retrieval; aortic root reconstruction; tricuspid valve repair. Note: Explanted valves were culture negative. Outcome: Deceased day 7.

Table 1 Infective Endocarditis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Aung <i>et al.</i> ³⁵	Case 1. 72-year-old male; LES 28.1%.	Transapical; 23 mm Edwards SAPIEN.	Uneventful.	3.5 months	Presentation: Fever. Blood culture: <i>Enterococcus faecalis</i> . Imaging: Multiple mitral valve vegetations; echo-lucent space anterior to THV; mild PVL.
	IE risks: DM; CKD.	Transfemoral; 29 mm CoreValve.	procedure; post-TAVI respiratory tract infection.	Definite IE 18 days	Treatment: Antibiotic therapy.
	Case 2. 91-year-old female; LES 15.2%.	Transfemoral; 29 mm CoreValve.	Uneventful	1 month	Outcome: Well at 1-year follow-up.
	IE risks: DM; CKD; breast cancer; cellulitis.	Transfemoral; 29 mm CoreValve within a bioprosthetic aortic valve	procedure; post-TAVI AKI with haemodialysis, and cellulitis	Definite IE 3 months	Presentation: Fever. Blood culture: <i>Streptococcus mitis</i> . Imaging: Mitral valve vegetation; normal THV function.
	Case 3. 88-year-old female; LES 55.3%; prior MVR.			Possible IE	Treatment: Antibiotic therapy. Outcome: Well at 1-year follow-up. Presentation: Fever.
	IE risks: Steroid therapy; DM; CKD; prior MVR IE.				Blood culture: <i>Enterococcus faecium</i> . Imaging: No vegetation; cavity suggestive of abscess anterior to THV.
	Case 4. 90-year-old female; LES 26.5%.				Treatment: Antibiotic therapy. Outcome: Well at 1-year follow-up.
	IE risks: Recurrent cellulitis; DM; CKD				Presentation: Lower limb cellulitis. Blood culture: <i>Enterococcus faecalis</i> . Imaging: No vegetation; mild PVL. Treatment: Antibiotic therapy.
					Outcome: Well at 1-year follow-up
					Presentation: Fever.
Hirnle <i>et al.</i> ³⁶	80-year-old female; LES 14.2%.	Transapical; 23 mm Edwards SAPIEN XT	Uneventful	1 month	Blood culture: <i>Enterococcus faecalis</i> . Imaging: Mitral valve vegetation.
	IE risks: N/A		procedure; post-TAVI TIA	Definite IE	Treatment: MVR.
					Outcome: Discharged to another hospital with tracheostomy day 14

Table 1 Infective Endocarditis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Seok Koh <i>et al.</i> ³⁷	85-year-old male; LES 25%; IE risks: N/A	Transfemoral; 26 mm Edwards SAPIEN	N/A	12 months Definite IE	Presentation: Fever; stroke. Blood culture: <i>Streptococcus angiosus</i> . Imaging: Multiple vegetations attached to THV. Treatment: Initial antibiotic therapy followed by THV retrieval and SAVR after stroke. Outcome: Discharged well
Drews <i>et al.</i> ³⁸	82-year-old female; LES 45%; STS 23%; prior MVR. IE risks: DM; CKD; MVR	Transapical; 23 mm Edwards SAPIEN	Uneventful procedure	8 months Definite IE	Presentation: N/A. Blood culture: N/A. Imaging: N/A. Treatment: Reoperation. Outcome: Deceased at 4 weeks from multiorgan failure
Pasic <i>et al.</i> ³⁹	N/A	Transapical; Edwards SAPIEN	N/A	3 months Definite IE	Presentation: N/A. Blood culture: N/A. Imaging: N/A. Treatment: Reoperation. Outcome: Discharged well
Nietlispach <i>et al.</i> ⁴⁰	N/A IE risks: Dental procedure without IE prophylaxis 6 weeks earlier.	Edwards SAPIEN	N/A	11 months Definite IE	Presentation: N/A Blood culture: <i>Streptococcus angiosus</i> . Imaging: N/A Treatment: THV retrieval, SAVR, and MVR Note: IE spread to the mitral valve at the contact point of the THV leading to mitral leaflet perforation and regurgitation. Outcome: Deceased

Table 1 Infective Endocarditis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing and IE classification	Case description
Bozdag-Turan <i>et al.</i> ⁴¹	80-year-old male; LES 10% IE risks: CKD	Transfemoral; CoreValve	Uneventful procedure	4 months Possible IE	Presentation: Fever; dyspnoea. Blood culture: Enterococcus faecalis. Imaging: Mobile (18 × 7 mm) mass on THV. Treatment: Antibiotic therapy. Outcome: Discharged well
Raschpichler <i>et al.</i> ⁴²	84-year-old male. IE risks: N/A	31 mm CoreValve	N/A	6 months Definite IE	Presentation: Fever; dyspnoea. Blood culture: Staphylococcus epidermis. Imaging: Moderate AR; perforation of the anterior mitral leaflet and severe MR. Treatment: THV retrieval, SAVR and MVR. Outcome: Discharged well

IE, infective endocarditis; STS, Society of Thoracic Surgeons mortality risk score; CKD, chronic kidney disease; THV, transcatheter heart valve; PID, post-implant dilation; PVL, paravalvular leak; MR, mitral regurgitation; SAVR, surgical aortic valve replacement; EF, ejection fraction; TAVI, transcatheter aortic valve implantation; ICD, implantable cardiac defibrillator; AR, aortic regurgitation; LVOT, left ventricular outflow tract; CHF, congestive heart failure; AS, aortic stenosis; MG, mean gradient; PG, peak gradient; LES, logistic EuroSCORE; AVA, aortic valve area; DM, diabetes mellitus; MRSA, methicillin-resistant staphylococcus aureus; MVR, mitral valve replacement; AKI, acute kidney injury; EOA, effective orifice area; N/A, not available; TIA, transient ischaemic attack.

prophylaxis, can also impact on the development of PVE.⁴⁵ Accurate quantification of the risk of THV PVE will require further study of large patient populations with extended follow-up.

While one can speculate that the less invasive nature of TAVI could be reflected in lower rates of early PVE, the converse is also plausible. The non-sterile environment of many cardiac catheterization laboratories, high-risk profile of TAVI patients, and specific technical issues, including the infrequent requirement to remove, resheath, and reim-plant a malpositioned THV could potentially increase the risk of PVE (*Figure 3*). It is therefore of critical importance that every effort is made to minimize the risk of PVE: patient education, especially regarding the importance of post-implantation antibiotic prophylaxis; early treatment of coincident infections; and maintenance of a sterile environment during the index procedure. Interestingly, 24% of PVE cases involved ‘satellite’ endocarditis of the mitral valve,^{17,18,20,35,36} suggesting that ‘bridging-PVE’ may occur when a low-lying aortic THV that is in direct contact with the mitral apparatus.⁴⁶ Secondary mitral valve involvement has been reported in ~10% of native aortic valve endocarditis cases and is associated with a poor prognosis.⁴⁷

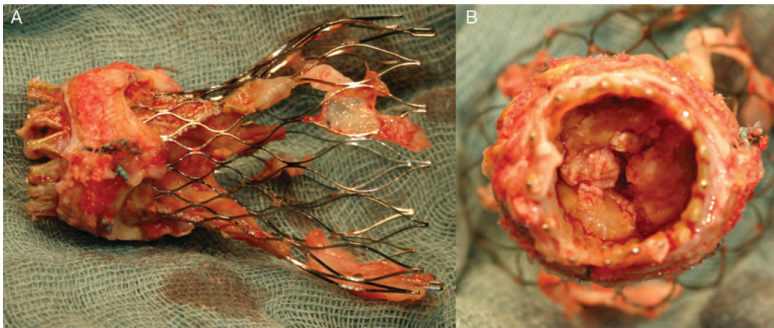


Figure 3 Transcatheter heart valve-prosthetic valve endocarditis. (A and B) An explanted CoreValve implanted within a 23-mm St. Jude Epic bioprosthesis with evidence of infective endocarditis. Reprinted with permission from Seeburger *et al.*²⁹

Confirming the diagnosis of THV PVE can be challenging as elderly TAVI patients may present insidious and atypical symptomatology, and have a co-existing predisposition to infectious pathogens.¹² High rates of empiric antibiotic therapy in the elderly and difficulty in assessing the typical echocardiographic features of PVE can also hinder diagnostic certainty.^{48,49} New valvular regurgitation is also difficult to differentiate from post-procedural paravalvular leaks and prosthetic dehiscence does not occur as radial force rather than sutures anchor the THV *in situ*. Consequently, the modified Duke criteria may be more difficult to apply in TAVI cohorts.¹² This diagnostic uncertainty is demonstrated by delayed diagnosis observed among several THV PVE cases.^{18,22,25,27,28}

Targeted antibiotic therapy remains the first line of treatment for THV PVE. While conventional indications for operative intervention in the setting of PVE may be less applicable to high-risk TAVI cohorts, in this series surgical management of PVE (THV retrieval and SAVR

and concomitant aortic root replacement, mitral or tricuspid repair) was associated with encouraging outcomes (75% survived to hospital discharge). Thus, surgery for PVE should not be discounted among TAVI recipients, and Heart Team discussion is encouraged for all such cases.

Late transcatheter heart valve embolization

Late THV embolization represents a new complication previously unreported in the surgical bioprosthetic valve literature. We identified 18 cases of late THV embolization associated with the Edwards SAPIEN ($n = 15$) and Medtronic CoreValve ($n = 3$) (Table 2).^{40,50–66} The mean age of these patients was 77 ± 6 years.

The initial THV position was described as correct in 4 patients and low in 6 (THV position not described in 8 cases: 6 uneventful procedures, 2 no procedural outcome reported). Suboptimal procedural outcomes resulted in implantation of a 2nd THV ($n = 2$), elevated transvalvular gradients ($n = 4$), and/or moderate aortic regurgitation ($n = 1$: severe transvalvular regurgitation; $n = 3$: moderate paravalvular regurgitation). The clinical presentation of THV embolization was usually with rapid haemodynamic collapse ($n = 2$) or acute pulmonary oedema ($n = 10$). Two patients had late embolization diagnosed as an incidental finding on echocardiography and one developed progressive heart failure. Echocardiographic studies demonstrated severe aortic incompetence in 10 (56%) of cases, LVOT obstruction in 5 (28%), and interaction with the anterior mitral valve leaflet and mitral regurgitation in 4 (22%).

Management of THV embolization included acute haemodynamic stabilization or heart failure management, as required. Subsequent surgical intervention (THV retrieval and SAVR) was performed in 14 of 18 patients (78%), with survival to hospital discharge noted in 62% of cases. One patient deteriorated rapidly following THV embolization, and the Heart Team considered further surgical intervention to be futile. Three patients were treated by implantation of a second THV within the embolized prostheses in the LVOT (TAV-in-TAV): successful implantation of a 29 mm Edwards SAPIEN within a 26 mm Edwards SAPIEN (patient discharged home); implantation of a 29 mm CoreValve within a 31 mm CoreValve (patient died from cerebral anoxia); and successful implantation of a 26 mm Edwards SAPIEN in a 29 mm CoreValve (patient discharged home).

Discussion: late transcatheter heart valve embolization

Several patient and procedural factors may pre-dispose to late THV embolization (Figure 4): (i) undersizing of the THV,^{54,63} (ii) underexpansion of an appropriately sized THV due to aortic root calcification,^{51,60} (iii) low implantation of the THV,^{56,57,60,64,65} (iv) bicuspid aortic valve,^{53,63} (v) sparsely calcified native anatomy providing insufficient THV anchoring,^{50,55,59} (vi) asymmetric aortic root calcification,^{55,60} (vii) presence of a surgical mitral bioprosthetic valve that may displace the THV superiorly,^{51,52} (viii) initial unstable THV position, and (ix) basal septal bulging.

Table 2 Late transcatheter heart valve embolization

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Clavel <i>et al.</i> ⁵⁰	79-year-old male; STS 11.5%; AVA 0.76 cm ² ; MG 20 mmHg; annulus diameter 24 mm; EF 28%	Transapical; 26 mm Edwards SAPIEN	Severe central AR after implant; 2nd 26 mm SAPIEN implanted. Final mild AR	2 days	Presentation: Refractory cardiogenic shock. Embolization: LV with LVOT obstruction. Treatment: THV retrieval and SAVR. Outcome: Progressive shock, multiorgan failure, and death
Maroto <i>et al.</i> ⁵¹	75-year-old female; LES 29.5%; AVA 0.4 cm ² ; PG 67 mmHg; annulus diameter 20 mm, EF 40%, mechanical MVR	Transapical; 23 mm Edwards SAPIEN	Acceptable acute THV position, mild PVL	21 days	Presentation: Acute CHF. Embolization: Aortic (tilted) with severe AR. Treatment: THV retrieval and SAVR. Outcome: Stroke and Deceased on Day 7
Baumbach <i>et al.</i> ⁵²	82-year-old female; ES 37%; STS 5.3%; AVA 0.7 cm ² ; PG 73 mmHg; annulus diameter 20–21 mm; bioprosthetic MVR	Transapical; 23 mm Edwards SAPIEN	Uneventful; MG 8 mmHg	MG 14 days	Presentation: Recurrent CHF. Embolization: Aortic (tilted) with severe AR. Treatment: THV retrieval, SAVR and aortic root replacement. Outcome: Discharged well on Day 14
Schroeter <i>et al.</i> ⁵³	85-year-old male; LES 20.1%; AVA 0.5 cm ² ; PG/MG 75/44 mmHg; aortic annulus 27 mm	Transapical; 29 mm Edwards SAPIEN XT	Uneventful; trace PVL	42 days	Presentation: Acute CHF. Embolization: LVOT (tilted) with severe AR. Treatment: THV retrieval, SAVR, and aortic root replacement. Note: Bicuspid aortic valve noted. Outcome: Discharged well on Day 7

Table 2 Late transcatheter heart valve embolization (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Radu <i>et al.</i> ⁵⁴	85-year-old male; LES 26%; STS 9.0%; AVA 0.6 cm ² ; MG 39 mmHg; EF 45%; aortic annulus 21.4 × 26.1 mm	Transfemoral; 23 mm Edwards SAPIEN XT	Uneventful; trace PVL, MG 19 mmHg	5 days	Presentation: Incidental finding on discharge echocardiography. Embolization: LVOT, impairing anterior mitral leaflet function. Treatment: THV retrieval and SAVR. Note: Aortic annulus was 24 mm diameter at SAVR. Outcome: Uneventful post-operative course
Pang <i>et al.</i> ⁵⁵	75-year-old male; LES 23%; STS 12.8%; AVA 0.4 cm ² ; MG 63 mmHg; aortic annulus 18 mm; EF 51%	Transfemoral; 23 mm Edwards SAPIEN XT	Uneventful; mild PVL, MG 24 mmHg	43 days	Presentation: Acute CHE. Embolization: LVOT and obstructing mitral inflow. Treatment: THV retrieval and SAVR. Note: THV was inverted at SAVR. Outcome: Discharged well on Day 7
Gul <i>et al.</i> ⁵⁶	75-year-old male; LES 18.4%; 2.8%; AVA 0.5 cm ² ; MG 55 mmHg; aortic annulus 22 mm; EF 30%	Transfemoral; 26 mm Edwards SAPIEN	Uneventful; mild PVL, MG 8 mmHg	4 h	Presentation: Acute haemodynamic instability. Embolization: LVOT, with LVOT obstruction, and severe MR. Treatment: Inotropic support, and CPR during which the TVH embolized into LV; THV retrieval and SAVR. Outcome: Discharged well; asymptomatic at 3 month follow-up
Nietlispach <i>et al.</i> ⁴⁰	N/A	Edwards SAPIEN	N/A	109 days	Presentation: N/A Embolization: LVOT with severe AR. Treatment: THV retrieval and SAVR. Outcome: Death

Table 2 Late transcatheter heart valve embolization (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Toggweiler <i>et al.</i> ⁵⁷	N/A	Transapical; Edwards SAPIEN	Initial THV implant was too low so a 2nd THV implanted	2 days	Presentation: N/A Embolization: Both THVs embolized to LVOT with severe AR. Treatment: THV retrieval and SAVR. Outcome: Death
Stangl <i>et al.</i> ⁵⁸	N/A	Transfemoral; 26 mm Edwards SAPIEN		2 months	Presentation: N/A Embolization: LVOT. Treatment: THV retrieval and SAVR. Outcome: N/A
Iida <i>et al.</i> ⁵⁹	77-year-old male; ES 20%; STS 17%; AVA 0.9 cm ² ; MG 27 mmHg; aortic annulus 23 mm; EF 30%	Transfemoral; 26 mm Edwards SAPIEN	Uneventful; moderate PVL; MG 9 mmHg	24 h	Presentation: Routine echocardiographic surveillance. Embolization: LVOT; moderate AS and severe AR. Treatment: THV retrieval and SAVR. Note: Moderate annular calcification. Outcome: Discharged well
Naganuma <i>et al.</i> ⁶⁰	67-year-old male; LES 32.5%; STS 13.6%; AVA 0.8 cm ² ; MG 60 mmHg; aortic annulus 24 mm; EF 50%; previous CABG with LIMA and RIMA	Transfemoral; 26 mm Edwards SAPIEN XT	Initial THV implant was slightly low; mild-moderate PVL	27 days	Presentation: Acute CHF. Embolization: LVOT with severe AR. Treatment: THV retrieval and SAVR complicated by LIMA occlusion and requirement for redo CABG. Outcome: Discharged to rehabilitation on day 8
Lauten <i>et al.</i> ⁶¹	72-year-old female	Transfemoral; 26 mm Edwards SAPIEN XT	MG 23 mmHg at 6 months	4 months	Presentation: Acute CHF. Embolization: LVOT with severe AR. Note: Native leaflets protruding over THV. Treatment: Transapical TAV-in-TAV. Outcome: Discharged well

Table 2 Late transcatheter heart valve embolization (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Wendeborn <i>et al.</i> ⁶²	84-year-old male; LES 19%	Subclavian; 31 mm CoreValve	Uneventful	N/A	Presentation: CHF and AKI. Embolization: LVOT with moderate paravalvular AR and severe MR. Note: MitraClip and transcatheter atrial septal defect closure 2 weeks earlier. Treatment: THV retrieval, SAVR, MVR, and CABG. Outcome: Discharged after 1 month; asymptomatic at 3 months
Wijesinghe <i>et al.</i> ⁶³	N/A	Transapical; 26 mm Edwards SAPIEN	Initial THV implant was low and undersized	63 days	Presentation: N/A. Embolization: LVOT with severe AS and worsening AR. Note: Native leaflets protruding over THV. Treatment: THV retrieval and SAVR. Outcome: Death
Nijhoff <i>et al.</i> ⁶⁴	83-year-old female	Transfemoral; 23 mm Edwards SAPIEN XT	Initial THV implant was low; trace AR	4 days	Presentation: Acute CHF. Embolization: LVOT obstruction and severe AR. Treatment: Patient deemed inoperable. Outcome: Death
Nijhoff <i>et al.</i> ⁶⁵	N/A	Transfemoral; 31 mm CoreValve	Initial THV implant was low	6 days	Presentation: Acute CHF. Embolization: LVOT with severe AR. Treatment: TAV-in-TAV with 29 mm CoreValve. Outcome: Death due to multiorgan failure
Schleger <i>et al.</i> ⁶⁶	59-year-old male; LES 24%; STS 13%	Transfemoral; 29 mm CoreValve	Residual grade II AR	1 year	Presentation: Progressive CHF. Embolization: LVOT with severe AR. Treatment: TAV-in-TAV with 26 mm Edwards SAPIEN. Outcome: Discharged well on day 10

CABG, coronary artery bypass grafting; CPR, cardiopulmonary resuscitation; ES, EuroSCORE; LIMA, left internal mammary artery; LV, left ventricle; RIMA, right internal mammary artery; TAV, transcatheter aortic valve. Other abbreviations as in *Table 1*.

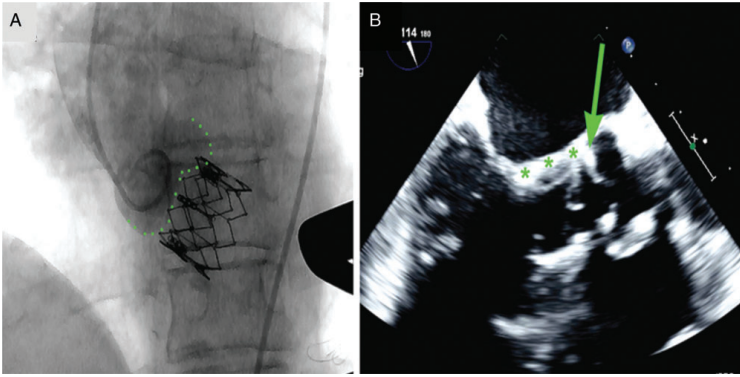


Figure 4 Late transcatheter heart valve embolization. (A and B) Fluoroscopic and echocardiographic images of late embolization of an Edwards SAPIEN valve into the left ventricular outflow tract. Green arrow showing the hinge point of the native valve leaflets. Reprinted with permission from Lauten *et al.*⁶¹

Suboptimal acute procedural results were noted in several cases of late THV embolization: moderate paravalvular aortic regurgitation,^{57,59} and high transvalvular gradients.^{54,55,61} In this setting, elevated gradients could potentially be explained by undersizing or incomplete expansion of the THV,⁵⁴ low implantation with consequent ‘overhang’ of the native stenotic leaflets,^{61,63} or by inversion of the THV following rotation within the LVOT.⁵⁵ Initial excessively deep implantation of the THV is obviously a risk factor for delayed embolization into the LVOT, and was described in 6 cases in the current series.^{56,57,60,63–65} Indeed, low implantation may have been more prevalent in this series, but the depth of prosthesis implantation was not described in all reports.

Left ventricular (89%) rather than aortic (11%) embolization was predictably more common given the fact that the retrograde forces acting on the THV in diastole amount to 10 times the anterograde forces in systole,¹³ and that deep THV implantation may have been a precipitating factor. The clinical presentation of late THV embolization was variable, but most patients (80%) developed abrupt left ventricular failure and cardiogenic shock. Urgent operative intervention, to remove the embolized THV and replace the aortic valve, was performed in most cases (78%). Two-thirds of patients that underwent urgent surgery survived to hospital discharge. This observation underscores the importance of the Heart Team and supports operative intervention among selected TAVI recipients. Among the three patients treated with TAV-in-TAV, two survived to hospital discharge. The haemodynamic results of the TAV-in-TAV procedures were not reported.

Structural valve failure

To date, 13 individual reports of THV SVF have been reported: 9 Edwards SAPIEN and 4 CoreValve (Table 3).^{67–77} The mean age of these patients was 80 + 7 years and the mean time to SVF was 24 + 26 months (range: several days to 5.5 years). Among the 7 cases detailing

acute procedural results, 3 had no aortic regurgitation, 3 mild paravalvular leaks, and 1 mild transvalvular leak. The latter case initially required post-implantation balloon dilatation for moderate paravalvular leak and over subsequent days developed progressive transvalvular aortic regurgitation requiring implantation of a 2nd THV. Excluding this patient, 3 asymptomatic patients were diagnosed with moderate valve dysfunction on echocardiography, and the remaining 7 cases represented with recurrent dyspnoea or congestive heart failure. Echocardiography demonstrated moderate prosthesis stenosis or regurgitation in 5 cases, severe stenosis in 5, and severe regurgitation in 3 cases.

Structural valve failure was attributed to severe leaflet calcification ($n = 3$), cusp rupture ($n = 1$), THV underexpansion ($n = 2$), and tissue ingrowth ($n = 2$) causing restrictive leaflet function. The failure mode was unclear or not described in 6 cases. Three asymptomatic patients with moderate valve dysfunction were managed conservatively, and the remaining patients underwent THV retrieval and SAVR ($n = 4$) or implantation of a second THV within the previously sited valve ($n = 6$) (TAV-in-TAV). Among the 4 patients who underwent THV retrieval and SAVR, intraoperative findings were: (Case 1) normal functioning CoreValve with no pannus or paravalvular leak, (Case 2) ingrowth of inflammatory tissue restricting the non-coronary leaflet of an Edwards SAPIEN XT, (Case 3) incomplete expansion of an Edwards SAPIEN valve within a 21 mm Hancock bioprosthesis, and (Case 4) severe calcification of both surfaces of the CoreValve leaflets. Favourable clinical outcomes were reported in all cases, except in one patient that underwent TAV-in-TAV and suffered a peri-procedural stroke.

Discussion: structural valve failure

Bioprosthetic SVF is a chronic degenerative process characterized by calcium phosphate deposition and extracellular matrix deterioration. The aetiology primarily relates to the chronic mechanical stresses on the valve leaflet's regions of maximal flexion, thus compromising structural integrity of leaflet tissue and initiating calcium deposition.⁷⁸ Glutaraldehyde fixation, residual leaflet antigenicity, and systemic^{79–81} atherosclerosis may also contribute to the pathogenesis of SVF.

With surgical bioprosthetic valves, freedom from re-operation or death at 10 and 15 years are between 70–90 and 50–80%, respectively.⁸² Freedom from re-operation or death, however, is not synonymous with SVF, which is defined according to echocardiographic or haemodynamic criteria. Thus, surgical SVF may be under-reported in the literature.

With respect to TAVI, the relative infancy of this technique prohibits meaningful discussion of the rates of long-term SVF. Nevertheless, the short- to medium-term incidences of THV SVF are low.^{14,75,83} In a pan-Canadian study of 339 TAVI recipients, Rodes-Cabau *et al.*¹⁴ reported no cases of SVF at a mean follow-up of 42 + 15 months. Among 88 consecutive patients with 5-year follow-up, Toggweiler *et al.*⁷⁵ reported structural valve deterioration in 3.4% of cases: moderate stenosis ($n = 1$), moderate regurgitation ($n = 1$), and moderate mixed

Table 3 Structural valve failure

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Pagnotta <i>et al.</i> ⁶⁷	73-year-old male; LES 36%; bicuspid aortic valve; EF 30%	Transfemoral; 29 mm CoreValve	PID required for PVL; final mild transvalvular AR	Several days	Presentation: Hypotension, renal failure, pulmonary oedema. Aetiology: Severe transvalvular AR. Failure Mode: Rupture of CoreValve cusp. Treatment: Transfemoral TAV-in-TAV with a 29 mm CoreValve. Outcome: Discharged well on day 7
Van der Lienden <i>et al.</i> ⁶⁸	87-year-old male	Transapical; 26 mm Edwards SAPIEN	Uneventful; no AR	10 months	Presentation: Persistent CHF. Aetiology: Moderate-severe transvalvular AR and decreased LVEF. Failure Mode: Unclear. Treatment: Transaortic TAV-in-TAV with a CoreValve. Outcome: Uneventful recovery
Blumenstein <i>et al.</i> ⁶⁹	83-year-old female; ES 26%; STS 7%	Transapical; Edwards SAPIEN XT	Uneventful; mild AR	12 months	Presentation: Recurrent CHF. Aetiology: Severe transvalvular AR with immobile non-coronary leaflet. Failure Mode: Histology: tissue ingrowth causing leaflet retraction. No THV IE or thrombosis. Treatment: THV retrieval and SAVR. Outcome: Discharged well
Klotz <i>et al.</i> ⁷⁰	74-year-old male	23 mm Edwards SAPIEN XT within a 23 mm Hancock bioprosthesis	Uneventful; no AR; MG 20 mmHg	3 months	Presentation: Recurrent CHF. Aetiology: Severe AS (MG 43 mmHg; EOA 0.6 cm ²). Failure Mode: Incomplete THV expansion within the Hancock with abnormal leaflet function. Treatment: THV/Hancock retrieval and redo SAVR. Outcome: Uneventful recovery

Table 3 Structural valve failure (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Ong <i>et al.</i> ⁷¹	74-year-old male	CoreValve	N/A	5 years	Presentation: N/A Aetiology: Severe AS (MG 53–79 mmHg). Failure Mode: Severe calcification of THV leaflets. Treatment: THV retrieval and SAVR Outcome: N/A
Hammerstingl <i>et al.</i> ⁷²	92-year-old female; LES 38.2%; STS 27%	Transfemoral; 26 mm CoreValve (2nd generation), with CPB	Successful	5.5 years	Presentation: Acute CHF. Aetiology: Severe AS (MG 54 mmHg; EOA 0.4 cm ²). Failure Mode: Severe calcification of THV leaflets. Treatment: Transfemoral TAV-in-TAV with a 26 mm CoreValve (3rd generation). Outcome: Discharged on day 8
Hoffmann <i>et al.</i> ⁷³	75-year-old male; LES 32%; EF 20%; haemodialysis	Transapical; 26 mm Edwards SAPIEN	Uneventful; MG 5 mmHg	3.5 years	Presentation: Recurrent dyspnoea. Aetiology: Severe AS (MG 45 mmHg). Failure Mode: Severe calcification of the THV leaflets. Treatment: Transfemoral TAV-in-TAV with a 26 mm CoreValve. Outcome: Successful procedure (MG 5 mmHg)
Kiefer <i>et al.</i> ⁷⁴	86-year-old male; LES 31%; STS 12%; EF 60%	Transapical; 26 mm Edwards SAPIEN XT	Uneventful; No AR; PG/MG 15/10 mmHg	3 years	Presentation: Recurrent dyspnoea. Aetiology: Severe AS (PG/MG 83/49 mmHg; EOA 0.4 cm ²) Failure Mode: Unclear. Treatment: Transapical TAV-in-TAV with 26 mm Edwards SAPIEN XT. Outcome: Successful procedure (PG/MG 14/10 mmHg). Post-operative stroke. Discharged to rehabilitation on day 7

Table 3 Structural valve failure (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Toggweiler <i>et al.</i> ⁷⁵	Case 1. N/A	Cribier-Edwards	N/A	5 years	Failure Mode: Moderate AS (MG 26 mmHg; EOA 1.2 cm ²) and moderate transvalvular regurgitation.
	Case 2. N/A	Cribier-Edwards	N/A	5 years	Treatment: None
	Case 3. N/A	Edwards		5 years	Failure Mode: Moderate transvalvular regurgitation.
	N/A	Edwards SAPIEN			Treatment: None
Thyregod <i>et al.</i> ⁷⁶	76-year-old male; LES	Transfemoral; 26 mm	Uneventful	4 months	Failure Mode: Moderate AS (MG 23 mmHg; EOA 1.1 cm ²)
	16%; STS 18%; Previous CABG	Core Valve			Treatment: None
					Presentation: Progressive dyspnoea.
					Aetiology: Moderate paravalvular and transvalvular AR. No AS.
Kiefer <i>et al.</i> ⁷⁷	53-year-old female; mechanical MVR; previous CABG; porcelain aorta	Transapical; 26 mm Edwards SAPIEN	N/A	3 years	Failure Mode: Unclear. No obvious paravalvular leak or pannus evident at surgery.
					Treatment: THV retrieval, SAVR and CABG.
					Outcome: Discharged to rehabilitation on day 8
					Presentation: Recurrent dyspnoea.
Other abbreviations as in Table 1. CPB, cardiopulmonary bypass.					

disease ($n = 1$). There were no cases of reoperation. Similarly, in the PARTNER trial (Cohort A), no patients in either the surgical or transcatheter groups had SVF at 2 years of follow-up.⁴ Although much longer-term follow-up (.10 years) will be required to demonstrate the true incidence of SVF associated with TAVI, this may be difficult to accrue due to the elderly and high-risk nature of TAVI recipients.

Among the reported cases of THV SVF, leaflet calcification, tissue ingrowth (pannus), and incomplete THV expansion were the most commonly described failure mechanisms.^{69,71–73,77} There may be, however, specific failure mechanisms unique to THV (*Figure 5*). In particular, the haemodynamic sheer stress on the THV leaflets may be significantly increased in cases of incomplete THV expansion or in very elliptical annuli.^{68,70,77,84,85} THV thrombosis can also mimic SVF, by presenting with elevated transvalvular gradients, and should be excluded using multimodal imaging. In one case, the authors speculated that post-implantation balloon dilatation may have resulted in tearing of a CoreValve leaflet, inducing severe transvalvular aortic regurgitation.⁶⁷ Balloon expansion has been demonstrated to cause microscopic leaflet

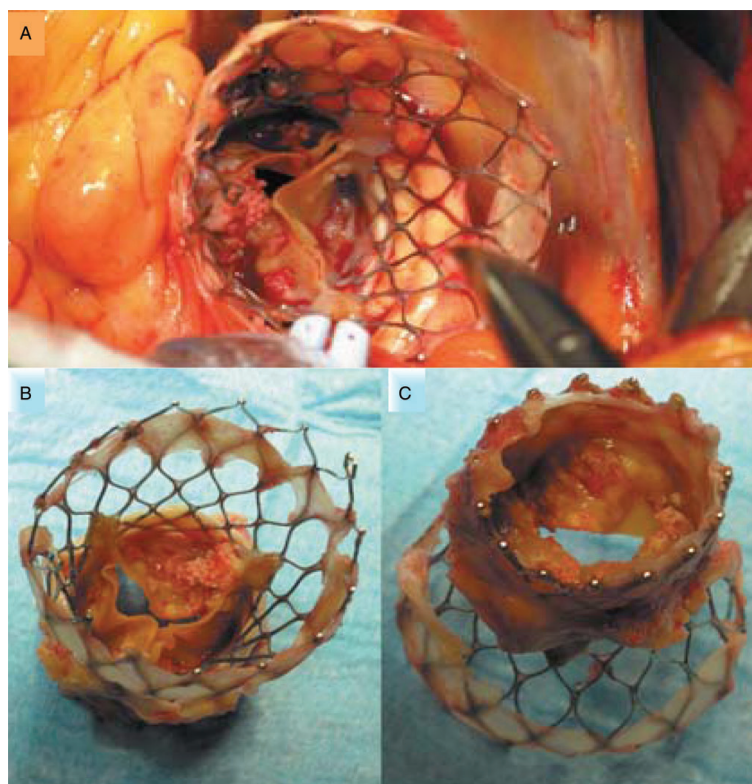


Figure 5 Transcatheter heart valve structural failure. (A–C) Extensive leaflet calcification on the outflow and inflow aspects of an explanted CoreValve. Reprinted with permission from Ong *et al.*⁷¹

injury;⁸⁶ however, the frequency with which post-implantation is performed suggests that balloon-related trauma is unlikely to represent an important cause of SVF. In surgically implanted bioprosthetic valves, tearing of valve leaflets has been observed in up to 70–80% of cases implanted for over 10 years, and is often accompanied by calcification.⁸⁷ Tearing of the valve leaflet in a horizontal plane running parallel to the sewing ring is unique and is reported in 10–15% of cases.⁸⁷ This type of leaflet tearing, to our knowledge, has not yet been observed in TAVI.

The majority of patients with SVF requiring intervention were treated with TAV-in-TAV (60%), rather than SAVR (40%). Outcomes of both procedures were excellent, with no deaths and only one peri-procedural stroke in a patient that underwent transapical TAV-in-TAV.⁷⁴

Transcatheter heart valve compression

Compression of a bioprosthetic heart valve is a recently described phenomenon that may be to be unique to balloon-expandable THVs. We identified seven cases of Edwards SAPIEN valve compression that occurred following CPR in the setting of cardiac arrest (*Table 4*).^{33,40,88–92} The median time to cardiac arrest was 3 days (range: 12 min to 42 days). Transcatheter heart valve compression was identified on fluoroscopy in one case and at autopsy in all others. Although the resuscitation efforts were ultimately unsuccessful in all patients, it was not possible to implicate THV compression in the demise of these patients that had suffered serious life-threatening complications. No patient received any specific intervention for THV compression.

Discussion: Transcatheter heart valve compression

Prior studies have reported compression of both coronary stents and of the Melody transcatheter pulmonary valve (Medtronic) following CPR.^{93,94} Despite the relative frequency of peri-procedural CPR in the setting of TAVI, THV compression remains a rarely reported event.⁹⁵ Underreporting is likely as almost all cases were diagnosed post-mortem. To date, all cases of THV compression involve balloon-expandable TAVI systems, specifically the Edwards SAPIEN prostheses. Although speculative, balloon-expandable THV may be more susceptible to deformation compared with self-expanding THV, as the stainless steel (SAPIEN) or cobalt-chromium (SAPIEN XT) composition does not have the shape memory properties of Nitinol (CoreValve) (*Figure 6*). Although normal CoreValve integrity has been reported following prolonged CPR (Personal communication; Nawwar Al-Attar, PCR London Valves 2011), self-expanding THV compression is conceivable in the presence of significant frame fracture, and thus, a thorough evaluation of THV function is recommended following CPR irrespective of the prosthesis design. Outside of the setting of CPR, THV frame fracture has not been reported.

It has been suggested that relocating the site of chest compressions toward the left hemithorax could provide adequate haemodynamic support and avoid potential THV

Table 4 Transcatheter heart valve compression

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Schermer <i>et al.</i> ⁸⁸	87-year-old female; LES 39%; STS 25%	Transapical; 23 mm Edwards SAPIEN	Uneventful	6 h	Event: Cardiac arrest with CPR. Compression: Autopsy revealed compressed and deformed THV. Outcome: Deceased
Kim <i>et al.</i> ⁸⁹	75-year-old male; LES 16.6%	Transapical; 26 mm Edwards SAPIEN	Uneventful; trace AR; MG 8 mmHg; post-TAVI shock	42 days	Event: In-hospital cardiac arrest with CPR. Compression: Fluoroscopy revealed severe THV deformation. Outcome: Deceased day 16
Kirov <i>et al.</i> ⁹⁰	N/A	Transapical; Edwards SAPIEN XT	Uneventful	5 days	Event: Cardiac arrest with CPR. Compression: Autopsy revealed severe THV deformation. Outcome: Deceased
Damen <i>et al.</i> ⁹¹	73-year-old female; ES 22.5%	Transfemoral; 23 mm Edwards SAPIEN	Uneventful	12 min	Event: Cardiac arrest post-TAVI with CPR. Compression: Autopsy revealed an inverted THV. Intraprocedural imaging suggested normal THV orientation, so inversion during CPR suspected. Outcome: Deceased day 1
Nietlisbach <i>et al.</i> ⁴⁰	Post-mortem series describing four cases of THV deformation	Edwards SAPIEN	N/A	N/A	Events: 8 cases of cardiac arrest with CPR. Compression: 4 of 8 cases had THV deformation at autopsy. Outcome: Deceased
Spangenberg <i>et al.</i> ⁹²	88-year-old female; ES II 12.3%	Transapical; 26 mm Edwards SAPIEN XT	Uneventful	5 days	Event: PEA cardiac arrest with CPR due to ruptured aortic aneurysm. Compression: Autopsy revealed severe THV deformation. Outcome: Deceased
Loeser <i>et al.</i> ³³	82-year-old female	Transfemoral; Edwards SAPIEN	N/A	1 day	Event: Cardiac arrest with CPR. Compression: Autopsy revealed subtotal THV compression. Outcome: Deceased

Other abbreviations as in *Table 1*.

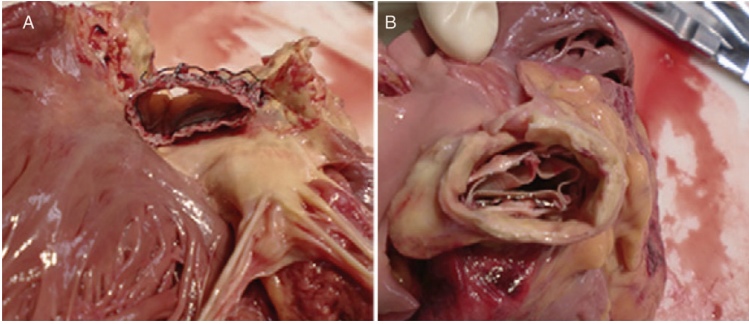


Figure 6 Transcatheter heart valve compression. (A and B) Autopsy finding of a deformed Edwards SAPIEN valve following cardiopulmonary resuscitation. Reprinted with permission from Kirov *et al.*⁹⁰

compression.⁸⁸ Treatment options for patients with THV deformation depend on the clinical scenario, and haemodynamic consequences of THV compression, but could include balloon post-dilatation, valve-in-valve implantation, or THV retrieval and SAVR.

Transcatheter heart valve thrombosis

Ten publications, comprising 15 individual cases of THV thrombosis, were identified (Table 5).^{96–105} The majority of cases (14 of 15) involved the Edwards SAPIEN THV. Excluding two cases of peri-procedural thrombosis, the mean time to diagnosis was 9 + 7 months (range: 1–24 months). The post-implantation antiplatelet regimen was described in 13 cases: 12 patients were prescribed dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel; one case was treated with aspirin monotherapy. One patient on aspirin alone and one non-compliant patient had THV thrombosis at 2 weeks and 8 months, respectively. The remaining patients had THV thrombosis after completing the recommended course of DAPT (on-going aspirin) ($n = 5$) or despite on-going DAPT ($n = 6$). Most patients with THV thrombosis presented with progressive dyspnoea ($n = 12$). One patient was asymptomatic and the thrombosis was evident on post-implantation CT, one had a non-ST-segment myocardial infarction, and one patient with peri-procedural THV thrombosis suffered cardiac arrest. The most commonly observed echocardiographic features were increasing transvalvular gradients ($n = 12$), thickened THV leaflets with impaired mobility ($n = 8$), and visualization of thrombus formation on the valve ($n = 5$).

Transcatheter heart valve thrombosis was treated with either systemic anticoagulation ($n = 11$) or surgical intervention ($n = 3$). Thrombolytic therapy was not performed in any case. In all patients treated with anticoagulation, the transvalvular gradients diminished towards the post-procedural gradient and leaflet mobility normalized. Favourable clinical outcomes were noted for all patients, except the case of peri-procedural THV thrombosis complicated by cardiac arrest, progressive cardiogenic shock and death. Protracted hospital stay was described for two of the three patients who underwent surgical thrombectomy and SAVR.

Table 5 Transcatheter heart valve thrombosis

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Trepels <i>et al.</i> ⁹⁶	84 year-old female; LES 22%	Transapical; 23 mm Edwards SAPIEN	Uneventful. Antiplatelet therapy: Non-compliance with DAPT from 6 weeks	8 months	Presentation: Progressive dyspnoea. Imaging: Increasing MG: 11, 19, 40, and 53 mmHg at 2, 7, 24, and 32 months, respectively. Echo-density on THV leaflet. Treatment: THV retrieval and SAVR. Note: Histology: non-infective thrombi on THV leaflets. Thrombophilia screen: mild protein S reduction, + cold agglutinin. Outcome: Discharged home
Kefer <i>et al.</i> ⁹⁷	78-year-old male; LES 44%. EF 30%	Transapical; 26 mm Edwards SAPIEN	Uneventful; trace AR; PG 15 mm Hg; AVA 1.6 cm ² Antiplatelet therapy: Initial DAPT, clopidogrel stopped at 1 month	4 months	Presentation: NSTEMI; CHF. Imaging: ICE and TTE showed thrombus on THV leaflets; severe AS with PG 72 mmHg; EOA 0.4 cm ² . Treatment: Anticoagulation. Note: Negative thrombophilia screen. Outcome: PG reduced to 22 mmHg at 1 month
Tay <i>et al.</i> ⁹⁸	Case 1. 66 year-old male; EF 30%. Case 2. 77-year-old female; prior MVR for rheumatic mitral stenosis	23 mm Edwards SAPIEN. Transapical; 26 mm Edwards SAPIEN within failing MVR	Uneventful procedure; post-TAVI TTE showed thrombi on THV. Antiplatelet therapy: On-going DAPT. Uneventful; no MR; MG reduced from 10 to 7 mmHg. Antiplatelet therapy: On-going DAPT	3 days 1 month	Presentation: Cardiac arrest. Treatment: Intravenous heparin continued post-TAVI. Note: Autopsy showed normal THV position and leaflet mobility with thrombi on the stent frame. Outcome: Deceased. Presentation: Dyspnoea. Imaging: TOE showed thrombus on edge of THV. Treatment: Anticoagulation. Outcome: Discharged home

Table 5 Transcatheter heart valve thrombosis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Latib <i>et al.</i> ⁹⁹	Case 1. 83-year-old male; ES 30%; STS 5%. EF normal.	Transfemoral; 26 mm Edwards SAPIEN XT.	Uneventful; no AR; MG 11 mmHg. Antiplatelet therapy: On-going DAPT.	6 months 15 months 24 months	Presentation: Dyspnoea. Imaging: Increasing MG: 47 and 68 mmHg 6 and 6.5 months, respectively; no THV thrombus. Treatment: Anticoagulation.
		Edwards	Uneventful; trivial AR; MG 8 mmHg.		Outcome: Asymptomatic at 8 months; THV MG 11 mmHg.
		SAPIEN XT.	Antiplatelet therapy: Initial DAPT, clopidogrel stopped at 3 months.		Presentation: Dyspnoea.
	Case 2. 81-year-old male; ES 11%; STS 3.9%.	83-year-old male; Edwards	Uneventful; mild AR; MG 8 mmHg.		Imaging: Normal THV function at 3 and 9 months; MG increased to 45 mmHg at 15 months; no thrombus seen.
		SAPIEN XT; LES	Antiplatelet therapy: N/A		Treatment: Anticoagulation.
	Case 3. 83-year-old male; LES 20%; STS 17%	20%; STS 17%			Treatment: Anticoagulation.
					Outcome: Asymptomatic; MG gradient 19 mmHg.
					Presentation: Dyspnoea.
					Imaging: Normal THV function at 12 months; MG increased to 37 mmHg; no thrombus seen.
					Treatment: Anticoagulation.
					Outcome: Symptom improved; MG 13 mmHg

Table 5 Transcatheter heart valve thrombosis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Cota <i>et al.</i> ¹⁰⁰	Case 1. 80-year-old male.	23 mm Edwards SAPIEN XT.	Uneventful; MG 10 mmHg.	10 months	Presentation: Dyspnoea.
	Case 2.	23 mm Edwards	Antiplatelet therapy: On-going DAPT.	4 months	Imaging: MG increased to 54 mmHg; suspected thrombotic fusion of
	81-year-old male; prior bioprosthetic SAVR	SAPIEN XT within 25 mm Carpentier	Uneventful; MG 15 mmHg. Antiplatelet therapy: N/A	2 months	two THV leaflets. Treatment: Anticoagulation.
	Case 3. 74-year-old female	Edwards. 26 mm Edwards SAPIEN XT	Uneventful; MG 7 mmHg. Antiplatelet therapy: On-going DAPT		Note: Thrombophilia screen: negative. Outcome: Asymptomatic; MG 13 mmHg. Presentation: Dyspnoea. Imaging: MG increased to MG 51 mmHg; suspected thrombotic fusion of two THV leaflets. Treatment: Anticoagulation. Outcome: Asymptomatic; MG 9 mmHg. Presentation: Dyspnoea. Imaging: MG increased to 34 mmHg; suspected thrombotic apposition of THV leaflets. Treatment: Anticoagulation. Outcome: Asymptomatic; MG 9 mmHg
Greason <i>et al.</i> ¹⁰¹	74-year-old female; STS 18.7%	Transilicac; 23 mm Edwards SAPIEN	Uneventful; MG 5 mmHg.	2 weeks	Presentation: Dyspnoea.
			Antiplatelet therapy: On-going aspirin monotherapy		Imaging: MG increased to of 43 mmHg with restricted leaflet mobility. Treatment: THV retrieval and SAVR. Note: Explanted THV thrombosis. Outcome: Discharged after long hospitalization

Table 5 Transcatheter heart valve thrombosis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Lancellotti <i>et al.</i> ¹⁰²	86-year-old male; ES 7%	26 mm CoreValve	Uneventful; Antiplatelet therapy: Initial DAPT, clopidogrel stopped at 3 months	12 months	Presentation: Dyspnoea. Imaging: MG increased to 41 mmHg; EOA 0.7 cm ² ; thickened restricted THV leaflets; no thrombus seen. Treatment: THV retrieval and SAVR. Note: Explanted THV showed thrombosis of THV with pannus restricting leaflet mobility. Outcome: Discharged after long hospitalization
Pache <i>et al.</i> ¹⁰³	86-year-old male	29 mm Edwards SAPIEN XT	Uneventful; Mild paravalvular AR. Antiplatelet therapy: Initial DAPT, post-TAVI heparin (for prior pulmonary embolism) stopped due to perianal bleeding	7 days	Presentation: Incidental finding on post-implant CT. Imaging: CT revealed a crescent shaped thrombus in THV left-coronary cusp. TOE showed restricted cusp movement but normal haemodynamic function (MG 9 mmHg). Treatment: Anticoagulation. Outcome: Discharged home. Repeat CT at 10 weeks showed no evidence of thrombus
Orbach <i>et al.</i> ¹⁰⁴	81-year-old female	26 mm Edwards SAPIEN	N/A Antiplatelet therapy: Initial DAPT, then aspirin monotherapy	21 months	Presentation: CHF. Imaging: MG increased to 53 mmHg; EOA _i 0.4 cm ² /m ² ; thickened restricted THV leaflets; distinct thrombus on TOE. Treatment: Anticoagulation. Outcome: Asymptomatic and normal THV function at 10 months

Table 5 Transcatheter heart valve thrombosis (continued)

Study	Patient characteristics	Access and THV characteristics	Procedural details	Timing	Case description
Pergolini <i>et al.</i> ¹⁰⁵	87-year-old male; ES 29%; STS 15.6%	29 mm Edwards SAPIEN XT	Uneventful; MG 8 mmHg. Antiplatelet therapy: Initial DAPT, clopidogrel stopped at 3 months. Aspirin interrupted 4 months later due to epistaxis and clopidogrel reinstated	8 months	Presentation: Progressive dyspnoea. Imaging: MG increased to 50 mmHg; thickened restricted THV leaflets; TOE showed echodense homogenous layer on aortic side of the three THV cusps. Treatment: Anticoagulation. Note: Negative thrombophilia workup. Outcome: Discharge on day 11 with gradual decrease in MG and resolution of symptoms

ICE, intracardiac echocardiogram; NSTEMI, non-ST elevation myocardial infarction; TOE, transoesophageal echocardiogram; THV, transcatheter heart valve; other abbrevia-
tions as in *Table 1*.

Discussion: Transcatheter heart valve thrombosis

Thrombosis of surgical aortic bioprostheses is rare, with incidence estimates of 0.03–0.7% per patient-year.^{106,107} Transcatheter heart valve thrombosis appears to be an equally rare event: there were no reported cases of prosthesis thrombosis in the PARTNER randomized trials or in large consecutive TAVI registries.^{4,5,16} One case of THV thrombosis (0.8%) was reported among the 130 TAVI recipients enrolled in the PARTNER EU trial.⁹⁶

There exist, however, several theoretical mechanisms that could potentially increase the risk of THV thrombosis relative to SAVR (*Figure 7*):¹⁰⁸ (i) the elderly TAVI population is more likely to have coexisting prothrombotic conditions (e.g. Cancer), (ii) the metallic THV frame could potentially provide a nidus for thrombosis, (iii) incomplete THV expansion can create leaflet folds and potential recesses for thrombus formation, (iv) incomplete THV apposition to the aortic wall may delay endothelialization, and (v) the native leaflets may overhang balloon-expandable systems creating areas of diminished blood flow and stagnation.

It appears that the highest risk of valve thrombosis following bioprosthetic SAVR occurs in the first 3–6 months post-operatively.¹⁰⁹ Consequently, aspirin therapy (75–100 mg) is recommended by societal guidelines.^{110,111} More recently, short-term use of oral anticoagulation has been associated with a reduction in thromboembolic events and cardiovascular mortality.¹⁰⁹ There are currently few data evaluating the efficacy of either antiplatelet or anticoagulant therapy following TAVI.¹¹² Dual antiplatelet therapy (aspirin and clo-pidogrel) is presently recommended for 3–6 months post-TAVI, though there is scant evidence to support the selection or duration of this regimen. This rather arbitrary duration of therapy aims to provide antiplatelet cover in the immediate post-operative period, allowing THV frame endothelialization, without exposing the patient to excessive bleeding risk. It is unclear if a short period of oral anticoagulation could reduce the risk of both stroke and potential for THV thrombosis without prohibitively increasing the bleeding risk. On-going research will help define the optimal duration of antiplatelet therapy post-TAVI (Aspirin Versus Aspirin and Clopidogrel

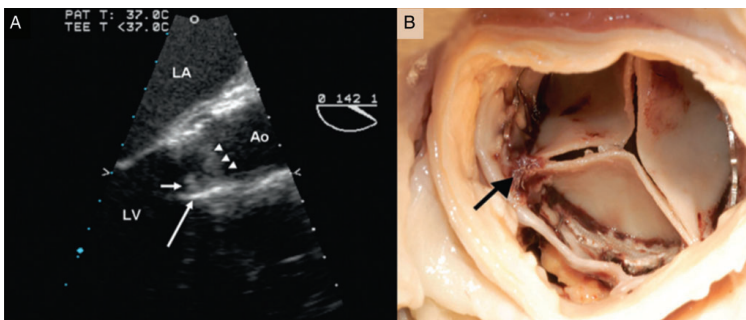


Figure 7 Transcatheter heart valve thrombosis. (A) Transesophageal echocardiogram of a case of transcatheter heart valve thrombosis demonstrating the valve stent (long white arrow), thrombus on the stent (short white arrow), and thickened valve leaflets. (B) Post-mortem image of thrombi on the outflow of the stent frame (black arrow). Reprinted with permission from Tay.⁹⁸

Following Transcatheter Aortic Valve Implantation: the ARTE Trial: NCT01559298) and/or need for anticoagulation.

It should be noted that the diagnosis of THV thrombosis requires a high index of suspicion: thrombus was not seen on either the THV leaflets or frame in two-thirds of cases. Diagnostic clues include a history of non-compliance with DAPT,⁹⁶ echocardiographic evidence of progressive valve dysfunction (usually stenosis),^{96,99,102,101–103} leaflet thickening, and immobility.

The optimal management of THV thrombosis is currently unclear. It is noteworthy that three-quarters of cases were successfully treated with prolonged systemic anticoagulation and that thrombolysis was not performed in any case, probably due to the high risk of bleeding in TAVI patients. Surgical thrombectomy and SAVR was successfully performed in three cases, without procedural mortality.

DISCUSSION

The main findings of this systematic review of published data on TAVI failure are that THVs appear to be susceptible to failure modes both similar to those of surgical bioprosthetic valves and unique to the specific design features of THVs. Late embolization and THV compression represent complications previously unreported in the surgical literature.

Surgical aortic valve replacement failure

Surgical bioprosthetic failure may be attributed to SVF, IE, thrombosis, or paravalvular leak. First generation bioprosthetic valves were particularly prone to SVF, with up to one-third of younger patients requiring reoperation within 10 years of implantation.¹¹³ Advances in prosthesis design, leaflet fixation, and anti-calcification treatment have rendered these early prostheses obsolete, and have improved valve durability: freedom from SVF at 15 years was reported in 43% of those treated with the first generation Hancock (Medtronic, Minneapolis, MN, USA) and in 19% treated with the second-generation Hancock.^{114,115} Current, third-generation bioprostheses are expected to further reduce the incidence of SVF and long-term follow-up data on these prostheses are eagerly awaited.

Transcatheter heart valve failure

We observed three THV failure modes (PVE, SVF, and thrombosis) that are synonymous with surgical bioprosthesis failure. We observed some variance, however, in the presentation and management of these complications between TAVI and SAVR. For example, confirming the diagnosis of PVE appeared to be more difficult among TAVI recipients than expected; echocardiographic diagnosis appeared to be hindered by limited visualization of the THV and by the frequent presence of post-implantation paravalvular leaks. Structural valve failure was also more frequently treated with redo TAVI rather than SAVR.

Two failure modes, unique to THVs were also identified. Late THV embolization is a rare, but potentially catastrophic complication of TAVI. The limited number of events precludes an analysis of potential risk factors for late embolization, though insufficient THV anchoring, low implantation, and the presence of a mitral prosthesis were prevalent amongst cases. Compression of balloon-expandable THV was reported among patients that had undergone CPR in the setting of fatal peri-procedural complications. Thus, THV function should be evaluated following CPR in all THV recipients.

Implications

Understanding the modes of TAVI failure, their presentation, treatment, and outcomes is of particular relevance as TAVI technology is applied to greater patient numbers worldwide and increasingly to intermediate-risk cohorts.^{1,2} The current study highlights several modes of TAVI failure that will be seen with greater frequency as experience with the technique increases. It is likely that the current case report and small series literature on TAVI failure reflects a significant underreporting of events. Therefore, determining the true incidence of adverse events will require high-quality dedicated post-marketing surveillance registries, such as the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry.¹¹⁶ The objective performance criteria developed by the U.S. Food and Drug Administration will provide benchmark performance for evaluating the long-term performance of TAVI technology.¹¹⁷ Systematic autopsy of TAVI recipients could also facilitate our understanding of the modes of TAVI failure as distinct from bioprosthetic SAVR failure.

Limitations

This study has the limitations inherent to all systematic reviews. We present only the information described in each individual publication and therefore potentially omit relevant data. All the articles in the literature were either case reports or small series, precluding comparison with the entire TAVI population at risk. Furthermore, accurate estimation of the true incident rates of each THV failure mode was not possible, and the likely underreporting of adverse events would be expected to result in a significant underestimation of event rates. In addition, the management of patients in published case reports and small series may not represent common clinical practice but nonetheless provide some clinical guidance in circumstances where an evidence base is not available. The results of this review are also subject to publication bias as the reported incidences and individual patient outcomes may have been superior to those that were not published. Furthermore, imaging data and other relevant background information were not available in all the reported cases.

CONCLUSIONS

Transcatheter heart valves appear to be susceptible to failure modes both similar to those of surgical bioprosthetic valves and unique to the specific design features of THVs. Late embolization and THV compression represent complications previously unreported in the surgical literature. Large patient series with extended follow-up are required to better characterize and quantify THV failure.

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REFERENCES

1. Mylotte D, Osnabrugge RL, Windecker S, Lefevre T, de Jaegere P, Jeger R, Wenaweser P, Maisano F, Moat N, Sondergaard L, Bosmans J, Teles RC, Martucci G, Manoharan G, Garcia E, Van Mieghem NM, Kappetein AP, Serruys PW, Lange R, Piazza N. Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. *J Am Coll Cardiol* 2013;62:210–219.
2. Lange R, Bleiziffer S, Mazzitelli D, Elhmidi Y, Opitz A, Krane M, Deutsch MA, Ruge H, Brockmann G, Voss B, Schreiber C, Tassani P, Piazza N. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2011;59:280–287.
3. Wenaweser P, Stortecky S, Schwander S, Heg D, Huber C, Pilgrim T, Gloekler S, O'Sullivan CJ, Meier B, Juni P, Carrel T, Windecker S. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. *Eur Heart J* 2013;34:1894–1905.
4. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686–1695.
5. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012;366:1696–1704.
6. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg* 2009;137:82–90.
7. Rahimtoola SH. Choice of prosthetic heart valve in adults an update. *J Am Coll Cardiol* 2010;55:2413–2426.
8. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol* 2000;36:1152–1158.
9. Stassano P, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N, Vosa C. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *J Am Coll Cardiol* 2009;54: 1862–1868.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151: 264–269, w64.
11. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *EuroIntervention* 2012;8:782–795.
12. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Muller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009;30:2369–2413.

13. Dwyer HA, Matthews PB, Azadani A, Ge L, Guy TS, Tseng EE. Migration forces of transcatheter aortic valves in patients with noncalcific aortic insufficiency. *J Thorac Cardiovasc Surg* 2009;138:1227–1233.
14. Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Osten M, Feindel CM, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson M, Thompson CR, Wood D, Toggweiler S, Gurvitch R, Lichtenstein SV, Doyle D, DeLarochelliere R, Teoh K, Chu V, Bainey K, Lachapelle K, Cheema A, Latter D, Dumesnil JG, Pibarot P, Horlick E. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. *J Am Coll Cardiol* 2012;60:1864–1875.
15. Thomas M, Schymik G, Walther T, Himbert D, Lefevre T, Treede H, Eggebrecht H, Rubino P, Colombo A, Lange R, Schwarz RR, Wendler O. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2011;124:425–433.
16. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetché D, Carrie D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Bosch J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bournon F, Bertrand B, Van Belle E, Laskar M. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012;366:1705–1715.
17. Wong DR, Boone RH, Thompson CR, Allard MF, Altwegg L, Carere RG, Cheung A, Ye J, Lichtenstein SV, Ling H, Webb JG. Mitral valve injury late after transcatheter aortic valve implantation. *J Thorac Cardiovasc Surg* 2009;137:1547–1549.
18. Comoglio C, Boffini M, El Qarra S, Sansone F, D'Amico M, Marra S, Rinaldi M. Aortic valve replacement and mitral valve repair as treatment of complications after percutaneous core valve implantation. *J Thorac Cardiovasc Surg* 2009;138:1025–1027.
19. Carnero-Alcazar M, Maroto Castellanos LC, Carnicer JC, Rodriguez Hernandez JE. Transapical aortic valve prosthetic endocarditis. *Interact Cardiovasc Thorac Surg* 2010;11:252–253.
20. Santos M, Thiene G, Sievers HH, Basso C. Candida endocarditis complicating transapical aortic valve implantation. *Eur Heart J* 2011;32:2265.
21. Gotzmann M, Mugge A. Fatal prosthetic valve endocarditis of the CoreValve ReValving system. *Clin Res Cardiol* 2011;100:715–717.
22. Head SJ, Dewey TM, Mack MJ. Fungal endocarditis after transfemoral aortic valve implantation. *Catheter Cardiovasc Interv* 2011;78:1017–1019.
23. Chrissoheris MP, Ferti A, Spargias K. Early prosthetic valve endocarditis complicating repeated attempts at CoreValve implantation. *J Invasive Cardiol* 2011;23: E291–E292.
24. Rafiq I, Parthasarathy H, Tremlett C, Freeman LJ, Mullin M. Infective endocarditis caused by *Moraxella nonliquefaciens* in a percutaneous aortic valve replacement. *Cardiovasc Revasc Med* 2011;12:184–186.
25. Castiglioni A, Pozzoli A, Maisano F, Alfieri O. Endocarditis after transfemoral aortic valve implantation in a patient with Osler-Weber-Rendu syndrome. *Interact Cardiovasc Thorac Surg* 2012;15:553–554.
26. Garcia-Pardo H, Revilla A, Sevilla T, Lopez J, Ortiz C, San Roman JA. Staphylococcus aureus endocarditis on transcatheter aortic valves. *Rev Esp Cardiol (Engl Ed)* 2012; 65:771–773.
27. Loh PH, Bundgaard H, Ndergaard SL. Infective endocarditis following transcatheter aortic valve replacement: diagnostic and management challenges. *Catheter Cardiovasc Interv* 2013;81:623–627.
28. Puls M, Eiffert H, Hunlich M, Schondube F, Hasenfuss G, Seipelt R, Schillinger W. Prosthetic valve endocarditis after transcatheter aortic valve implantation: the incidence in a single-centre cohort and reflections on clinical, echocardiographic and prognostic features. *EuroIntervention* 2013;8:1407–1418.

29. Seeburger J, Weiss G, Borger MA, Mohr FW. Structural valve deterioration of a Corevalve prosthesis 9 months after implantation. *Eur Heart J* 2013;34:1607.
30. Citro R, Mirra M, Baldi C, Protta C, Palumbo B, Piscione F, La Canna G. Concomitant dynamic obstruction and endocarditis after “valve in valve” TAVI implantation. *Int J Cardiol* 2013;167:e27–e29.
31. Orban M, Sinnecker D, Mair H, Nabauer M, Kupatt C, Schmitz C, Massberg S, Laugwitz KL, Barthel P. Transcatheter aortic-valve endocarditis confirmed by transesophageal echocardiography. *Circulation* 2013;127:e265–e266.
32. Zytowski M, Erb M, Albes JM, Hartrumpf M. Infective endocarditis 4 months after transapical aortic valve implantation with Edwards SAPIEN XT. *Eur J Cardiothorac Surg* 2013;44:769.
33. Loeser H, Wittersheim M, Puetz K, Friemann J, Buettner R, Fries JW. Potential complications of transcatheter aortic valve implantation (TAVI)—an autopsy perspective. *Cardiovasc Pathol* 2013;22:319–323.
34. Wilbring M, Tugtekin SM, Matschke K, Kappert U. Surgery for Fulminant Prosthetic Valve Endocarditis after Transapical Transcatheter Aortic Valve-in-Valve Implantation. *Thorac Cardiovasc Surg* 2013;62:80–82.
35. Aung T, Poon K, Horvath R, Coulter C, Walters DL. A case series of medically managed infective endocarditis after transcatheter aortic valve replacement. *Scand J Infect Dis* 2013;45:489–493.
36. Hirnle G, Holzhey D, Borger M, Mohr FW. Infective mitral valve endocarditis after transapical aortic valve implantation. *Interact Cardiovasc Thorac Surg* 2013;16: 394–395.
37. Seok Koh Y, Hyoung Moon M, Hyun Jo K, Wook Kim H. Infective endocarditis in transcatheter aortic valve implantation. *Eur J Cardiothorac Surg* 2013;45:582.
38. Drews T, Pasic M, Buz S, Unbehaun A, Dreyse S, Kukucka M, Mladenow A, Hetzer R. Transapical aortic valve implantation after previous mitral valve surgery. *J Thorac Cardiovasc Surg* 2011;142:84–88.
39. Pasic M, Unbehaun A, Dreyse S, Buz S, Drews T, Kukucka M, Hetzer R. Transapical aortic valve implantation after previous aortic valve replacement: clinical proof of the “valve-in-valve” concept. *J Thorac Cardiovasc Surg* 2011;142:270–277.
40. Nietlispach F, Webb JG, Ye J, Cheung A, Lichtenstein SV, Carere RG, Gurvitch R, Thompson CR, Ostry AJ, Matzke L, Allard MF. Pathology of transcatheter valve therapy. *JACC Cardiovasc Interv* 2012;5: 582–590.
41. Bozdag Turan I, Kische S, D’Ancona G, Nienaber CA, Ince H. Suspected endocarditis after CoreValve implantation: a word of caution. *Anadolu Kardiyol Derg* 2013; 13:395–396.
42. Raschpichler M, Seeburger J, Strasser RH, Misfeld M. Corevalve prosthesis causes anterior mitral leaflet perforation resulting in severe mitral regurgitation and subsequent endocarditis. *Eur Heart J* 2014;35: 1587.
43. Genereux P, Head SJ, Van Mieghem NM, Kodali S, Kirtane AJ, Xu K, Smith C, Serruys PW, Kappetein AP, Leon MB. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol* 2012; 59:2317–2326.
44. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, Gewitz MH, Shulman ST, Nouri S, Newburger JW, Hutto C, Pallasch TJ, Gage TW, Levison ME, Peter G, Zuccaro G Jr. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *JAMA* 1997;277:1794–1801.
45. Seto TB, Kwiat D, Taira DA, Douglas PS, Manning WJ. Physicians’ recommendations to patients for use of antibiotic prophylaxis to prevent endocarditis. *JAMA* 2000;284:68–71.
46. Piazza N, Marra S, Webb J, D’Amico M, Rinaldi M, Boffini M, Comoglio C, Scacciarella P, Kappetein AP, de Jaegere P, Serruys PW. Two cases of aneurysm of the anterior mitral valve leaflet associated with transcatheter aortic valve endocarditis: a mere coincidence? *J Thorac Cardiovasc Surg* 2010;140: e36–e38.

47. Piper C, Hetzer R, Korfer R, Bergemann R, Horstkotte D. The importance of secondary mitral valve involvement in primary aortic valve endocarditis: the mitral kissing vegetation. *Eur Heart J* 2002;23:79–86.
48. Hujer AM, Bethel CR, Hujer KM, Bonomo RA. Antibiotic resistance in the institutionalized elderly. *Clin Lab Med* 2004;24:343–361.
49. Zamorano JL, Badano LP, Bruce C, Chan KL, Goncalves A, Hahn RT, Keane MG, La Canna G, Monaghan MJ, Nihoyannopoulos P, Silvestry FE, Vanoverschelde JL, Gillam LD. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. *Eur Heart J* 2011;32: 2189–2214.
50. Clavel MA, Dumont E, Pibarot P, Doyle D, De Larochelliere R, Villeneuve J, Bergeron S, Couture C, Rodes-Cabau J. Severe valvular regurgitation and late prosthesis embolization after percutaneous aortic valve implantation. *Ann Thorac Surg* 2009;87:618–621.
51. Maroto LC, Rodriguez JE, Cobiella J, Silva J. Delayed dislocation of a transapically implanted aortic bioprosthesis. *Eur J Cardiothorac Surg* 2009;36:935–937.
52. Baumbach H, Hill S, Hansen M, Franke UF. Severe aortic insufficiency after transapical aortic valve implantation. *Ann Thorac Surg* 2011;92:728–729.
53. Schroeter T, Subramanian S, Lehmann S, Kempfert J, Misfeld M, Mohr FW, Borger MA. Dislocation of a transapically implanted aortic valve prosthesis with a functionally bicuspid aortic valve and ascending aortic aneurysm. *Thorac Cardiovasc Surg* 2011;59:503–506.
54. Radu C, Raffoul R, Brochet E, Himbert D. Delayed migration of a transfemorally implanted aortic bioprosthesis. *J Thorac Cardiovasc Surg* 2012;143:e1–e3.
55. Pang PY, Chiam PT, Chua YL, Sin YK. A survivor of late prosthesis migration and rotation following percutaneous transcatheter aortic valve implantation. *Eur J Cardiothorac Surg* 2012;41:1195–1196.
56. Gul M, Erkanli K, Erol MK, Bakir I. Ventricular embolization of Edwards SAPIEN prosthesis following transcatheter aortic valve implantation. *J Invasive Cardiol* 2012;24:537–538.
57. Toggweiler S, Wood DA, Rodes-Cabau J, Kapadia S, Willson AB, Ye J, Cheung A, Leipsic J, Binder RK, Gurvitch R, Freeman M, Thompson CR, Svensson LG, Dumont E, Tuzcu EM, Webb JG. Transcatheter valve-in-valve implantation for failed balloon-expandable transcatheter aortic valves. *JACC Cardiovasc Interv* 2012; 5:571–577.
58. Stangl V, Baldenhofer G, Knebel F, Zhang K, Sanad W, Spethmann S, Grubitzsch H, Sander M, Wernecke KD, Baumann G, Stangl K, Laule M. Impact of gender on three-month outcome and left ventricular remodeling after transfemoral transcatheter aortic valve implantation. *Am J Cardiol* 2012;110:884–890.
59. Iida R, Welsh RC, Meyer SR, Tyrrell BD, Taylor DA, Shanks M. Pre-dismissal surveillance echocardiography second day after TAVR. *JACC Cardiovasc Imaging* 2012;5: 1182–1184.
60. Naganuma T, Latib A, Agricola E, Alfieri O, Spagnolo P, Colombo A, Maisano F. Late downward dislocation of a balloon expandable valve into the left ventricular outflow tract following transfemoral transcatheter aortic valve implantation. *Circ J* 2013;77:1345–1347.
61. Lauten A, Hamadanchi A, Doenst T, Figulla HR. Late migration of balloon-expandable transcatheter aortic valve. *Eur Heart J* 2013;34:2509.
62. Wendeborn J, Donndorf P, Westphal B, Steinhoff G. Surgical double valve replacement after transcatheter aortic valve implantation and interventional mitral valve repair. *Interact Cardiovasc Thorac Surg* 2013;17:909–911.
63. Wijesinghe N, Ye J, Rodes-Cabau J, Cheung A, Velianou JL, Natarajan MK, Dumont E, Nietlispach F, Gurvitch R, Wood DA, Tay E, Webb JG. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. *JACC Cardiovasc Interv* 2010;3:1122–1125.

64. Nijhoff F, Agostoni P, Samim M, Ramjankhan FZ, Kluin J, Doevendans PA, Stella PR. Optimisation of transcatheter aortic balloon-expandable valve deployment: the two-step inflation technique. *EuroIntervention* 2013;9:555–563.
65. Nijhoff F, Agostoni P, Amrane H, Latib A, Testa L, Oreglia JA, De Marco F, Samim M, Bedogni F, Maisano F, Bruschi G, Colombo A, Van Boven AJ, Stella PR. Transcatheter aortic valve implantation in patients with severe aortic valve stenosis and large aortic annulus, using the self-expanding 31-mm Medtronic CoreValve prosthesis: First clinical experience. *J Thorac Cardiovasc Surg* 2013;01:157–154.
66. Schleger S, Kasel M, Vogel J, Lieber M, Antoni D, Hoffmann E, Eichinger WB. Successful transapical implantation of an Edwards Sapien valve within an insufficient aortic CoreValve prosthesis: an initial experience. *Ann Thorac Surg* 2013;95: 1070–1072.
67. Pagnotta P, Ferrante G, Presbitero P. Rescue “valve in valve” implantation after late onset corevalve cusp rupture leading to acute massive aortic insufficiency. *Catheter Cardiovasc Interv* 2014;83:E283–E286.
68. van der Lienden BT, Swinkels BM, Heijmen RH, Mast EG, De Kroon TL, Ten Berg JM. First valve-in-valve direct transaortic CoreValve implantation in an insufficient Sapien valve. *JACC Cardiovasc Interv* 2011;4:1049–1050.
69. Blumenstein J, Van Linden A, Kim WK, Skwara W, Schoenburg M, Arsalan M, Moellmann H, Niederhagen M, Kempfert J, Walther T. Early SAPIEN transcatheter heart valve dysfunction due to tissue ingrowth in an octogenarian. *Clin Res Cardiol* 2013;102:237–240.
70. Klotz S, Scharfswerdth M, Richardt D, Sievers HH. Failed valve-in-valve transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2012;5:591–592.
71. Ong SH, Mueller R, Iversen S. Early calcific degeneration of a CoreValve transcatheter aortic bioprosthesis. *Eur Heart J* 2012;33:586.
72. Hammerstingl C, Nickenig G, Grube E. Treatment of a degenerative stenosed Cor-eValve((R)) aortic bioprosthesis by transcatheter valve-in-valve insertion. *Catheter Cardiovasc Interv* 2012;79:748–755.
73. Hoffmann R, Mollmann H, Lotfi S. Transcatheter aortic valve-in-valve implantation of a corevalve in a degenerated stenotic sapien heart valve prosthesis. *Catheter Cardiovasc Interv* 2012;82:E922–E925.
74. Kiefer P, Seeburger J, Chu MW, Ender J, Vollroth M, Noack T, Mohr FW, Holzhey DM. Reoperative transapical aortic valve implantation for early structural valve deterioration of a SAPIEN XT valve. *Ann Thorac Surg* 2013;95:2169–2170.
75. Toggweiler S, Humphries KH, Lee M, Binder RK, Moss RR, Freeman M, Ye J, Cheung A, Wood DA, Webb JG. 5-year outcome after transcatheter aortic valve implantation. *J Am Coll Cardiol* 2013;61: 413–419.
76. Thyregod HG, Lund JT, Engstrom T, Steinbruchel DA. Transcatheter aortic valve prosthesis surgically replaced 4 months after implantation. *Eur J Cardiothorac Surg* 2010;37:494–496.
77. Kiefer P, Lehmkuhl L, Seeburger J, Vollroth M, Noack T, Schroter T, Mohr FW, Holzhey D. Symetis Acurate aortic valve-in-valve implantation for early degeneration of a Sapien THV prosthesis. *Ann Thorac Surg* 2013;96:1880.
78. Thubrikar MJ, Deck JD, Aouad J, Nolan SP. Role of mechanical stress in calcification of aortic bioprosthetic valves. *J Thorac Cardiovasc Surg* 1983;86:115–125.
79. Schoen FJ, Levy RJ. Calcification of tissue heart valve substitutes: progress toward understanding and prevention. *Ann Thorac Surg* 2005;79:1072–1080.
80. Manji RA, Zhu LE, Nijjar NK, Rayner DC, Korbitt GS, Churchill TA, Rajotte RV, Koshal A, Ross DB. Glutaraldehyde-fixed bioprosthetic heart valve conduits calcify and fail from xenograft rejection. *Circulation* 2006;114:318–327.
81. Ruel M, Kulik A, Rubens FD, Bedard P, Masters RG, Pipe AL, Mesana TG. Late incidence and determinants of reoperation in patients with prosthetic heart valves. *Eur J Cardiothorac Surg* 2004;25:364–370.

82. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation* 2009;119:1034–1048.
83. Gurvitch R, Wood DA, Tay EL, Leipsic J, Ye J, Lichtenstein SV, Thompson CR, Carere RG, Wijesinghe N, Nietlispach F, Boone RH, Lauck S, Cheung A, Webb JG. Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. *Circulation* 2010;122: 1319–1327.
84. Sun W, Li K, Sirois E. Simulated elliptical bioprosthetic valve deformation: implications for asymmetric transcatheter valve deployment. *J Biomech* 2010;43: 3085–3090.
85. Al-Attar N, Himbert D, Vahanian A, Nataf P. Severe intraprosthetic regurgitation by immobile leaflet after trans-catheter aortic valve implantation. *Eur J Cardiothorac Surg* 2011;39:591–592.
86. Zegdi R, Bruneval P, Blanchard D, Fabiani JN. Evidence of leaflet injury during percutaneous aortic valve deployment. *Eur J Cardiothorac Surg* 2011;40:257–259.
87. Butany J, Leong SW, Cunningham KS, D'Cruz G, Carmichael K, Yau TM. A 10-year comparison of explanted Hancock-II and Carpentier-Edwards supraannular bioprostheses. *Cardiovasc Pathol* 2007; 16:4–13.
88. Scherner M, Madershahian N, Strauch JT, Wippermann J, Wahlers T. Transapical valve implantation and resuscitation: risk of valve destruction. *Ann Thorac Surg* 2011;92:1909–1910.
89. Kim EK, Choi SH, Song PS, Park SJ. Valve prosthesis distortion after cardiac compression in a patient who underwent transcatheter aortic valve implantation (TAVI). *Catheter Cardiovasc Interv* 2012;83: E165–E167.
90. Kirov HM, Bothe W, Breuer M, Clasen I, Mall EG, Schluter A, Ferrari M, Doenst T. Deformation of a transapical aortic valve after cardiopulmonary resuscitation: a potential risk of stainless steel stents. *J Am Coll Cardiol* 2012;60:1838.
91. Damen T, Sunnermalm L, Friberg O, Zagodzón L, Cederstrand B, Kellert T. Inverted valve after initially successful transfemoral aortic valve implantation. *Ann Thorac Surg* 2012;94:636–639.
92. Spangenberg T, Frerker C, Bader R, Schafer U. Complete crush of a balloon-expandable bioprosthesis after prolonged cardiopulmonary resuscitation. *Circ Cardiovasc Interv* 2013;6:e1–e2.
93. Windecker S, Maier W, Eberli FR, Meier B, Hess OM. Mechanical compression of coronary artery stents: potential hazard for patients undergoing cardiopulmonary resuscitation. *Catheter Cardiovasc Interv* 2000;51:464–467.
94. McElhinney DB, Cheatham JP, Jones TK, Lock JE, Vincent JA, Zahn EM, Hellenbrand WE. Stent fracture, valve dysfunction, and right ventricular outflow tract reintervention after transcatheter pulmonary valve implantation: patient-related and procedural risk factors in the US Melody Valve Trial. *Circ Cardiovasc Interv* 2011;4:602–614.
95. Moreno R, Calvo L, Salinas P, Dobarro D, Santiago JV, Sanchez-Recalde A, Galeote G, Riera L, Moreno-Gomez I, Mesa J, Plaza I, Lopez-Sendon J. Causes of peri-operative mortality after transcatheter aortic valve implantation: a pooled analysis of 12 studies and 1223 patients. *J Invasive Cardiol* 2011;23: 180–184.
96. Trepels T, Martens S, Doss M, Fichtlscherer S, Schachinger V. Images in cardiovascular medicine. Thrombotic restenosis after minimally invasive implantation of aortic valve stent. *Circulation* 2009;120: e23–e24.
97. Kefer J, Astarci P, Renkin J, Glineur D, Pierard S, Seldrum S, Vanoverschelde JL. Images and case reports in interventional cardiology. Thrombotic aortic restenosis after transapical Sapien valve implantation. *Circ Cardiovasc Interv* 2010;3:289–292.
98. Tay EL, Gurvitch R, Wijesinghe N, Nietlispach F, Wood D, Allard M, Munt B, Cheung A, Webb JG. Valve thrombosis after transcatheter heart valve implantation. *EuroIntervention* 2011;7:170–171.

99. Latib A, Messika-Zeitoun D, Maisano F, Himbert D, Agricola E, Brochet E, Alfieri O, Colombo A, Vahanian A. Reversible Edwards Sapien XT dysfunction due to prosthesis thrombosis presenting as early structural deterioration. *J Am Coll Cardiol* 2013;61:787–789.
100. Cota L, Stabile E, Agrusta M, Sorropago G, Pucciarelli A, Ambrosini V, Mottola G, Esposito G, Rubino P. Bioprostheses “thrombosis” after transcatheter aortic valve replacement. *J Am Coll Cardiol* 2013;61:789–791.
101. Greason KL, Mathew V, Sarano ME, Maleszewski JJ, Suri RM, Rihal CS. Early transcatheter aortic valve thrombosis. *J Card Surg* 2013;28:264–266.
102. Lancellotti P, Radermecker MA, Weisz SH, Legrand V. Subacute transcatheter CoreValve thrombotic obstruction. *Circ Cardiovasc Interv* 2013;6:e32–e33.
103. Pache G, Blanke P, Zeh W, Jander N. Cusp thrombosis after transcatheter aortic valve replacement detected by computed tomography and echocardiography. *Eur Heart J* 2013;34:3546.
104. Orbach A, Karkabi B, Shiran A. Reversible restenosis after transcatheter aortic valve implantation. *Eur Heart J Cardiovasc Imaging* 2014;15:350.
105. Pergolini A, Pino PG, Zampi G, Polizzi V, Musumeci F. Thrombotic aortic restenosis after transapical SAPIEN valve implantation. *J Card Surg* 2014;29:204–208.
106. Puvimanasinghe JP, Steyerberg EW, Takkenberg JJ, Eijkemans MJ, van Herwerden LA, Bogers AJ, Habbema JD. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation. *Circulation* 2001;103:1535–1541.
107. Brown ML, Park SJ, Sundt TM, Schaff HV. Early thrombosis risk in patients with biologic valves in the aortic position. *J Thorac Cardiovasc Surg* 2012;144:108–111.
108. Rodes-Cabau J, Dauerman HL, Cohen MG, Mehran R, Small EM, Smyth SS, Costa MA, Mega JL, O'Donoghue ML, Ohman EM, Becker RC. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. *J Am Coll Cardiol* 2013;62:2349–2359.
109. Merie C, Kober L, Skov Olsen P, Andersson C, Gislason G, Skov Jensen J, Torp-Pedersen C. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA* 2012;308:2118–2125.
110. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;33:2451–2496.
111. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:e521–e643.
112. Collet JP, Montalescot G. Antithrombotic and antiplatelet therapy in TAVI patients: a fallow field? *EuroIntervention* 2013;9(Suppl.):S43–S47.
113. Chikwe J, Filsoufi F, Carpentier AF. Prosthetic valve selection for middle-aged patients with aortic stenosis. *Nat Rev Cardiol* 2010;7:711–719.
114. Cohn LH, Collins JJ Jr, Rizzo RJ, Adams DH, Couper GS, Aranki SF. Twenty-year follow-up of the Hancock modified orifice porcine aortic valve. *Ann Thorac Surg* 1998;66:S30–S34.
115. David TE, Ivanov J, Armstrong S, Feindel CM, Cohen G. Late results of heart valve replacement with the Hancock II bioprosthesis. *J Thorac Cardiovasc Surg* 2001;121: 268–277.
116. Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, Shahian D, Tuzcu EM, Peterson ED, Rumsfeld JS, Hewitt K, Shewan C, Michaels J, Christensen B, Christian A, O'Brien S, Holmes

- D. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013;310:2069–2077.
117. Grunkemeier GL, Jin R, Starr A. Prosthetic heart valves: objective performance criteria versus randomized clinical trial. *Ann Thorac Surg* 2006;82:776–780.

TRANSCATHETER MITRAL VALVE IMPLANTATION



Chapter 17 Transcatheter mitral valve implantation: a brief review

Mylotte D, Piazza N.

EuroIntervention. 2015; 11: Suppl W:W67-70

Chapter 18 Quantitative multi-slice computed tomography assessment of the mitral valvular complex for transcatheter mitral valve interventions part 1: systematic measurement methodology and inter-observer variability.

Thériault-Lauzier P, *Mylotte D*, Dorfmeister M, Spaziano M, Andalib A, Mamane S, Chetrit M, Blanke P, Cecere R, Buithieu J, Martucci G, Tchetché D, Modine T, van Mieghem N, Lange R, Windecker S, Bilodeau L, Leipsic J, Piazza N.

EuroIntervention 2016;12:e1011-e1020.

Chapter 19 Quantitative multi-slice computed tomography assessment of the mitral valvular complex for transcatheter mitral valve interventions part 2: geometrical measurements in patients with functional mitral regurgitation.

Thériault-Lauzier PP, Dorfmeister M, *Mylotte D*, Andalib A, Spaziano M, Blanke P, Martucci G, Lange R, Leipsic J, Bilodeau L, Piazza N.

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TRANSCATHETER MITRAL VALVE IMPLANTATION

17

Transcatheter mitral valve implantation: a brief review

Mylotte D, Piazza N.

EuroIntervention. 2015; 11: Suppl W:W67-70

ABSTRACT

In the last year transcatheter mitral valve implantation (TMVI) has seen a major jump in development. This technique offers the potential to treat a great number of elderly and/or high-risk patients with severe mitral regurgitation (MR). Such patients are declined surgical intervention either because the institutional Heart Team considers the risk of intervention to exceed the potential benefit, or because the patients and their families believe the morbidity of mitral surgery to be excessive. The advent of a less invasive transcatheter treatment could, therefore, potentially appeal to both clinicians and patients alike. In this overview paper, we describe briefly these recent developments in TVMI technologies as an introduction to the dedicated TVMI technical device parade later in this supplement.

Keywords: mitral regurgitation, mitral valve, transcatheter mitral valve implantation, transcatheter mitral valve replacement

Finally! The past year has seen transcatheter mitral valve implantation (TMVI) begin in earnest. As the prevalence of mitral valve disease is almost three times that of aortic valve disease¹, this technique offers the potential to treat a great number of elderly and/or high-risk patients with severe mitral regurgitation (MR). Indeed, the Euro Heart Survey suggested that half of all patients hospitalised with symptomatic severe MR do not undergo potentially curative surgical repair/replacement due to advanced age, comorbid illnesses, and left ventricular dysfunction^{2,3}. More specifically, as few as 16% of patients with severe symptomatic functional MR and 53% of those with degenerative MR actually undergo surgery⁴. Furthermore, population-based data suggest that in the USA only 2% of eligible patients (MR \geq grade 3) undergo mitral valve surgery⁵⁻⁷. Such patients are declined surgical intervention either because the institutional Heart Team considers the risk of intervention to exceed the potential benefit⁸, or because the patients and their families believe the morbidity of mitral surgery to be excessive. The advent of a less invasive transcatheter treatment could, therefore, potentially appeal to both clinicians and patients alike.

Of course, there remains a great deal to learn about which patients could benefit from TMVI. Dr Elliot C. Cutler performed the first surgical mitral valve repair in 1923⁹, yet the mode of repair/replacement and the timing of the intervention still remain topics of some debate^{10,11}. As with transcatheter aortic valve implantation (TAVI), patient selection is determined by anatomical and clinical criteria. Both involve complex decision matrices which require much clarification. Anatomically, TMVI is a veritable minefield: a large, non-circular, saddle-shaped, highly dynamic, non-calcified annulus without the ability for radial anchoring which is tethered to a complex, highly individualised, subvalvular apparatus, and intimately related to the left ventricular outflow tract (LVOT), the coronary sinus, and the left circumflex

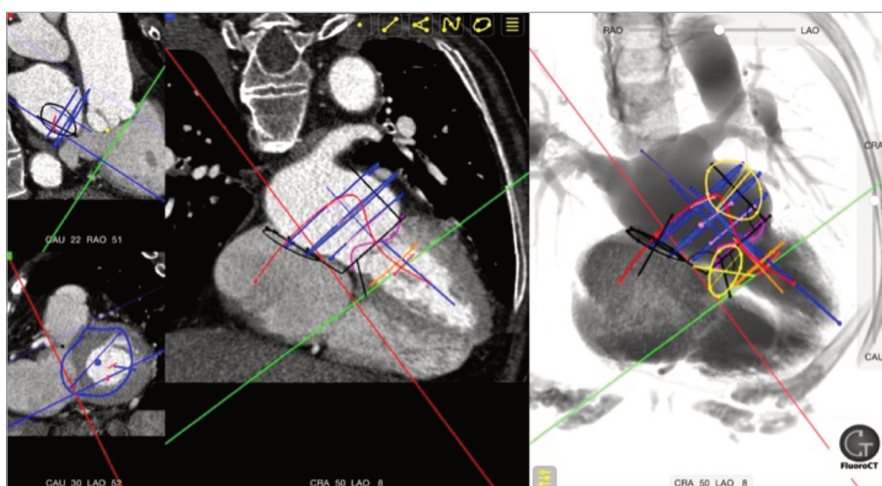


Figure 1 Mitral valve CT analysis. Multislice computed tomography of the mitral valvular complex using the FluoroCT App.

coronary artery. Detailed multislice computed tomography analysis is imperative for patient selection and preoperative procedural planning (**Figure 1**)¹². Clinically, while patient selection continues to evolve, there remain significant questions regarding the implications of large delivery sheath insertion in the left ventricle and the restoration of mitral valve competency in patients with very poor left ventricular function.

On June 12th, 2012, Lars Søndergaard and the Heart Team at Rigshospitalet in Copenhagen, Denmark, performed the first TMVI on an inoperable 86-year-old patient¹³. Using the first-generation CardiAQ valve system (CardiAQ Valve Technologies, Inc., Irvine, CA, USA), a successful transfemoral transseptal implantation was achieved with stable valve position and haemodynamics¹⁴. Although the patient succumbed to multi-organ failure on postoperative day three, TMVI feasibility had been demonstrated.

To date, five transcatheter mitral valve systems have been implanted in humans: CardiAQ valve system (CardiAQ Valve Technologies, Inc.); Tiara™ valve (Neovasc Inc., Richmond, Canada); FORTIS valve (Edwards Lifesciences, Irvine, CA, USA); Tendyne valve (Tendyne Inc., Roseville, MN, USA); and Twelve valve (Twelve, Inc., Redwood City, CA, USA). These devices share common features: nitinol self-expanding frames, trileaflet valves, bovine pericardial leaflets (Tendyne is porcine), fabric sealing skirt (CardiAQ is pericardial), and transapical delivery (CardiAQ also transseptal). Each of these systems, and those in preclinical development (Medtronic Mitral¹⁵ [Medtronic, Minneapolis MN, USA]; HighLife [HighLife Inc., Paris, France]), offer innovative design solutions to overcome the challenging anatomy of the mitral valve complex (**Figure 2**). TMVI systems must be flexible to deal with the complex and variable anatomy, provide large effective orifice areas, and deal with high transvalvular gradients (**Figure 3**). They must anchor without reliance on radial force (axial sealing), accommodate significant dislodgement forces, and avoid LVOT obstruction. Given these obstacles,

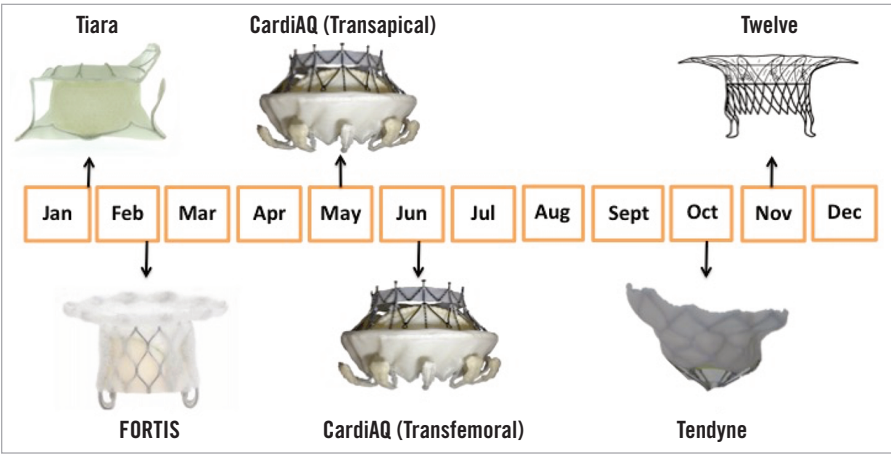


Figure 2 Transcatheter mitral valve development timeline. Tiara (Neovasc Inc.); FORTIS (Edwards Lifesciences); CardiAQ (CardiAQ Valve Technologies, Inc.); Tendyne (Tendyne Inc.); Twelve (Twelve, Inc.).

TMVI design targets		Potential concerns	
Anchor & seal	Adaptable	Stent fatigue/fracture	Leaflet durability
User friendly	Durable	Valve dislodgement	PVL & haemolysis
Avoid interference	Reposition/recapture	LVOT obstruction	Large size matrix

Figure 3 TMVI design targets and potential concerns. LVOT: left ventricular outflow tract; PVL: paravalvular leak

additional areas of concern include stent fatigue and fracture, valve thrombosis, embolisation, leaflet durability, and paravalvular leak with resultant haemolysis.

On January 30th, 2014, Drs Anson Cheung and John Webb successfully implanted the first-in-human Tiara valve (Neovasc Inc.)¹⁶. The valve frame is asymmetric to fit the D-shaped mitral annulus. The 32 Fr transapical delivery catheter allows prosthesis recapture and repositionability, and the system anchors and seals using an atrial skirt and ventricular anchoring arms¹⁷. To date, four patients have been treated with successful device position and function in all cases. All patients were alive at 30 days.

In February and March 2014, Drs Martyn Thomas and Vinnie Bapat treated the first human patients with the FORTIS transcatheter valve (Edwards Lifesciences)¹⁸. The system is delivered via a 42 Fr sheathless delivery catheter, and anchors and seals using an atrial flange and symmetric paddles that clip the mitral leaflets on the ventricular side. Among 12 reported cases, successful delivery and valve function occurred in 11 cases, and 30-day mortality occurred in 25%. In May 2015, Edwards Lifesciences announced suspension of the FORTIS programme to investigate more thoroughly the presence of valve thrombosis.

On May 13th, 2015, almost two years after performing the first-in-human TMVI with the first-generation CardiAQ valve, Lars Søndergaard and the Rigshospitalet Heart Team implanted the second-generation CardiAQ implant (CardiAQ Valve Technologies, Inc.), using a transapical delivery system. A month later, Francesco Romeo and Gian Paolo Ussia performed the first transfemoral transseptal implant of the second-generation device in Tor Vergata Hospital in Rome, Italy¹⁹. This system achieves sealing and anchoring using both left ventricular and left atrial anchors. Among eight treated patients, successful valve delivery and function was reported in seven cases. The 30-day mortality was 50%.

October 2014 witnessed the first human implants of the Tendyne valve (Tendyne Inc.) by Mr Neil Moat and the Heart Team at the Royal Brompton, London. The valve consists of a D-shaped frame that houses porcine pericardial leaflets. The prosthesis can be repositioned and

is retrievable, and achieves sealing and anchoring by an atrial skirt and a left ventricular apical tether. Successful prosthesis delivery and function was achieved in all 12 patients treated. There were no 30-day deaths²⁰.

Therefore, as PCR London Valves moves east (temporarily) to Berlin from its spiritual home in London, another important transition is evident. Transcatheter heart valve technology has moved south from the aortic to the mitral valve, and TMVI has emerged as a clinical reality. Much work is required to iterate these devices and to optimise patient selection. This journey starts at PCR London Valves (Berlin) 2015.

CONFLICT OF INTEREST STATEMENT

D. Mylotte has no conflicts of interest to declare. N. Piazza is a member of the Scientific Advisory Board of Medtronic and a consultant and equity shareholder with HighLife.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005-11.
2. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24:1231-43.
3. Mirabel M, Iung B, Baron G, Messika-Zeitoun D, D  taint D, Vanoverschelde JL, Butchart EG, Ravaud P, Vahanian A. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J*. 2007;28:1358-65.
4. Bach DS, Awais M, Gurm HS, Kohnstamm S. Failure of guideline adherence for intervention in patients with severe mitral regurgitation. *J Am Coll Cardiol*. 2009;54:860-5.
5. Gammie JS, Sheng S, Griffith BP, Peterson ED, Rankin JS, O'Brien SM, Brown JM. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann Thorac Surg*. 2009;87:1431-7; discussion 1437-9.
6. Patel JB, Borgeson DD, Barnes ME, Rihal CS, Daly RC, Redfield MM. Mitral regurgitation in patients with advanced systolic heart failure. *J Card Fail*. 2004;10:285-91.
7. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2008;118:e523-661.
8. Andalib A, Mamane S, Schiller I, Zakem A, Mylotte D, Martucci G, Lauzier P, Alharbi W, Cecere R, Dorfmeister M, Lange R, Brophy J, Piazza N. A systematic review and meta-analysis of surgical outcomes following mitral valve surgery in octogenarians: implications for transcatheter mitral valve interventions. *EuroIntervention*. 2014;9:1225-34.
9. Cohn LH, Tchanchaleishvili V, Rajab TK. Evolution of the concept and practice of mitral valve repair. *Ann Cardiothorac Surg*. 2015;4:315-321.
10. Kang DH, Park SJ, Sun BJ, Cho EJ, Kim DH, Yun SC, Song JM, Park SW, Chung CH, Song JK, Lee JW, Park PW. Early surgery versus conventional treatment for asymptomatic severe mitral regurgitation: a propensity analysis. *J Am Coll Cardiol*. 2014;63:2398-407.
11. Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, Smith PK, Hung JW, Blackstone EH, Puskas JD, Argenziano M, Gammie JS, Mack M, Ascheim DD, Bagiella E, Moquete EG, Ferguson TB, Horvath KA, Geller NL, Miller MA, Woo YJ, D'Alessandro DA, Ailawadi G, Dagenais F, Gardner TJ, O'Gara PT, Michler RE, Kron IL. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. 2014;370:23-32.
12. Blanke P, Dvir D, Naoum C, Cheung A, Ye J, Th  riaux-Lauzier P, Spaziano M, Boone RH, Wood DA, Piazza N, Webb JG, Leipsic J. Prediction of fluoroscopic angulation and coronary sinus location by CT in the context of transcatheter mitral valve implantation. *J Cardiovasc Comput Tomogr*. 2015;9:183-92.
13. S  ndergaard L, De Backer O, Franzen OW, Holme SJ, Ihlemann N, Vejlsr  up NG, Hansen PB, Quadri A. First-in-Human Case of Transfemoral CardiAQ Mitral Valve Implantation. *Circ Cardiovasc Interv*. 2015 Jul;8(7).

14. De Backer O, Piazza N, Banai S, Lutter G, Maisano F, Herrmann HC, Franzen OW, Søndergaard L. Percutaneous transcatheter mitral valve replacement: an overview of devices in preclinical and early clinical evaluation. *Circ Cardiovasc Interv.* 2014;7:400-9.
15. Piazza N, Bolling S, Moat N, Treede H. Medtronic transcatheter mitral valve replacement. *EuroIntervention.* 2014;10:U112-4.
16. Cheung A, Webb J, Verhey S, Moss R, Boone R, Leipsic J, Ree R, Banai S. Short-term results of transapical transcatheter mitral valve implantation for mitral regurgitation. *J Am Coll Cardiol.* 2014;64:1814-9.
17. Cheung A, Stub D, Moss R, Boone RH, Leipsic J, Verhey S, Banai S, Webb J. Transcatheter mitral valve implantation with Tiara bioprosthesis. *EuroIntervention.* 2014;10:U115-9.
18. Bapat V, Buellesfeld L, Peterson MD, Hancock J, Reineke D, Buller C, Carrel T, Praz F, Rajani R, Fam N, Kim H, Redwood S, Young C, Munns C, Windecker S, Thomas M. Transcatheter mitral valve implantation (TMVI) using the Edwards FORTIS device. *EuroIntervention.* 2014;10:U120-8.
19. Ussia GP, Quadri A, Cammalleri V, De Vico P, Muscoli S, Marchei M, Ruvolo G, Søndergaard L, Romeo F. Percutaneous transfemoral-transseptal implantation of second-generation CardiAQ™ mitral valve bioprosthesis: first procedure description and 30-day follow-up. *EuroIntervention* 2015;11:1126-1131.
20. Moat N, Duncan A, Lindsay A, Quarto C, Blanke P, Leipsic J, Grayburn P, Davies S. Transcatheter mitral valve replacement for the treatment of mitral regurgitation: in-hospital outcomes of an apically tethered device. *J Am Coll Cardiol.* 2015;65:2352-3.

**QUANTITATIVE MULTI-SLICE
COMPUTED TOMOGRAPHY
ASSESSMENT OF THE MITRAL
VALVULAR COMPLEX FOR
TRANSCATHETER MITRAL
VALVE INTERVENTIONS PART
1: SYSTEMATIC MEASUREMENT
METHODOLOGY AND INTER-
OBSERVER VARIABILITY**

Quantitative multi-slice computed tomography assessment of the mitral valvular complex for transcatheter mitral valve interventions part 1: systematic measurement methodology and inter-observer variability.

Thériault-Lauzier P, Mylotte D, Dorfmeister M, Spaziano M, Andalib A, Mamane S, Chetrit M, Blanke P, Cecere R, Buithieu J, Martucci G, Tchetché D, Modine T, van Mieghem N, Lange R, Windecker S, Bilodeau L, Leipsic J, Piazza N.

EuroIntervention 2016;12:e1011-e1020.

ABSTRACT

Aims

Transcatheter mitral valve replacement (TMVR) is an emerging technology with the potential to treat patients with severe mitral regurgitation at excessive risk for surgical mitral valve surgery. Multimodal imaging of the mitral valvular complex and surrounding structures will be an important component for patient selection for TMVR. Our aim was to describe and evaluate a systematic multi-slice computed tomography (MSCT) image analysis methodology that provides measurements relevant for transcatheter mitral valve replacement.

Methods and results

A systematic step-by-step measurement methodology is described for structures of the mitral valvular complex including: the mitral valve annulus, left ventricle, left atrium, papillary muscles and left ventricular outflow tract. To evaluate reproducibility, two observers applied this methodology to a retrospective series of 49 cardiac MSCT scans in patients with heart failure and significant mitral regurgitation. For each of 25 geometrical metrics, we evaluated inter-observer difference and intra-class correlation. The inter-observer difference was below 10% and the intra-class correlation was above 0.81 for measurements of critical importance in the sizing of TMVR devices: the mitral valve annulus diameters, area, perimeter, the inter-trigone distance, and the aorto-mitral angle.

Conclusions

MSCT can provide measurements that are important for patient selection and sizing of TMVR devices. These measurements have excellent inter-observer reproducibility in patients with functional mitral regurgitation.

Keywords: congestive heart failure, mitral regurgitation, multi-slice computed tomography, transcatheter heart valve, transcatheter mitral valve replacement

INTRODUCTION

Following the successes of transcatheter aortic valve replacement (TAVR), transcatheter mitral valve replacement (TMVR) has emerged as a promising therapeutic option for patients with mitral regurgitation who are at excessive surgical risk^{1,2}. Novel transcatheter devices aim to replace the dysfunctional mitral valve without the need for open heart surgery.

The anatomy of the mitral valve is more complex than that of the aortic valve. One has to appreciate the anatomical features that are in close proximity to the mitral valve when planning transcatheter mitral valve therapy. The anatomy of the mitral valve is further complicated by its saddle-shaped annulus that undergoes a series of dynamic changes during the cardiac cycle.

Given the inherent anatomical complexity of the mitral valvular complex, pre-procedural screening is likely to be of considerable importance for patient and device selection during TMVR. Echocardiography remains the gold standard imaging modality, allowing quantitative and qualitative anatomical assessment³. However, multi-slice computed tomography (MSCT) has emerged as the imaging modality of choice for assessment of the aortic valvular complex in the setting of TAVR⁴. Compared to echocardiography, MSCT affords more accurate measurements of the aortic annulus and, when applied to transcatheter heart valve sizing, results in superior procedural and clinical outcomes^{5,6}. MSCT has been investigated to assess the function and anatomy of the mitral valve. In the context of mitral regurgitation, MSCT can be used to determine the disease aetiology^{7,8}, to quantify the severity^{9,10}, to describe changes in the geometry of the valvular complex^{11,12}, and to diagnose mitral valve prolapse^{13–15}. However, a detailed methodology for analysing the geometry of the mitral valvular complex specifically for the purposes of TMVR has not yet been described.

Herein, we present a systematic approach for the interrogation of an MSCT data set for potential TMVR recipients. This measurement methodology was applied to patients with significant mitral regurgitation to study inter-observer reliability.

METHODS

MSCT image acquisition protocol

MSCT imaging protocols have been described for patients undergoing TAVR^{4,16,17}. Similar guidelines can be followed when designing an acquisition protocol for TMVR. The heart as well as access sites should be scanned. The cardiac acquisition should be performed using ECG gating on a scanner with at least 64 detector rows, and a slice thickness of less than 1 mm should be selected. The mitral valvular complex being a dynamic structure, multiphase imaging should be used to obtain images during systole and diastole. Retrospective gating is suggested for more flexibility in image reconstruction, which is particularly important in

patients with arrhythmias. Supplemental beta-blockade is not generally necessary; at heart rates above 70 bpm, multi-segment reconstruction should be used. The dose of ionising radiation imparted to patients should be minimised but not at the expense of image quality. Indeed, potential patients for TMVR are likely to be elderly and to suffer from multiple comorbidities, which therefore mitigates the benefit of dose reduction. The tube potential should be selected as 100 kVp in patients weighing less than 90 kg or with a body mass index less than 30 kg/m², and otherwise should be selected as 120 kVp. Tube current is dependent on specific scanners. Intravenous iodinated contrast agent at a rate of 3–5 mL/s should be injected to visualise cardiac and vascular structures. The timing of the contrast agent injection can be done via a test bolus or via bolus triggering. The duration of the injection should be such that the left atrium, left ventricle, and ascending aorta are opacified.

MSCT data set analysis: Measurement methodology

The methodology proposed in this article was developed using 3mensio Structural Heart 6.1 (Pie Medical Imaging BV, Maastricht, The Netherlands). This software package offers a dedicated work-flow for mitral valve analysis¹⁸. However, the methodology should be general enough to be applicable to any software providing double-oblique multi-planar reconstructions (MPR). The mitral valvular complex comprises the left atrium, mitral annulus, valve leaflets, chordae tendineae, papillary muscles, and the left ventricular cavity. For the purposes of this manuscript, these structures are described according to their anatomical position rather than the more traditional Valentine position. Attitudinal anatomy assumes the subject is facing the observer and standing upright¹⁹.

MITRAL VALVE ANNULUS

Similar to transcatheter aortic valve implantation (TAVI), assessment of the valve annular dimensions is of critical importance for valve sizing in the setting of TMVR. However, unlike the aortic valve, the mitral valve is rarely calcified. Accurate and precise sizing of the device may reduce the risk of excessive oversizing, which may result in annular rupture or left ventricular outflow tract (LVOT) obstruction with a suboptimal cardiac output. It may also mitigate complications of insufficient oversizing that may result in paravalvular leak or prosthesis embolisation.

Two perpendicular diameters of the mitral valve are measured: the aorto-mural and intercommissural diameters. The aorto-mural diameter is analogous to the anteroposterior diameter defined in echocardiography. To ensure repeatability of measurements, the aorto-mural diameter of the mitral annulus is measured along the line that bisects the aortic root at the level of the mitral annulus (**Figure 1**). This line also crosses the geometrical centre of the annulus. The intercommissural diameter is measured in the direction perpendicular to the

aorto-mural diameter and passing through the annular geometrical centre. Note that while the intercommissural diameter is often parallel with the coaptation line of the leaflets, it does not represent the leaflet apposition length. The tridimensional annulus is projected onto its best-fit plane before the annular area and perimeter are measured.

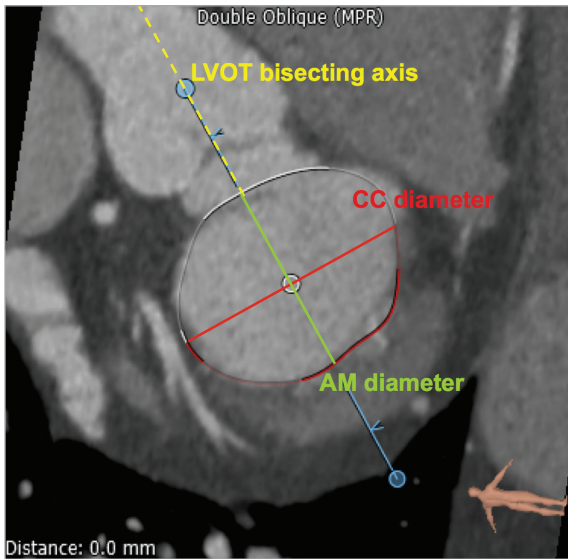


Figure 1 Mitral annular dimensions. The aorto-mural (AM) and intercommissural (CC) diameters on a short-axis MPR. The oval annulus is displayed. The aorto-mural diameter is measured parallel to the LVOT axis, while the intercommissural diameter is perpendicular.

The accuracy and reproducibility of the measurements described above depend on consistent selection of the mitral annulus. We propose the following methodology:

- Step 1: A double oblique MPR is computed such that two views are displayed: (1) a long-axis slice with a plane that passes through the left ventricular apex and the mitral valve centre point, and (2) a short-axis view orthogonal to the long axis.
- Step 2: The user can rotate the long-axis plane around the mitralvalve-to-apex axis in order to choose a view to begin selecting the annulus. We suggest selecting a plane in a region where the mitral annular hinge point is easily discernible, e.g., the left fibrous trigone.
- Step 3: The annulus contour is defined by successively selecting 10 to 20 closed spline control points in the long-axis oblique MPR. The long-axis plane is rotated incrementally after each control point is positioned. The annulus-leaflet attachment point may have a different morphology depending on the region of the annulus (fibrous or muscular) and on the physical properties of the leaflet. These factors impact on the annulus selection procedure. Therefore, we describe the method in each region separately.
 - Muscular annular region: In this region, the selection is done in the long-axis view. The four annular sections shown in **Figure 2** demonstrate different situations en-

- countered. In all cases, we extrapolate the left ventricle and left atrium endocardial borders over the leaflet and select the point at the intersection of the two lines. Because of the increased curvature of the atrial cavity, the point of attachment is often selected on the atrial aspect of thickened or calcified leaflets. This accounts for the observation that annular calcification is typically encountered beneath the surface of the mitral leaflets²⁰.
- **Fibrous annular region:** The method described for the muscular annular region cannot be readily applied in the region of the aorto-mitral curtain. In this region, the annulus is selected using the short-axis view. For planes intersecting the annulus (**Figure 3**), there is a difference in attenuation coefficient and thickness between the annulus and extensions from the fibrous trigones. Therefore, the leaflet is defined as the central lower attenuation portion of the curtain. The annulus point is therefore selected at the interface between those two regions.

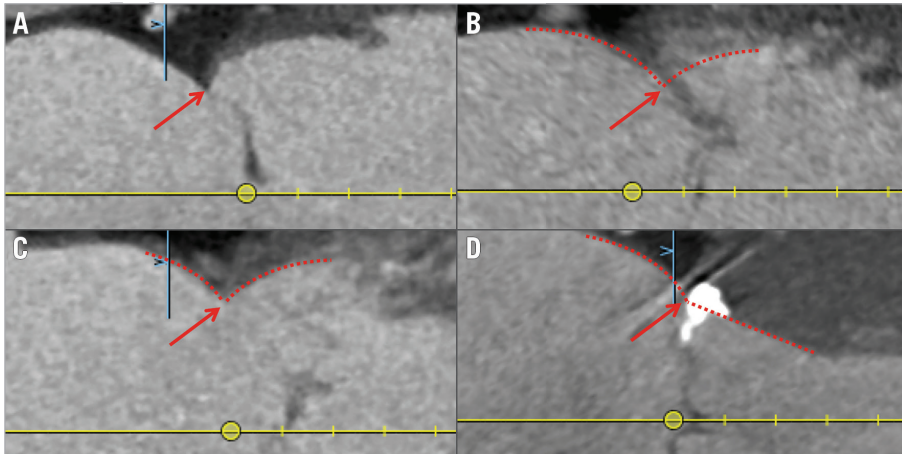


Figure 2 Mitral annulus: muscular region. Different types of annulus-leaflet attachments in the muscular annular region in the long-axis view. The types are: A) visible leaflet with clearly defined attachment; B) non-visible leaflet with clearly defined attachment; C) visible leaflet with thickened attachment; D) visible leaflet with calcified attachment. The annulus-leaflet attachment is selected at the intersection of the extrapolation of the left ventricle and LA endocardial borders.

PAPILLARY MUSCLES

Papillary muscles may present physical obstacles within the left ventricle that limit the potential space for prosthesis deployment. The number of papillary muscles and their relative distance from the mitral annulus may have implications for certain TMVR prototypes.

This analysis focuses on the muscular projections that extend closest to the plane of the annulus, as these are the most likely to have an impact on TMVR devices. Measurements are

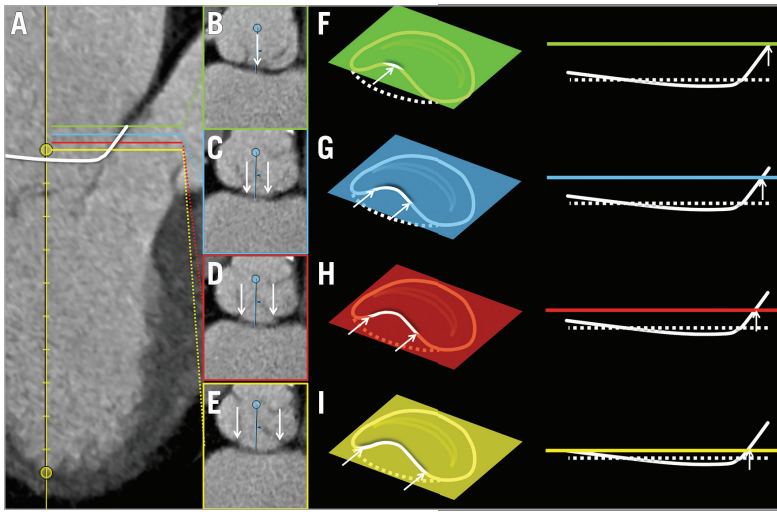


Figure 3 Mitral annulus: fibrous region. Annular-leaflet attachments in the fibrous (aortic) annular region. In panel A, the long-axis MPR shows sections through the annulus at four levels. Panels B to E represent short-axis sections through the annulus at regular intervals from the base-to-apex direction. In panels F to I, schematic representations of the image planes in B to E are shown relative to the mitral annulus in a perspective view and in a side view. In all cases, arrows indicate points of the annulus intersected by the image plane.

performed for the papillary muscle head closest to the mitral annulus for each of the infero-septal (IS) and superolateral (SL) divisions of the chordopapillary support²¹. After selection of the two muscle heads, the tridimensional linear distance between the heads is measured (**Figure 4**). The tridimensional linear distance between the geometrical centre and each papillary muscle head, as well as the perpendicular distance between the annulus best-fit plane and each papillary muscle head are measured. Finally, the distance between the papillary muscle head and its associated endocardial wall is measured perpendicular to the axis between the geometrical centre and the left ventricular apex.

In order to ensure reproducible measurements, we propose the following methodology for the selection of the muscle heads:

- Step 1: The selection of the papillary muscle heads is performed relative to the mitral annulus. The mitral annulus must first be created as described in the previous section.
- Step 2: The muscle heads are selected in short-axis view. The distance between the plane of the MPR and the annulus is gradually increased until a papillary muscle appears within the left ventricular cavity.
- Step 3: The MPR short-axis plane is set at the distance where only the tip of the papillary muscle is visible. A marker is placed on the papillary muscle head in the short-axis view.

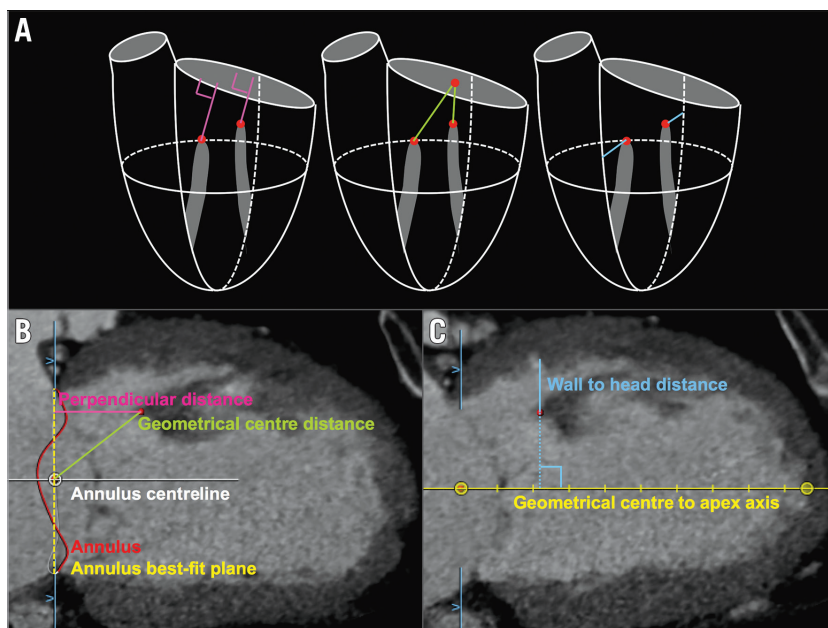


Figure 4 Papillary muscle evaluation. A) Proposed papillary muscle measurements in three dimensions. Panels B and C illustrate the measurements performed on CT images.

LEFT VENTRICLE

Transcatheter valve implantation at the level of the mitral annulus gives rise to potential interactions between the prosthesis and the anatomical structures on the atrial and/or ventricular side of the annulus. Therefore, accurate assessment of the “structure-free space” or “landing zone” (long and short axis, area, and perimeter) is of importance for TMVR. The anatomical relationship of the mitral valve and the LVOT suggests that there is the potential for LVOT obstruction if a rigid oversized prosthesis is implanted within the mitral annulus. Furthermore, tethering of the chordae in mitral regurgitation could reduce the ventricle wall to annulus distance, thus increasing the risk of LVOT obstruction and systolic anterior motion of the mitral valve.

The left ventricle measurements aim to describe the shape of the cavity and, most importantly, define in detail the region just beneath the mitral annulus, including the LVOT. We measure the left ventricle long-axis diameter, which is defined as the distance between the mitral annulus geometrical centre and the left ventricular apex (**Figure 5**). The width of the left ventricle is measured at two specific distances from the geometrical centre: (1) at 50% of the left ventricle long-axis diameter; and (2) at a point halfway between the papillary muscle heads. In both cases, papillary muscle tissue is considered to be part of the left ventricular cavity.

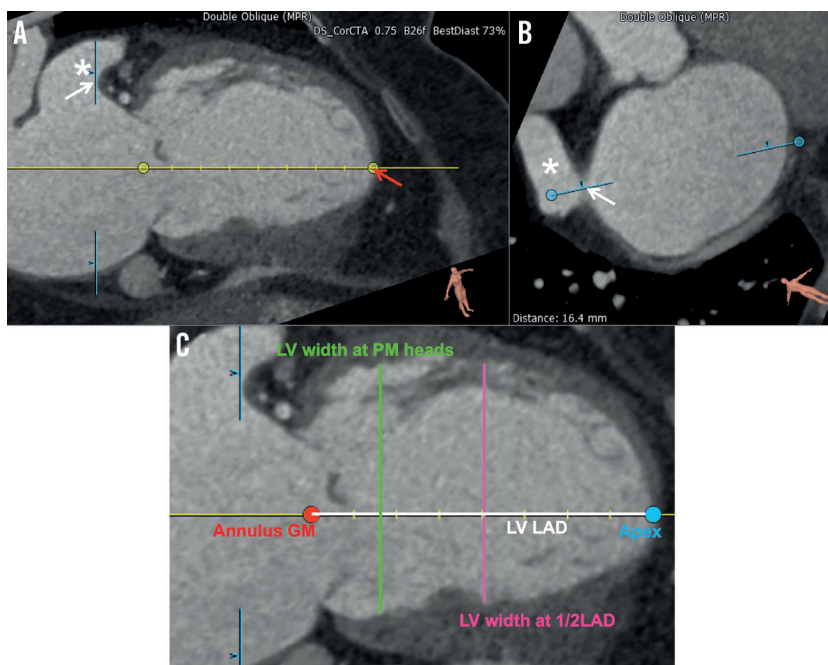


Figure 5 Left ventricular assessment. A) & B) Illustration of the long-axis MPR selected for measurements on the left ventricle (LV). The left atrial appendage is indicated by the star (*). The red arrow indicates the LV apex. The white arrows indicate the anterior aspect of the appendage used as a landmark in the selection of the long-axis view. The MPR planes are indicated by the light blue lines. C) Measurements of the LV in long-axis view. The LV long-axis diameter (LV LAD) and the LV width at half LAD are pictured.

The left ventricular measurements are performed in a long-axis MPR whose plane bisects the left atrial appendage. This view is selected as follows:

- Step 1: The mitral annulus is first selected using a curved spline as described above.
- Step 2: The left ventricular axis is adjusted such that the left ventricular apex marker is placed at the point of the endocardium that is most distal from the annulus geometrical centre (**Figure 5**).
- Step 3: The long-axis plane is then rotated such that it bisects the left atrial appendage as shown by the arrow in **Figure 5**. The measurements are pre-formed in the view thus obtained.

The region just beneath the mitral annulus is of particular interest since it may constitute a landing zone for TMVR prostheses. In a short-axis MPR that is parallel to the annulus best-fit plane, we draw a region of interest that outlines the endocardial border (**Figure 6**). For this analysis, the papillary muscles and trabeculae carneae are considered to be part of the ventricular wall. The short- and long-axis diameters (parallel to the annulus aorto-mural and intercommissural directions), the area, and the perimeter are recorded for each region of

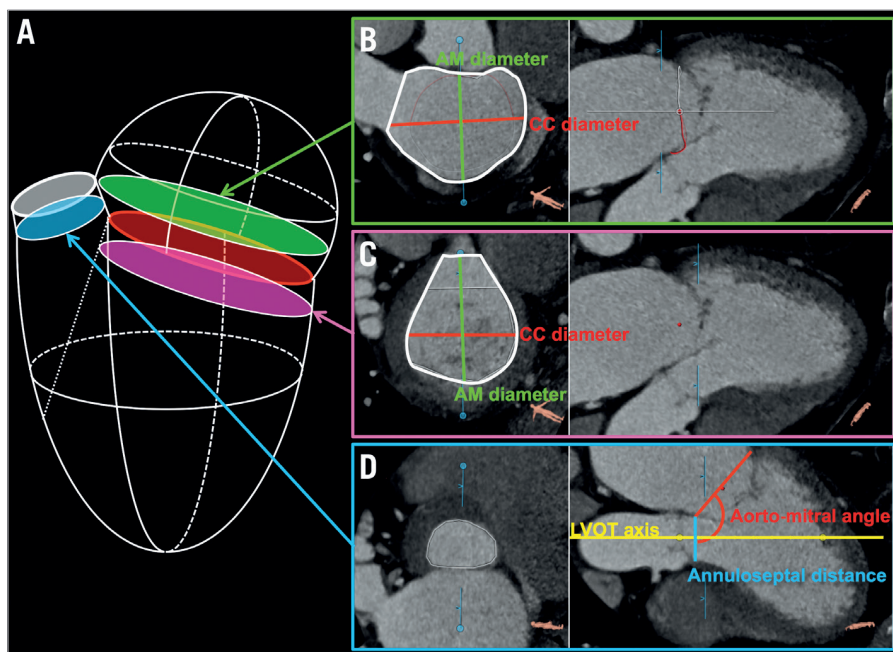


Figure 6 Left atrial, ventricular, and outflow tract dimensions. A) Anatomical location of the MPR planes for the left atrium (B), the left ventricle (C), and the left ventricular outflow tract (D).

interest. These measurements are repeated at 5 mm intervals below the mitral annulus up to 20 mm.

To assess the relationship between the mitral annulus and the LVOT, several measurements are of particular interest in the context of TMVR. The aorto-mitral angle, which lies between the axis of the LVOT and the centreline of the mitral annulus, is noted (**Figure 6**). The distance between the medial aspect of the mitral annulus and the septal aspect of the LVOT is measured. Then, the positions of the right and left fibrous trigones are marked and the aorto-trigonal distance - defined as the perpendicular distance from each trigone to the aortic valve annulus - is recorded (**Figure 7**). It quantifies the distance along the LVOT into which a TMVR device could extend before potentially interacting with the aortic valve leaflets.

LEFT ATRIUM

Transcatheter devices may be delivered using transseptal, transatrial or transapical approaches. The first two methods require direct interaction with the left atrium. MSCT can be used to examine the configuration of pulmonary veins and the anatomy of the atrial septum qualitatively. Furthermore, MSCT can also be used to quantify the geometry of the region.

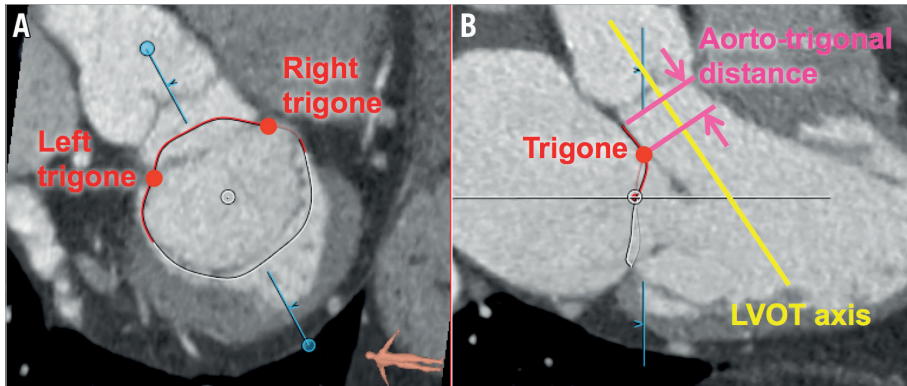


Figure 7 The fibrous trigones and aorto-trigonal distance. A) Short-axis view of the right and left fibrous trigones. B) Long-axis view of the trigones and illustration of the aorto-trigonal distance.

The left atrium measurements are similar to those described for the left ventricle, and aim to characterise the shape of the left atrium and carefully assess the region immediately above the mitral annulus. The left atrium long-axis diameter is measured between the annulus geometrical centre and the posterior atrial wall in the direction of the annulus centreline (**Figure 8**). The left atrium width at 50% of the long-axis diameter is measured perpendicular to the annulus centreline, midway between the annulus geometrical centre and the posterior atrial wall. The left atrial appendage and the pulmonary veins are excluded from the measurements. The distance between the ostium of the left atrial appendage and the mitral annulus is measured in both axial and radial directions (**Figure 8**). As with the left ventricle, left atrium polygons are drawn at 5 mm increments from the mitral annular plane up to a maximum of 20 mm. The

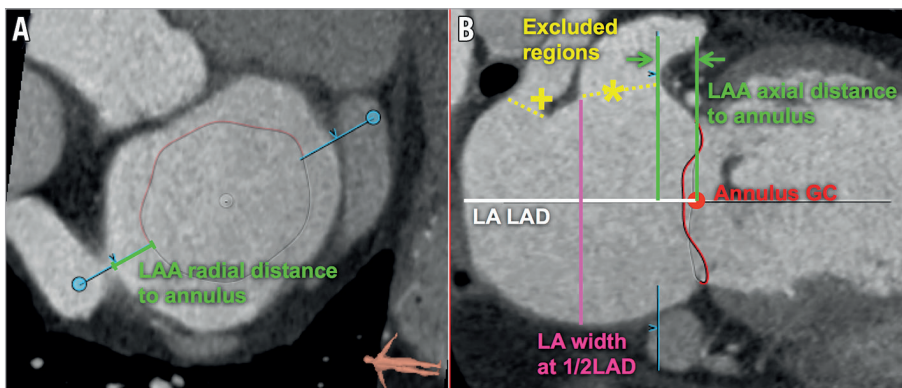


Figure 8 Left atrium assessment. Measurements of the LA in the short-axis (A) and long-axis (B) views. Note, the left atrial appendage (*) and a pulmonary vein (+) are excluded.

short- and long-axis diameters, area and perimeter of the polygons are recorded (**Figure 6**). These measurements, together with their annular and left ventricular counterparts, provide information about potential landing zones for prostheses.

Study population

In this article, we performed a retrospective analysis in subjects recruited from the PTOLEMY-2 (NCT00787293) and PTOLEMY2Canada (NCT00815386) clinical trials of the Viacor percutaneous transvenous mitral annuloplasty system (Viacor, Inc., Wilmington, MA, USA) in 15 European and Canadian centres. Written consent was obtained from patients and the study was conducted with the approval of institutional ethics review boards. The trial was conducted to evaluate the implantation of this device in patients in heart failure with functional mitral regurgitation. The PTOLEMY-2 and PTOLEMY2Canada studies were suspended due to a high rate of complications. At the conclusion of the studies, the MSCT data sets were made available for research purposes to collaborating investigators, including authors of this manuscript. Preoperative MSCT images were available in 32 patients: 15 scans included only a diastolic phase and 17 scans included both a systolic and a diastolic phase.

Statistical analysis

Two independent observers measured 25 different geometrical properties of the mitral valve apparatus using the above-described methodology. The inter-observer agreement was studied using the intra-class correlation and the coefficient of variation, for all scans irrespective of cardiac phase. Thus, 49 individual samples were used from 17 systolic scans and 32 diastolic scans. The statistical analysis was performed using MATLAB R2013a (MathWorks, Natick, MA, USA). Confidence intervals were computed using the bias corrected and accelerated percentile bootstrap method with 2,000 samples.

RESULTS AND DISCUSSION

The baseline characteristics of the 32 patients are presented in **Table 1**. The average age was 70.1 years old, 40.6% of patients were female, and most patients suffered from left ventricular systolic dysfunction with an ejection fraction of 34.8%. Thirty of the 32 patients had moderate or severe mitral regurgitation, while two patients had mild mitral regurgitation.

The variability between the two observers was quantified using the inter-observer difference and the intra-class correlation (**Table 2**). The inter-observer difference was generally below 10%, except for the annulus height and the left atrial appendage distance to the mitral annulus. Both of these structures have a dimension of less than 10 mm and an absolute inter-observer difference approximately equal to the slice thickness. The intra-class correlation shows excellent inter-observer agreement for most measurements. The intra-class correlation

Table 1 Baseline characteristics of study population.

Subjects, n		32
Age*, years		70.1±11.7
Female gender, n (%)		13 (40.6)
Body surface area*, m ²		1.85±0.20
Left ventricular ejection fraction*, %		34.8±11.4
MR severity	Mild, n (%)	2 (6.3)
	Moderate, n (%)	15 (46.9)
	Severe, n (%)	15 (46.9)
MR aetiology	Ischaemic, n (%)	15 (46.9)
	Non-ischaemic, n (%)	9 (28.1)
	Not reported, n (%)	8 (25.0)
NYHA functional class	I, n (%)	0 (0.0)
	II, n (%)	5 (15.6)
	III, n (%)	22 (68.8)
	IV, n (%)	2 (6.3)
	Not reported, n (%)	3 (9.4)

* mean±standard deviation.

is greater than 0.60 except for the annulus height with 0.31. This measurement is highly dependent on precise selection of the fibrous region of the mitral valve annulus.

We presented a detailed step-by-step methodology for analysing an MSCT data set for the purposes of TMVR. This information is of relevance for those involved in the design and development of these novel transcatheter devices, and will be of importance in determining patient suitability in the future. Previous literature on mitral valve MSCT focused on establishing diagnosis and characterising pathological states^{7–15,22}. Furthermore, the measurement methodology and nomenclature are heterogeneous among different authors. The systematic methodology presented here has the potential to facilitate the comparison of studies and the communication of results.

MSCT has proven to be of considerable importance in the assessment of aortic annular diameters and valve sizing for patients undergoing TAVI^{5,6,23}. Imaging techniques, such as two-dimensional transoesophageal echocardiography (2DTEE) and MSCT, provide complementary information on the anatomy and spatial relationships of the mitral valve²⁴. While 2DTEE has a higher temporal resolution and enables assessment of blood flow, it remains a two-dimensional modality that may not provide accurate dimensions of complex tridimensional structures. MSCT offers temporally resolved volumetric imaging with high, nearly isotropic spatial resolution. Given the dynamic, non-planar geometry of the mitral annulus, it can be expected that MSCT may provide more accurate measurements than 2DTEE. As demonstrated here, MSCT has minimal operator dependence for the assessment of the mitral valve

Table 2 Inter-observer variation.

	Mean measurement	Inter-observer difference (95% CI)		Intra-class
		Absolute	Relative	correlation (95% CI)
Annulus				
CC diameter	41.5 mm	−0.2 (−0.7 - 0.2) mm	−0.4 (−1.6 - 0.5)%	0.93 (0.89 - 0.96)
AM diameter	39.6 mm	−1.3 (−1.8 - −0.8) mm	−3.3 (−4.6 - −2.1)%	0.91 (0.85 - 0.95)
Projected area	13.3 cm ²	−0.6 (−0.9 - −0.3) cm ²	−4.2 (−6.5 - −2.4)%	0.93 (0.89 - 0.96)
Projected perimeter	129.8 mm	−1.9 (−2.9 - −1.1) mm	−1.4 (−2.3 - −0.8)%	0.97 (0.94 - 0.98)
3D perimeter	134.8 mm	−3.2 (−4.3 - −2.1) mm	−2.4 (−3.2 - −1.6)%	0.94 (0.90 - 0.97)
Inter-trigone distance	30.3 mm	0.6 (−0.1 - 1.2) mm	2.1 (−0.3 - 4.1)%	0.81 (0.69 - 0.89)
Annulus height	7.1 mm	0.9 (0.4 - 1.4) mm	12.9 (6.0 - 19.9)%	0.32 (0.04 - 0.55)
Papillary muscles				
Distance between heads	38.4 mm	0.5 (−0.5 - 1.6) mm	1.4 (−1.2 - 4.1)%	0.79 (0.66 - 0.88)
Distance to mitral valve centroid IS	31.8 mm	−1.1 (−1.9 - −0.4) mm	−3.6 (−5.9 - −1.3)%	0.88 (0.80 - 0.93)
Distance to mitral valve centroid SL	28.1 mm	−0.8 (−1.3 - −0.1) mm	−2.7 (−4.7 - −0.5)%	0.92 (0.87 - 0.96)
Projected distance to mitral plane IS	23.3 mm	−1.8 (−2.7 - −1.0) mm	−7.9 (−11.7 - −4.1)%	0.79 (0.66 - 0.88)
Projected distance to mitral plane SL	20.3 mm	−1.7 (−2.3 - −1.1) mm	−8.6 (−11.5 - −5.5)%	0.88 (0.80 - 0.93)
Distance to ventricular wall IS	14.2 mm	−1.1 (−2.5 - 0.0) mm	−7.7 (−17.5 - −0.1)%	0.65 (0.45 - 0.78)
Distance to ventricular wall SL	14.7 mm	−1.4 (−2.5 - −0.4) mm	−9.5 (−16.9 - −2.5)%	0.82 (0.70 - 0.89)
Left ventricle				
LAD	96.7 mm	−0.7 (−1.1 - −0.1) mm	−0.7 (−1.2 - −0.1)%	0.98 (0.97 - 0.99)
Width at papillary muscle head level	66.5 mm	−3.6 (−5.2 - −2.3) mm	−5.5 (−7.9 - −3.5)%	0.89 (0.82 - 0.94)
Width at half LAD	60.2 mm	−4.0 (−5.8 - −1.4) mm	−6.6 (−9.6 - −2.3)%	0.86 (0.77 - 0.92)
Left atrium				
LAD	60.2 mm	0.4 (0.0 - 0.9) mm	0.7 (0.0 - 1.4)%	0.99 (0.97 - 0.99)
Width at half LAD	57.2 mm	0.3 (−0.3 - 1.0) mm	0.6 (−0.6 - 1.8)%	0.96 (0.93 - 0.98)
Appendage axial distance to mitral annulus	6.1 mm	0.7 (0.3 - 1.1) mm	10.8 (4.3 - 17.5)%	0.83 (0.72 - 0.90)
Appendage radial distance to mitral annulus	8.1 mm	−0.5 (−1.0 - 0.0) mm	−5.6 (−11.8 - 0.4)%	0.77 (0.62 - 0.86)

Table 2 Inter-observer variation. (continued)

	Mean measurement	Inter-observer difference (95% CI)		Intra-class
		Absolute	Relative	correlation (95% CI)
LVOT				
Aorto-mitral angle	130.8 °	−0.7 (−2.4 - 0.9) °	−0.5 (−1.8 - 0.7)%	0.79 (0.66 - 0.88)
Left aorto-trigonal distance	4.7 mm	0.3 (−0.1 - 0.8) mm	7.1 (−1.6 - 16.2)%	0.71 (0.54 - 0.82)
Right aorto-trigonal distance	10.3 mm	0.6 (0.0 - 1.1) mm	5.5 (0.2 - 10.7)%	0.74 (0.59 - 0.85)
Mitral annulus to septal endocardium	21.0 mm	0.2 (−0.4 - 0.8) mm	1.0 (−1.7 - 3.9)%	0.79 (0.66 - 0.88)

AM: aorto-mural; CC: intercommissural; IS: inferoseptal; LAD: long-axis diameter; SL: superolateral

annulus. When coupled with a dedicated analysis software package, MSCT-derived measurements of the mitral valve have a low inter-observer variability relative to echocardiography. Accurate, standardised, tridimensional measurements of the mitral valve and its surrounding structures, as detailed in this manuscript, will be important for determining patient suitability for these complex structural heart interventions. We believe that, in the future, physicians involved in transcatheter treatment of the mitral valve will need to understand the value and limitations of tomographic measurements. The advantages of MSCT do not diminish the crucial role of 2DTEE for real-time intraoperative guidance of transcatheter procedures. Furthermore, advances in tridimensional transoesophageal echocardiography (3DTEE) may alleviate concerns regarding inter-observer agreement; in preliminary studies 3DTEE showed good agreement with MSCT²⁵ and greater accuracy compared to 2DTEE²⁶ for measurements of the mitral valvular complex.

All proposed TMVR devices are in active development with ongoing device iteration based on preclinical testing and in-depth imaging analysis of the mitral valve. To this end, the standardised method for MSCT analysis of the mitral valvular complex presented here and the application of the anatomical findings may assist valve design and development. An analysis of dynamic stresses and strains applied on these devices may eventually be performed based on MSCT images. Moreover, it is hoped that the continued use of MSCT in the evaluation of inoperable patients with severe mitral regurgitation will help to define anatomical inclusion or exclusion criteria for each device.

Limitations

A few limitations of the study presented here should be noted. This study does not provide a validation of the methodology based on gold standard anatomical measurements. Further work is necessary to address this issue. Overall, the number of CT scans included in the study was limited. However, we believe that the study was sufficiently well powered to study inter-

observer variability. Furthermore, it is important to note that the results reported here depend on the expertise of the user as well as the appropriate CT protocol. For optimal images to be obtained, it is crucial that interventionalists communicate with the medical imaging specialist about the goals to be achieved with regard to contrast-to-noise ratio, temporal and spatial resolution.

The CT scan protocols used in this study were heterogeneous. While this can be perceived as a limitation, it can be hypothesised that the measurement methodology is robust with regard to CT protocol selection given the high inter-observer reliability. Data regarding heart rate and rhythm are not available for a large majority of the subjects included in this study. However, all patients were imaged using an ECG-gated protocol. Heart rate is important because of the limited temporal resolution of CT scanners; heart rhythm is of interest because an irregular rhythm, such as in atrial fibrillation, may lead to erroneous ECG gating and significant image artefacts in multi-segment reconstruction. Retrospective gating may help correct this limitation.

CONCLUSION

The advent of transcatheter mitral valve repair and replacement demands a detailed assessment of the mitral valvular complex. We present a comprehensive step-by-step approach to analysing an MSCT data set for the purposes of TMVR. We demonstrated that this methodology provides measurements of the mitral valve annulus with high intra-class correlation and low inter-observer variation.

IMPACT ON DAILY PRACTICE

Transcatheter mitral valve replacement is a developing treatment modality, which will require highly accurate anatomical measurements of the mitral valvular complex for patient selection and device sizing. This article describes an analysis methodology that can be adopted by clinicians to provide such measurements in a reproducible manner.

CONFLICT OF INTEREST STATEMENT

P. Thériault-Lauzier is a consultant for HighLife Medical. G. Martucci is a proctor for Medtronic. R. Lange is a consultant for Medtronic. N. Piazza is a proctor and consultant for Medtronic. S. Windecker is a scientific advisory board member of Cardialysis BV. The other authors have no conflicts of interest to declare.

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ABBREVIATIONS

LVOT	left ventricular outflow tract
MPR	multi-planar reconstruction
MSCT	multi-slice computed tomography
TAVR	transcatheter aortic valve replacement
TMVR	transcatheter mitral valve replacement

REFERENCES

1. Feldman T, Ali O. Transcatheter mitral valve interventions: current status and future perspective. *EuroIntervention*. 2012;8 Suppl Q:Q53-9.
2. Maisano F, Buzzatti N, Taramasso M, Alfieri O. Mitral transcatheter technologies. *Rambam Maimonides Med J*. 2013;4:e0015.
3. Debonnaire P, Palmen M, Marsan NA, Delgado V. Contemporary imaging of normal mitral valve anatomy and function. *Curr Opin Cardiol*. 2012;27:455-64.
4. Achenbach S, Delgado V, Hausleiter J, Schoenhagen P, Min JK, Leipsic JA. SCCT expert consensus document on computed tomography imaging before transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR). *J Cardiovasc Comput Tomogr*. 2012;6:366-80.
5. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB; PARTNER Trial Investigators. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med*. 2012;366: 1696-704.
6. Hayashida K, Bouvier E, Lefevre T, Hovasse T, Morice MC, Chevalier B, Romano M, Garot P, Mylotte D, Farge A, Donzeau-Gouge P, Cormier B. Impact of CT-guided valve sizing on post-procedural aortic regurgitation in transcatheter aortic valve implantation. *EuroIntervention*. 2012;8:546-55.
7. Killeen RP, Arnous S, Martos R, Abbara S, Quinn M, Dodd JD. Chronic mitral regurgitation detected on cardiac MDCT: differentiation between functional and valvular aetiologies. *Eur Radiol*. 2010;20: 1886-95.
8. Kim K, Kaji S, An Y, Yoshitani H, Takeuchi M, Levine RA, Otsuji Y, Furukawa Y. Mechanism of asymmetric leaflet tethering in ischemic mitral regurgitation: 3D analysis with multislice CT. *JACC Cardiovasc Imaging*. 2012;5:230-2.
9. Alkadhi H, Wildermuth S, Bettex DA, Plass A, Baumert B, Leschka S, Desbiolles LM, Marincek B, Boehm T. Mitral regurgitation: quantification with 16-detector row CT--initial experience. *Radiology*. 2006;238:454-63.
10. Guo YK, Yang ZG, Ning G, Rao L, Dong L, Pen Y, Zhang TM, Wu Y, Zhang XC, Wang QL. Sixty-four-slice multidetector computed tomography for preoperative evaluation of left ventricular function and mass in patients with mitral regurgitation: comparison with magnetic resonance imaging and echocardiography. *Eur Radiol*. 2009;19:2107-16.
11. Delgado V, Tops LF, Schuijff JD, de Roos A, Brugada J, Schalij MJ, Thomas JD, Bax JJ. Assessment of mitral valve anatomy and geometry with multislice computed tomography. *JACC Cardiovasc Imaging*. 2009;2:556-65.
12. Shudo Y, Matsumiya G, Sakaguchi T, Miyagawa S, Yoshikawa Y, Yamauchi T, Takeda K, Saito S, Nakatani S, Taniguchi K, Izutani H, Sawa Y. Assessment of changes in mitral valve configuration with multidetector computed tomography: impact of papillary muscle imbrication and ring annuloplasty. *Circulation*. 2010;122:S29-36.
13. Feuchtner GM, Alkadhi H, Karlo C, Sarwar A, Meier A, Dichtl W, Leschka S, Blankstein R, Gruenenfelder J, Stolzmann P, Cury RC. Cardiac CT angiography for the diagnosis of mitral valve prolapse: comparison with echocardiography. *Radiology*. 2010; 254:374-83.
14. Shah RG, Novaro GM, Blandon RJ, Wilkinson L, Asher CR, Kirsch J. Mitral valve prolapse: evaluation with ECG-gated cardiac CT angiography. *AJR Am J Roentgenol*. 2010;194:579-84.

15. Ghosh N, Al-Shehri H, Chan K, Mesana T, Chan V, Chen L, Yam Y, Chow BJ. Characterization of mitral valve prolapse with cardiac computed tomography: comparison to echocardiographic and intraoperative findings. *Int J Cardiovasc Imaging*. 2012;28: 855-63.
16. Leipsic J, Gurvitch R, Labounty TM, Min JK, Wood D, Johnson M, Ajlan AM, Wijesinghe N, Webb JG. Multidetector computed tomography in transcatheter aortic valve implantation. *JACC Cardiovasc Imaging*. 2011;4:416-29.
17. Schoenhagen P, Hausleiter J, Achenbach S, Desai MY, Tuzcu EM. Computed tomography in the evaluation for transcatheter aortic valve implantation (TAVI). *Cardiovasc Diagn Ther*. 2011;1:44-56.
18. de Vaan J, Verstraeten L, de Jaegere P, Schultz C. The 3mensio Valves™ multimodality workstation. *EuroIntervention*. 2012;7: 1464-9.
19. Anderson R, Kanani M. Mitral valve repair: critical analysis of the anatomy discussed. *Multimed Man Cardiothorac Surg*. 2007 Jan 1;2007(102):mmcts.2006.002147.
20. Fulkerson PK, Beaver BM, Auseon JC, Graber HL. Calcification of the mitral annulus: etiology, clinical associations, complications and therapy. *Am J Med*. 1979;66:967-77.
21. Van Mieghem NM, Piazza N, Anderson RH, Tzikas A, Nieman K, De Laat LE, McGhie JS, Geleijnse ML, Feldman T, Serruys PW, de Jaegere PP. Anatomy of the mitral valvular complex and its implications for transcatheter interventions for mitral regurgitation. *J Am Coll Cardiol*. 2010;56:617-26.
22. Messika-Zeitoun D, Serfaty JM, Laissy JB, Berhili M, Brochet E, Iung B, Vahanian A. Assessment of the mitral valve area in patients with mitral stenosis by multislice computed tomography. *J Am Coll Cardiol*. 2006;48:411-3.
23. Schultz C, Moelker A, Tzikas A, Piazza N, de Feyter P, van Geuns RJ, Serruys PW, Krestin GP, de Jaegere P. The use of MSCT for the evaluation of the aortic root before transcatheter aortic valve implantation: the Rotterdam approach. *EuroIntervention*. 2010;6:505-11.
24. van Bommel RJ, Marsan NA, Delgado V, Borleffs CJ, van Rijnsoever EP, Schalij MJ, Bax JJ. Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk. *Circulation*. 2011;124:912-9.
25. Shanks M, Delgado V, Ng AC, van der Kley F, Schuijff JD, Boersma E, van de Veire NR, Nucifora G, Bertini M, de Roos A, Kroft L, Schalij MJ, Bax JJ. Mitral valve morphology assessment: three-dimensional transesophageal echocardiography versus computed tomography. *Ann Thorac Surg*. 2010;90:1922-9.
26. Hien MD, Grossgasteiger M, Weymann A, Rauch H, Rosendal C. Reproducibility in echocardiographic two- and three-dimensional mitral valve assessment. *Echocardiography*. 2014;31:311-7.

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QUANTITATIVE MULTI-SLICE COMPUTED TOMOGRAPHY ASSESSMENT OF THE MITRAL VALVULAR COMPLEX FOR TRANSCATHETER MITRAL VALVE INTERVENTIONS PART 2: GEOMETRICAL MEASUREMENTS IN PATIENTS WITH FUNCTIONAL MITRAL REGURGITATION

Quantitative multi-slice computed tomography assessment of the mitral valvular complex for transcatheter mitral valve interventions part 2: geometrical measurements in patients with functional mitral regurgitation.
Thériault-Lauzier PP, Dorfmeister M, Mylotte D, Andalib A, Spaziano M, Blanke P, Martucci G, Lange R, Leipsic J, Bilodeau L, Piazza N.
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ABSTRACT

Aims

Transcatheter mitral valve replacement (TMVR) is an emerging technology with the potential to treat patients with mitral regurgitation at excessive risk for mitral valve surgery. Geometrical measurements of the mitral valvular complex may have implications for the design of TMVR devices and for patient selection. This study sought to quantify the dynamic geometry of the mitral valvular complex in patients with significant functional mitral regurgitation (FMR) using multi-slice computed tomography (MSCT).

Methods and results

MSCT images were acquired in 32 patients with symptomatic, significant FMR. Two independent observers analysed image sets using a dedicated software package and a standard measurement methodology. In patients with FMR, the mean mitral annulus intercommissural and aorto-mural diameters were, respectively, 41.5 ± 5.2 mm and 38.7 ± 5.9 mm in systole, and were 41.5 ± 4.4 mm and 40.0 ± 4.7 mm in diastole. In patients without MR, the diameters were, respectively, 33.6 ± 5.1 mm and 28.8 ± 8.0 mm in systole, and 36.2 ± 4.5 mm and 31.6 ± 7.9 mm in diastole. The obstacle-free zone below the mitral annulus averaged more than 20.0 mm and varied by less than 1 mm between systole and diastole, which is not statistically significant. The aorto-mitral angle was $129.7 \pm 10.5^\circ$ in systole and $131.0 \pm 9.4^\circ$ in diastole.

Conclusions

The mitral annulus is larger in dimension, more circular, and less dynamic in patients with FMR. The obstacle-free zone below the mitral annulus is relatively constant during the cardiac cycle. Measurements of the mitral valvular apparatus vary considerably between patients, which suggests that tridimensional imaging will play an important role in the sizing of TMVR devices.

Keywords: mitral regurgitation, mitral valve, multi-slice computed tomography, transcatheter heart valve, transcatheter mitral valve replacement

INTRODUCTION

Mitral regurgitation (MR) is the most prevalent valvular heart disease in adults¹. Unfortunately, due to advanced disease or comor-bidities, patients are often never operated surgically. To fill this therapeutic gap, and bolstered by the success of transcatheter aortic valve implantation (TAVI)², a substantial effort has been directed towards the development of transcatheter mitral valve implantation. A handful of patients have recently been treated with experimental transcatheter mitral valves in Denmark (2012), Canada (2014), and the United Kingdom (2014).

The mitral valvular complex includes the mitral annulus, mitral leaflets, papillary muscles, the left ventricle and the left atrium³. The complex may also interact with the left ventricular outflow tract (LVOT). These structures undergo several geometrical modifications in patients with MR⁴. Some of these changes, regardless of their contribution to the pathogenesis of MR, may be critical in the context of transcatheter mitral valve therapies.

The high spatial and temporal resolution of multi-slice computed tomography (MSCT) makes this imaging modality an ideal tool to study the geometry of the mitral valvular complex. Herein, we apply a systematic MSCT measurement methodology specifically designed for transcatheter mitral valve therapies⁵ to characterise the mitral valvular complex in patients with functional MR (FMR). To draw a comparison with our measurements, we also performed a meta-analysis of studies reporting measurements of the mitral valvular complex in patients without MR. The information gathered in this study may be valuable in determining patient selection criteria for transcatheter mitral valve therapies. This study may also provide important data for the design of transcatheter mitral valve devices.

METHODS

Study population

In this article series, the patients studied were recruited from the PTOLEMY-2 (NCT00787293) and PTOLEMY2Canada (NCT00815386) clinical trials of the Viacor percutaneous trans-venous mitral annuloplasty system (Viacor, Inc., Wilmington, MA, USA) from 15 European and Canadian centres. Written consent was obtained from patients and the trials were conducted with the approval of institutional ethics review boards. The trials were conducted to evaluate the implantation of this device in patients in heart failure with functional MR. The PTOL-EMY-2 and PTOLEMY2Canada studies were suspended due to a high rate of complications. At the conclusion of studies, MSCT data sets were made available for research purposes to collaborating investigators, including authors of this manuscript. Preoperative MSCT images were available in 32 patients: 15 scans included only a diastolic phase and 17 scans included both a systolic and a diastolic phase.

Data acquisition

MSCT scanners from three manufacturers – GE Healthcare (Waukesha, WI, USA) in four patients, Siemens Healthcare (Erlangen, Germany) in 26 patients, and Philips Healthcare (Eindhoven, The Netherlands) in two patients – were used in this study. The scanning protocol varied between each of the centres involved in the PTOLEMY-2 and PTOLEMY2Canada trials but overall it fulfilled the guidelines described in part 1 of this article. Electrocardiographic gating was used in all patients. Diastolic phases were available in 32 patients, with a mean R-R phase of 75.4%. Of these patients, 17 had also been scanned in systole, with a mean R-R phase of 38.5%. Iodinated contrast agent was injected in all patients.

As a part of trial protocols, patients were evaluated using echocardiography. Echocardiographic data were gathered at each centre and were sent to Duke Clinical Research Institute core laboratory, Durham, NC, USA, for centralised analysis. Left ventricular ejection fraction presented in **Table 1** was estimated using Simpson's biplane method of discs.

Table 1 Baseline characteristics of study population.

Subjects, n		32
Age*, years		70.1±11.7
Female gender, n (%)		13 (40.6)
Body surface area*, m ²		1.85±0.20
Left ventricular ejection fraction*,%		34.8±11.4
MR severity	Mild, n (%)	2 (6.3)
	Moderate, n (%)	15 (46.9)
	Severe, n (%)	15 (46.9)
MR aetiology	Ischaemic, n (%)	15 (46.9)
	Non-ischaemic, n (%)	9 (28.1)
	Not reported, n (%)	8 (25.0)
NYHA functional class	I, n (%)	0 (0.0)
	II, n (%)	5 (15.6)
	III, n (%)	22 (68.8)
	IV, n (%)	2 (6.3)
	Not reported, n (%)	3 (9.4)

* mean±standard deviation.

MSCT image analysis

Two trained and independent observers performed the MSCT image analysis on the 32-subject data set using 3mensio Structural Heart 6.1 (Pie Medical Imaging BV, Maastricht, The Netherlands). This software package offers a dedicated workflow for assessment of the mitral valve⁶. It also incorporates measurement tools for tridimensional distances, angles, and regions of interest.

Mitral valvular complex geometry

The measurements performed in this study can be classified based on anatomical structures. We highlight salient points of the systematic measurement methodology in this section.

The mitral annulus was selected using a tridimensional spline with 16 control points. The intercommissural diameter was measured along the line segment that is parallel to the opening of the valve and crosses the geometrical centre of the mitral annulus. The aorto-mural diameter was measured perpendicular to the intercommissural diameter, crossing the geometrical centre of the mitral annulus and bisecting the LVOT. The annulus tridimensional perimeter was measured. The annulus was projected onto its best-fit plane (mitral annulus plane), and

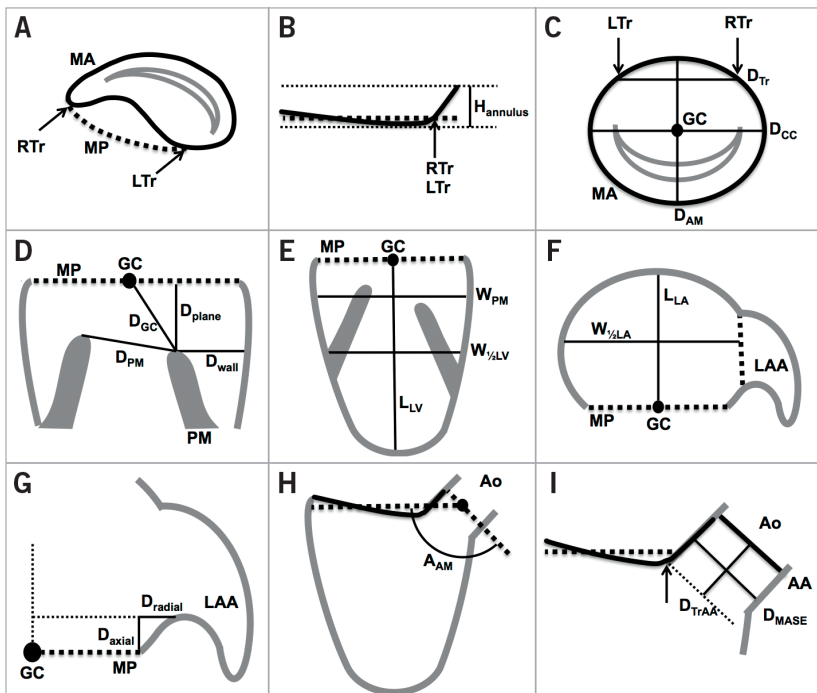


Figure 1 Schematic illustration of mitral valvular complex geometrical measurements. A) - C) Mitral annulus. D) Papillary muscles. E) Left ventricle. F) Left atrium. G) Left atrial appendage. H) & I) Left ventricular outflow tract. AA: aortic annulus; A_{AM} : aorto-mitral angle; Ao: aorta; D_{AM} : aorto-mural diameter; Daxial: axial distance to ostium of LAA; D_{CC} : intercommissural diameter; D_{GC} : papillary muscle head to GC distance; D_{MASE} : mitral annulus to septal endocardium distance; D_{plane} : papillary muscle head to mitral plane distance; D_{PM} : distance between papillary muscle heads; D_{radial} : radial distance to ostium of LAA; D_{Tr} : inter-trigone distance; D_{TrAA} : trigone to aortic annulus distance; D_{wall} : wall to papillary muscle head distance; GC: geometrical centre of mitral annulus; $H_{annulus}$: height of mitral annulus; LAA: left atrial appendage; L_{LA} : left atrium long-axis diameter; L_{LV} : left ventricle length; LTr: left trigone; MA: mitral annulus; MP: mitral annulus plane; RTr: right trigone; $W_{1/2LA}$: width of left atrium at half L_{LA} ; $W_{1/2LV}$: width of left ventricle at half L_{LV} ; W_{PM} : left ventricle width at level of papillary muscle heads

the projected area and perimeter were measured. The annulus height was measured as the sum of the maximum out-of-plane distance on the atrial and ventricular aspects of the valve. The right and left fibrous trigones were marked and the inter-trigone distance was measured. The mitral annulus measurements are illustrated in **Figure 1A-Figure 1C**.

The heads of the inferoseptal and superolateral papillary muscles were defined as the points closest to the mitral plane. The distance between heads was measured. For each head, the following distances were recorded: the distance to the mitral annulus centroid, the projected distance to the mitral annulus plane, and the distance to the ventricular wall. The papillary muscle measurements are illustrated in **Figure 1D**.

The left ventricle long-axis diameter was defined as the greatest distance between the mitral annulus centroid and the endocardial border. The width of the left ventricle was measured at the average level of the papillary muscle heads. It was also measured midway between the mitral annulus centroid and the left ventricle apex. The measurements are summarised in **Figure 1E**.

The left atrium long-axis diameter was defined as the distance between the atrial wall and the annulus geometrical centre in the normal direction of the mitral annulus plane. The width of the atrium was measured midway between the wall and the geometrical centre in a plane that showed the widest section through the orifice of the left atrial appendage. The left atrial appendage and pulmonary veins were excluded from the width measurements. The distance of the left atrial appendage ostium from the mitral annulus plane was measured in axial and radial directions. The axial distance measurement was performed along the mitral plane normal direction, while the radial distance was measured radially outward from the mitral annulus. The measurements are illustrated in **Figure 1F** and **Figure 1G**.

The aorto-mitral angle was defined as the angle subtended by the mitral and aortic valve annulus plane. We also measured the distance between each fibrous trigone and the aortic annulus plane – defined as the plane uniting the nadirs of each aortic leaflet. The distance between the mitral annulus and the septal endocardium was also recorded. **Figure 1H** and **Figure 1I** illustrate these measurements.

Transcatheter mitral valve device landing zone

Transcatheter mitral valve replacement devices will probably extend into the regions of the ventricular and atrial cavities immediately adjacent to the mitral annulus. To characterise this zone, splines were drawn to outline the endocardial border at 5 mm intervals on the atrial and ventricular aspects of the mitral annulus. A total of eight regions of interest were drawn at 5, 10, 15, and 20 mm above and below the mitral annulus. The area, perimeter, aorto-mural and intercommissural diameters of these regions were recorded.

Meta-analysis of studies reporting measurements in patients without mitral regurgitation

A meta-analysis of previously published studies reporting measurements in patients without MR was performed to enable comparison of mitral valvular complex geometrical measurements between patients with and without FMR. This was necessary since the subject population from the PTOLEMY-2 trial did not include patients without MR. Studies performed in adults using computed tomography, echocardiography, and magnetic resonance imaging, as well as *post mortem* anatomical studies were screened for inclusion by a single observer. The criteria for inclusion were as follows: reporting of measurements equivalent to those performed in the current study and reporting of measurements without normalisation.

Statistical analysis

The statistical analysis was performed using MATLAB Release 2013a (MathWorks, Natick, MA, USA). Every measurement from each subject was averaged between two independent observers. For geometrical measurements in diastole and systole, the mean and the standard deviation, as well as the median, first quartile, and third quartile were calculated. A paired-samples analysis was conducted to study dynamic variations between systole and diastole in 17 patients for whom images were available in both of these cardiac phases. Confidence intervals were computed using the bias corrected and accelerated percentile bootstrap method with 2,000 samples. For the meta-analysis of studies in patients without MR, the measurements were combined using the standard methodology⁷.

RESULTS

The baseline characteristics of the 32 patients are presented in **Table 1**. The average age was 70.1 years old, 40.6% of patients were female, and most patients suffered from left ventricular systolic dysfunction with an ejection fraction of 34.8%. Equal numbers of patients with moderate and severe FMR were included in the study.

Mitral valvular complex geometry

Mitral annulus

The mitral annulus was nearly circular with the intercommissural diameter being less than 3 mm larger than the aorto-mural diameter (diastole: 41.5 mm intercommissural vs. 40.0 mm aorto-mural; systole: 41.5 mm intercommissural vs. 38.7 mm aorto-mural) (**Table 2**). For all annulus measurements, the standard deviation was generally well above 10%, which demonstrated a relatively large amount of inter-patient variability. The annulus contracted slightly during systole (**Figure 2**). The dynamic changes of the annulus during the cardiac

Table 2 Mitral valvular complex geometrical measurements in all patients.

	Diastole (n=32)			Systole (n=17)		
	Mean±SD	Median	[Q1, Q3]	Mean±SD	Median	[Q1, Q3]
Annulus						
CC diameter, mm	41.5±4.4	42.0	[39.3, 44.0]	41.5±5.2	42.0	[39.8, 46.5]
AM diameter, mm	40.0±4.7	39.8	[36.9, 43.2]	38.7±5.9	38.1	[33.7, 45.1]
Projected area, cm ²	13.5±2.8	13.7	[11.6, 15.2]	13.0±3.3	13.0	[10.5, 16.1]
Projected perimeter, mm	130.7±14.2	132.3	[122.1, 139.0]	128.1±16.3	128.1	[117.2, 141.3]
3D perimeter, mm	135.5±14.6	137.3	[127.0, 144.7]	133.5±16.6	133.4	[122.3, 146.6]
Inter-trigone distance, mm	30.9±3.9	30.9	[28.4, 33.5]	29.1±3.4	28.9	[26.6, 30.6]
Annulus height, mm	6.9±1.4	7.3	[5.7, 8.0]	7.4±1.4	7.6	[6.3, 8.4]
Papillary muscles						
Distance between heads, mm	40.0±5.3	40.8	[37.0, 43.3]	35.2±5.0	36.4	[31.3, 40.3]
Distance to mitral valve centroid IS, mm	32.9±5.4	32.5	[30.4, 36.8]	29.7±5.4	29.9	[25.2, 34.4]
Distance to mitral valve centroid SL, mm	28.6±5.3	29.6	[24.7, 32.2]	27.1±5.7	28.2	[23.1, 31.9]
Projected distance to mitral plane IS, mm	23.7±5.7	24.3	[19.8, 27.2]	22.5±5.0	21.1	[18.5, 27.1]
Projected distance to mitral plane SL, mm	20.2±4.9	20.9	[16.6, 24.6]	20.6±6.7	20.1	[16.0, 25.3]
Distance to ventricular wall IS, mm	14.9±4.6	15.4	[12.9, 17.2]	12.8±5.2	13.1	[9.1, 15.1]
Distance to ventricular wall SL, mm	16.6±5.8	16.4	[12.9, 19.5]	11.2±5.8	10.2	[8.3, 13.9]
Left ventricle						
Long-axis diameter (LAD), mm	98.8±10.4	99.3	[91.4, 105.9]	92.8±12.3	94.3	[82.0, 101.9]
Width at papillary muscle head level, mm	71.8±10.4	72.3	[62.4, 78.9]	56.4±13.2	60.4	[46.7, 65.1]
Width at half LAD, mm	65.1±11.6	65.5	[56.4, 71.0]	51.1±19.1	54.0	[32.9, 66.3]
Left atrium						
Long-axis diameter (LAD), mm	59.0±8.8	60.5	[53.1, 64.3]	62.6±10.9	63.3	[58.1, 67.2]
Width at half LAD, mm	57.2±8.5	56.5	[51.1, 62.5]	57.0±9.1	56.1	[49.9, 61.2]
Appendage axial distance to mitral annulus, mm	6.6±2.6	6.5	[4.5, 8.7]	5.2±2.5	5.1	[3.4, 6.5]
Appendage radial distance to mitral annulus, mm	8.3±2.5	8.5	[6.3, 9.7]	7.7±2.7	8.2	[5.8, 9.9]
LVOT						
Aorto-mitral angle, degrees	131.7±9.4	132.1	[124.7, 137.0]	129.7±10.5	130.6	[123.8, 136.4]
Left trigone-aortic annulus distance, mm	4.8±1.7	4.5	[3.8, 6.1]	4.6±2.3	4.1	[3.1, 5.8]
Right trigone-aortic annulus distance, mm	10.9±2.5	10.9	[9.2, 12.5]	9.1±2.8	8.3	[7.1, 11.6]
Mitral annulus to septal endocardium, mm	21.1±3.0	21.4	[19.6, 22.6]	20.9±3.5	20.3	[17.0, 23.9]

AM: aorto-mural; CC: intercommissural; IS: inferoseptal; LAD: long-axis diameter; SL: superolateral

cycle were of relatively low amplitude – less than 2% – and were greater along the aorto-mural direction. Small statistically significant dynamic variations were observed for the aorto-mural diameter, the projected perimeter, and the annulus height.

Papillary muscles

The papillary muscle heads were on average more than 20 mm below the mitral annulus plane and more than 27 mm from the mitral annulus centroid (**Table 2**). There was, however, substantial inter-subject variability in these measurements, with standard deviations of 5 to 6

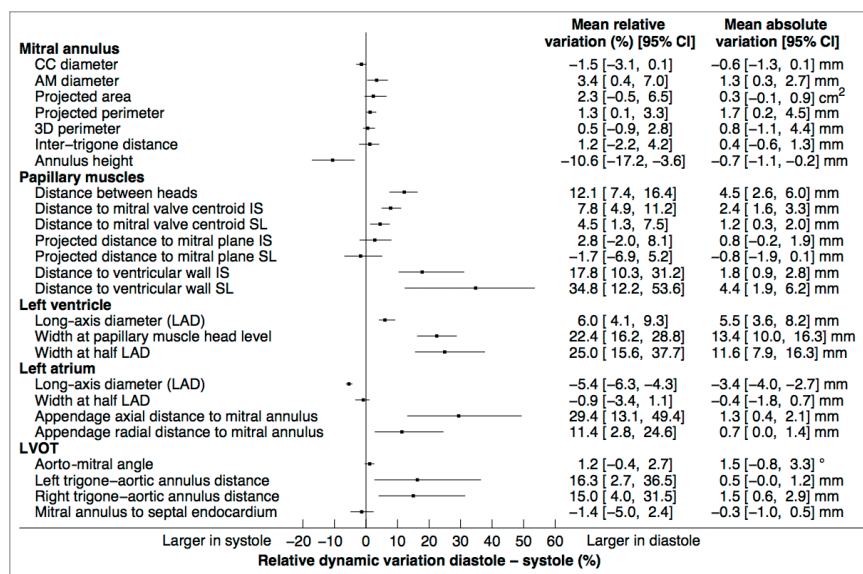


Figure 2 Paired-sample analysis of cardiac cycle dynamic variations in the mitral valvular complex geometrical measurements. 3D: tridimensional; AM: aorto-mural; CC: intercommissural; IA: inferoanterior; LAD: long-axis diameter; 95% CI: 95% confidence interval; SP: superoposterior

mm. The projected distance between the papillary muscle head and the mitral plane varied by less than 1.2 mm (4.5%) between systole and diastole, which was not statistically significant.

Left ventricle

The width of the left ventricle was on average greater at the level of the papillary muscle heads than midway between the mitral annulus geometrical centre and the apex (**Table 2**).

Left atrium

The left atrial width was nearly equal to the long-axis diameter (**Table 2**). The atrial contraction manifested itself during diastole by a 5% reduction in the long-axis diameter and a mostly constant width (**Figure 2**). The ostium of the left atrial appendage was further from the mitral annulus during diastole than during systole in both the radial and axial directions.

LVOT

Several LVOT measurements are noteworthy. The aorto-mitral angle was approximately 131° on average but varied considerably between patients with a standard variation of approximately 10° (**Table 2**). The angle varied slightly but not significantly during systole (**Figure 2**). The right trigone was approximately twice as far as the left trigone from the aortic valve an-

nulus plane (10.9 mm vs. 4.8 mm in diastole and 9.1 mm vs. 4.6 mm in systole). The trigone to aortic annulus distances were significantly greater during diastole (**Figure 2**).

Transcatheter mitral valve device landing zone geometry

The perivalvular landing zones of transcatheter prostheses were evaluated up to 20 mm away from the mitral annulus plane on its atrial and ventricular aspects (**Figure 3**). The aorto-mural diameter, intercommissural diameter, perimeter and surface area are smaller in systole than in diastole in the left ventricle. In the left atrium, these measurements are larger in diastole. Overall, the majority of measurements on the atrial aspect of the valve do not demonstrate a significant dynamic variation between systole and diastole (**Figure 3**). This also holds true for the measurements of the mitral annulus, presented at distance 0 mm.

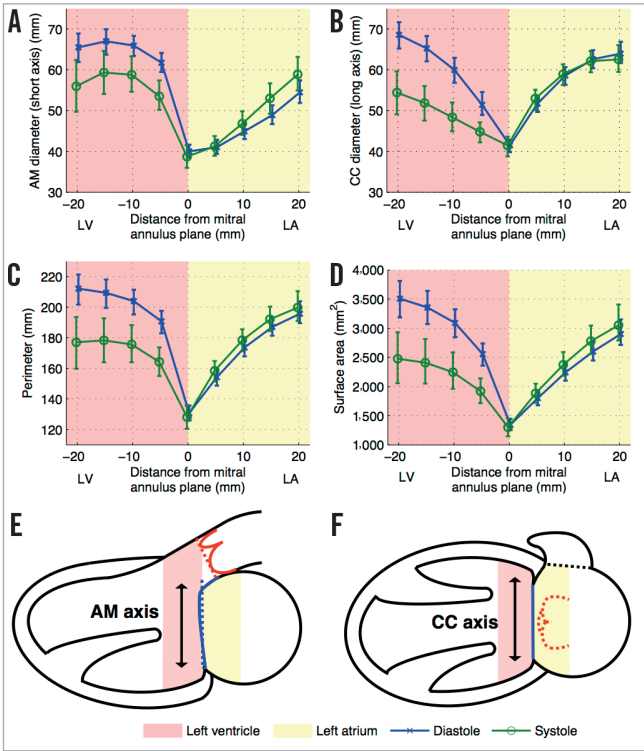


Figure 3 Transcatheter mitral valve device landing zone dynamic geometrical measurements. Each plot (A-D) shows a different measurement of the regions of interest drawn at the endocardial border in double-oblique planes parallel to the mitral annulus plane. The measurements at distance 0 mm represent the mitral annulus projected measurements. The error bars indicate 95% confidence intervals. A) Aorto-mural (AM) diameter. B) Intercommissural (CC) diameter. C) Perimeter. D) Surface area. E) & F) Schematic representation of the ventricular and atrial cavities. LA: left atrium; LV: left ventricle

Meta-analysis of studies reporting measurements in patients without mitral regurgitation

From a total of 238 studies screened, 24 studies fulfilled the inclusion criteria^{8–31}. The results are presented in **Table 3** and are divided by imaging modality in **Table 4**. Of the 25 measurements of the mitral valvular complex described in the current study, 11 measurements had previously been published for patients without MR. We classified measurements into systole or diastole if the cardiac phase was specified.

DISCUSSION

Mitral valvular complex geometrical changes in FMR

FMR occurs as a result of left ventricular dysfunction following an ischaemic or non-ischaemic injury to cardiac myocytes. In affected patients, a series of changes occurs in the dimensions and dynamics of the mitral valvular complex⁴, most of which are reflected in the measurements presented in this study.

Table 3 Meta-analysis of 24 studies reporting mitral valvular complex measurements in patients without mitral regurgitation.

	Diastole		Systole		Unspecified phase	
	Mean±SD	n	Mean±SD	n	Mean±SD	n
Annulus						
CC diameter, mm	36.2±4.5	51	33.6±5.1	51	37.3±4.9	120
AM diameter, mm	31.6±7.9	51	28.8±8.0	51	28.8±3.9	120
Projected area, cm ²	8.3±2.3	151	6.8±2.2	151	7.9±1.9	137
Perimeter, mm	107.9±16.7	40	98.2±31.5	40	96.2±11.2	50
Inter-trigone distance, mm	21.0±1.0	5	23.0±2.0	5	21.7±3.7	43
Height, mm	6.5±1.6	73	8.6±2.0	73	7.0±2.1	53
Papillary muscles						
Distance between heads, mm	24.8±0.4	11	18.6±9.8	11	25.7±6.3	71
Left ventricle						
Long-axis diameter, mm	88.2±8.1	51	68.2±8.6	51	–	–
Width, mm	50.0±4.6	134	32.7±4.8	134	–	–
Left atrium						
Width at half LAD, mm	–	–	36.2±4.0	32	39.4±5.3	72
LVOT						
Aorto-mitral angle, degrees	136.2±12.6	24	129.4±11.0	24	127.6±13.5	38

AM: aorto-mural; CC: intercommissural; LAD: long-axis diameter; n: number of subjects included in the combined measurement; SD: standard deviation

Table 4 Meta-analysis of 24 studies reporting mitral valvular complex measurements in patients without mitral regurgitation for different imaging modalities or post-mortem examination.

	Echocardiography						MRI		CT		Post-mortem				
	Diastole		Systole		Unspecified phase		Diastole		Systole		Unspecified phase		-		
	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	
Annulus															
CC diameter, mm	37.1±4.3	40	34.2±5.5	40	36.6±5.3	78	33.0±3.6	11	31.2±2.5	11	39.0±4.0	23	38.0±3.0	19	-
AM diameter, mm	31.0±8.7	40	27.9±8.7	40	27.8±3.6	78	33.6±3.4	11	32.0±3.6	11	30.0±4.0	23	31.0±4.0	19	-
Projected area, cm ²	8.2±2.3	140	6.7±2.3	140	7.5±1.8	66	8.8±1.7	11	7.9±1.3	11	8.7±1.8	32	9.4±1.4	19	6.1±1.3
Perimeter, mm	107.9±16.7	40	98.2±31.5	40	101.7±9.2	30	-	-	-	-	-	-	-	-	88.0±8.7
Inter-trigone distance, mm	21.0±1.0	5	23.0±2.0	5	-	-	-	-	-	-	24.0±3.0	23	-	-	19.0±2.4
Height, mm	6.5±1.6	73	8.6±2.0	73	7.8±2.1	30	-	-	-	-	6.0±1.8	23	-	-	-
Papillary muscles															
Distance between heads, mm	-	-	-	-	23.2±3.9	51	24.8±0.4	11	18.6±9.8	11	-	-	-	-	32.0±7.0
Left ventricle															
Long-axis diameter, mm	-	-	-	-	-	-	88.2±8.1	51	68.2±8.6	51	-	-	-	-	-
Width, mm	50.7±4.8	83	33.1±5.2	83	-	-	49.0±4.0	51	32.0±4.0	51	-	-	-	-	-
Left atrium															
Width at half LAD, mm	-	-	36.2±4.0	32	40.3±5.2	53	-	-	-	-	-	-	37.0±5.0	19	-
IVOT															
Aorto-mitral angle, degrees	136.2±12.6	24	129.4±11.0	24	127.6±13.5	38	-	-	-	-	-	-	-	-	-

AM: aorto-mitral; CC: intercommissural; LAD: long-axis diameter; n: number of subjects included in the combined measurement; SD: standard deviation

The mitral annulus increases in size (**Figure 2, Table 2, Table 4**) and systolic contraction is reduced, which agrees with previous studies^{11,13,17–19,24,29,32,33}. The annulus also becomes more circular in patients with MR and its height is slightly reduced. This deformation is believed to contribute to the pathophysiology of FMR^{11,33}.

Papillary muscles become misaligned in FMR. We found a large increase in the distance between papillary muscles, which is attributable to the pathological changes in the left ventricular cavity. The misalignment increases the tethering force brought to bear on the mitral valve leaflets. The resulting leaflet tenting has been shown to be a major pathophysiologic mechanism in FMR^{24,30}. We observed that the left ventricular cavity dilates and assumes a more spherical shape in FMR, which is consistent with previous studies^{11,14,25,26}. These changes are considered to be a strong predictor of the severity of FMR. We demonstrated a large increase in the size of the left atrium in FMR. This change is consistent with previously published literature^{12,14,20}.

The aorto-mitral angle showed only a small, non-significant dynamic change in FMR patients, while this angle varied considerably more in patients without MR²⁷. The systolic angle was mostly preserved but the diastolic angle was less in FMR.

Implications for transcatheter mitral valve design and patient selection

This study is the first to evaluate the mitral valvular complex focusing on measurements relevant for transcatheter mitral valve replacement in patients with FMR. Most proposed devices are mounted on a catheter, inserted across the mitral valve and then deployed. The mitral annular dimensions are critical for the design of prostheses. We demonstrated that, in patients with FMR, the mitral annulus is approximately symmetrical between its two major axes. The annulus also contracts less than 2% in systole. This may alleviate concerns that contractions of the mitral annulus may cause excessive stress on the prosthetic valve frame. Nonetheless, we showed that the region of the left ventricle immediately below the mitral annulus is highly dynamic, which may potentially cause substantial stress on a device. Conversely, a rigid ventricular device may be prone to injure the endocardial surface of the cavity.

The frame of transcatheter valve implants may protrude on either aspect of the mitral annulus. In the ventricular cavity, papillary muscles can represent an obstacle to the deployment of transcatheter devices. We demonstrated here that the projected distance between the mitral plane and the heads of papillary muscles - in other words, the axial obstacle-free zone for the prosthesis deployment - is approximately constant during the cardiac cycle.

Prosthetic structures extend radially outward to anchor the device within its landing zone and to prevent perivalvular leaks. We described the space available for the deployment of such anchoring structures up to 20 mm above and below the mitral annulus plane. We showed that the atrium is considerably less dynamic than the ventricle and may thus constitute a more adequate region for hosting a transcatheter device.

On the ventricular aspect, the left ventricular outflow tract is in close proximity to the mitral annulus. Thus, there exists a potential for outflow tract obstruction in some circum-

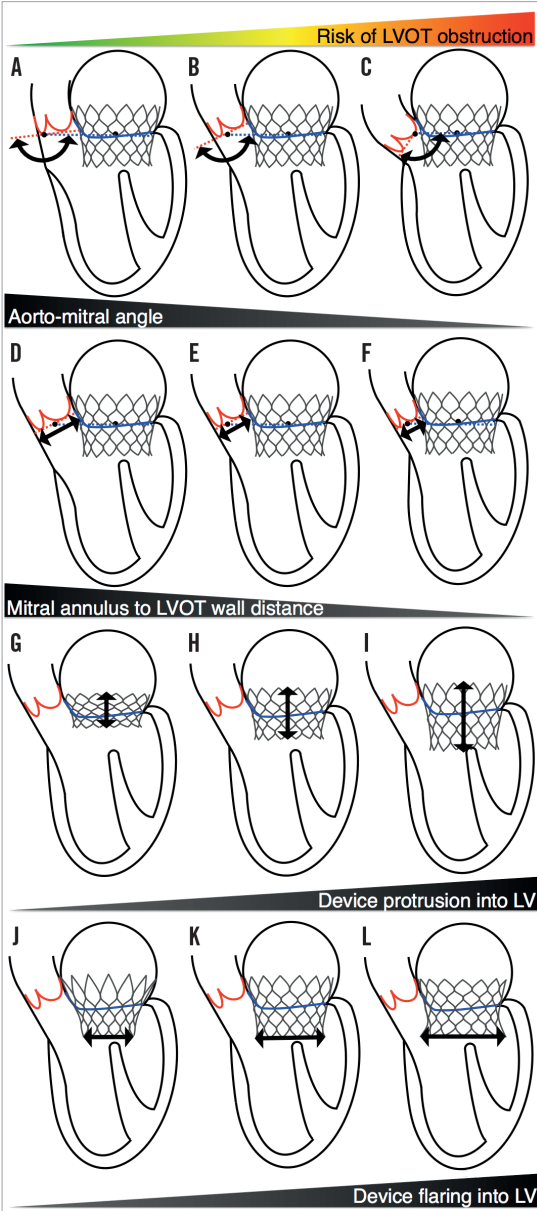


Figure 4 Potential mechanisms of left ventricular outflow tract obstruction in transcatheter mitral valve replacement. A-C) Increasingly acute angle between the mitral plane and the aortic annulus. D-F) Decreasing mitral annulus to septal endocardium distance. G-I) Increasing protrusion of the device in the left ventricular cavity. J-L) Increasing flaring of the device in the left ventricle. LV: left ventricle; LVOT: left ventricular outflow tract

stances (**Figure 4**): 1) an excessively acute angle between the mitral plane and the aortic annulus, 2) small mitral annulus to septal endocardium distance, 3) excessive protrusion of the device in the left ventricular cavity, or 4) excessive flaring of the device at the ventricular end. Furthermore, an implant may directly impinge on the aortic valve; prosthetic valves may have anchoring structures that protrude along the LVOT and directly abut against the aortic valve leaflets. A reduced trigone to aortic annulus distance – demonstrating the proximity of the aortic valve along the LVOT – may pose an increased risk of impingement. Finally, the aorto-mitral curtain that separates the aortic valve from the left atrium is a thin and relatively compliant structure. Thus, a device deployed within the left atrium may cause a deformation of the aorto-mitral curtain and interfere with the geometry of the aortic root. Hypothetically, a direct impingement on the aortic valve may result in aortic regurgitation.

Limitations

The scans were obtained from 15 different institutions, each of which used different CT scanner models. This variability made the systematic selection of an end-systolic and end-diastolic phase impossible. The temporal resolution of MSCT scans is also limited. The results may thus underestimate the dynamics of the structures studied. Also, the number of patients included in the study was limited.

CONCLUSION

The mitral annulus is on average larger in size, more circular, and less dynamic in patients with FMR versus those without MR. The obstacle-free zone below the mitral annulus is relatively constant during the cardiac cycle. The aorto-mitral angle, which may predict the risk of left ventricular outflow tract obstruction after transcatheter device implantation, varies considerably among patients.

IMPACT ON DAILY PRACTICE

Transcatheter mitral valve replacement is a developing treatment modality for inoperable patients with severe symptomatic mitral regurgitation. This article provides a reference range for the size of cardiac structures in the patient population targeted by these interventions.

CONFLICT OF INTEREST STATEMENT

P. Thériault-Lauzier is a consultant for HighLife Medical. G. Martucci is a proctor for Medtronic. R. Lange is a consultant for Medtronic. N. Piazza is a proctor and consultant for Medtronic. The other authors have no conflicts of interest to declare.

ABBREVIATIONS

LVOT	left ventricular outflow tract
MPR	multi-planar reconstruction
MSCT	multi-slice computed tomography
TAVR	transcatheter aortic valve replacement
TMVR	transcatheter mitral valve replacement

REFERENCES

1. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol*. 2011;8: 162-72.
2. Mylotte D, Osnabrugge RL, Windecker S, Lefevre T, de Jaegere P, Jeger R, Wenaweser P, Maisano F, Moat N, Sondergaard L, Bosmans J, Teles RC, Martucci G, Manoharan G, Garcia E, Van Mieghem NM, Kappetein AP, Serruys PW, Lange R, Piazza N. Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. *J Am Coll Cardiol*. 2013;62:210-9.
3. Van Mieghem NM, Piazza N, Anderson RH, Tzikas A, Nieman K, De Laat LE, McGhie JS, Geleijnse ML, Feldman T, Serruys PW, de Jaegere PP. Anatomy of the mitral valvular complex and its implications for transcatheter interventions for mitral regurgitation. *J Am Coll Cardiol*. 2010;56:617-26.
4. Sabbah HN, Rosman H, Kono T, Alam M, Khaja F, Goldstein S. On the mechanism of functional mitral regurgitation. *Am J Cardiol*. 1993;72:1074-6.
5. Thériault-Lauzier P, Mylotte D, Dorfmeister M, Andalib A, Mamane S, Chetrit M, Cecere R, Buithieu J, Martucci G, Tchetché D, Modine T, Van Mieghem N, Lange R, Windecker S, Piazza N. Quantitative multi-slice computed tomography assessment of the mitral valvular complex for transcatheter mitral valve interventions part 1: systematic measurement methodology and inter-observer variability. *Euro-Intervention* 2016;12:e1011-e1020.
6. de Vaan J, Verstraeten L, de Jaegere P, Schultz C. The 3mensio Valves multimodality workstation. *EuroIntervention*. 2012;7:1464-9.
7. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 [updated March 2011]; Higgins JPT, Deeks JJ (editors) Chapter 7: Selecting studies and collecting data. The Cochrane Collaboration; 2011.
8. Ahmad RM, Gillinov AM, McCarthy PM, Blackstone EH, Apperson-Hansen C, Qin JX, Agler D, Shiota T, Cosgrove DM. Annular geometry and motion in human ischemic mitral regurgitation: novel assessment with three-dimensional echocardiography and computer reconstruction. *Ann Thorac Surg*. 2004; 78:2063-8.
9. Caiani EG, Fusini L, Veronesi F, Tamborini G, Maffessanti F, Gripari P, Corsi C, Naliato M, Zanobini M, Alamanni F, Pepi M. Quantification of mitral annulus dynamic morphology in patients with mitral valve prolapse undergoing repair and annuloplasty during a 6-month follow-up. *Eur J Echocardiogr*. 2011;12:375-83.
10. Chandra S, Salgo IS, Sugeng L, Weinert L, Tsang W, Takeuchi M, Spencer KT, O'Connor A, Cardinale M, Settlemier S, Mor-Avi V, Lang RM. Characterization of degenerative mitral valve disease using morphologic analysis of real-time three-dimensional echocardiographic images: objective insight into complexity and planning of mitral valve repair. *Circ Cardiovasc Imaging*. 2011;4:24-32.
11. D'Ancona G, Biondo D, Mamone G, Marrone G, Pirone F, Santise G, Sciacca S, Pilato M. Ischemic mitral valve regurgitation in patients with depressed ventricular function: cardiac geometrical and myocardial perfusion evaluation with magnetic resonance imaging. *Eur J Cardiothorac Surg*. 2008;34: 964-8.
12. Kim DH, Handschumacher MD, Levine RA, Choi YS, Kim YJ, Yun SC, Song JM, Kang DH, Song JK. In vivo measurement of mitral leaflet surface area and subvalvular geometry in patients with asymmetrical septal hypertrophy: insights into the mechanism of outflow tract obstruction. *Circulation*. 2010;122: 1298-307.
13. De Simone R, Wolf I, Mottl-Link S, Hoda R, Mikhail B, Sack FU, Meinzer HP, Hagl S. A clinical study of annular geometry and dynamics in patients with ischemic mitral regurgitation: new insights into asymmetrical ring annuloplasty. *Eur J Cardiothorac Surg*. 2006;29:355-61.

14. Gertz ZM, Raina A, Saghy L, Zado ES, Callans DJ, Marchlinski FE, Keane MG, Silvestry FE. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol*. 2011;58:1474-81.
15. Grewal J, Suri R, Mankad S, Tanaka A, Mahoney DW, Schaff HV, Miller FA, Enriquez-Sarano M. Mitral annular dynamics in myxomatous valve disease: new insights with real-time 3-dimensional echocardiography. *Circulation*. 2010;121:1423-31.
16. Hueb AC, Jatene FB, Moreira LF, Pomerantzeff PM, Kallas E, de Oliveira SA. Ventricular remodeling and mitral valve modifications in dilated cardiomyopathy: new insights from anatomic study. *J Thorac Cardiovasc Surg*. 2002;124:1216-24.
17. Kaji S, Nasu M, Yamamuro A, Tanabe K, Nagai K, Tani T, Tamita K, Shiratori K, Kinoshita M, Senda M, Okada Y, Morioka S. Annular geometry in patients with chronic ischemic mitral regurgitation: three-dimensional magnetic resonance imaging study. *Circulation*. 2005;112:1409-14.
18. Kaplan SR, Bashein G, Sheehan FH, Legget ME, Munt B, Li XN, Sivarajan M, Bolson EL, Zeppa M, Arch MZ, Martin RW. Three-dimensional echocardiographic assessment of annular shape changes in the normal and regurgitant mitral valve. *Am Heart J*. 2000;139:378-87.
19. Kihara T, Gillinov AM, Takasaki K, Fukuda S, Song JM, Shiota M, Shiota T. Mitral regurgitation associated with mitral annular dilation in patients with lone atrial fibrillation: an echocardiographic study. *Echocardiography*. 2009;26:885-9.
20. Killeen RP, Arnous S, Martos R, Abbara S, Quinn M, Dodd JD. Chronic mitral regurgitation detected on cardiac MDCT: differentiation between functional and valvular aetiologies. *Eur Radiol*. 2010;20:1886-95.
21. Kwan J, Shiota T, Agler DA, Popovic ZB, Qin JX, Gillinov MA, Stewart WJ, Cosgrove DM, McCarthy PM, Thomas JD; Real-time three-dimensional echocardiography study. Geometric differences of the mitral apparatus between ischemic and dilated cardiomyopathy with significant mitral regurgitation: real-time three-dimensional echocardiography study. *Circulation*. 2003;107:1135-40.
22. Maffessanti F, Marsan NA, Tamborini G, Sugeng L, Caiani EG, Gripari P, Alamanni F, Jeevanandam V, Lang RM, Pepi M. Quantitative analysis of mitral valve apparatus in mitral valve prolapse before and after annuloplasty: a three-dimensional intraoperative transesophageal study. *J Am Soc Echocardiogr*. 2011;24:405-13.
23. Ormiston JA, Shah PM, Tei C, Wong M. Size and motion of the mitral valve annulus in man. I. A two-dimensional echocardiographic method and findings in normal subjects. *Circulation*. 1981;64:113-20.
24. Otsuji Y, Kumano T, Yoshifuku S, Matsukida K, Koriyama C, Kisanuki A, Minagoe S, Levine RA, Tei C. Isolated annular dilation does not usually cause important functional mitral regurgitation: comparison between patients with lone atrial fibrillation and those with idiopathic or ischemic cardiomyopathy. *J Am Coll Cardiol*. 2002;39:1651-6.
25. Schiros CG, Dell'Italia LJ, Gladden JD, Clark D 3rd, Aban I, Gupta H, Lloyd SG, McGiffin DC, Perry G, Denney TS Jr, Ahmed MI. Magnetic resonance imaging with 3-dimensional analysis of left ventricular remodeling in isolated mitral regurgitation: implications beyond dimensions. *Circulation*. 2012;125:2334-42.
26. Suri RM, Grewal J, Mankad S, Enriquez-Sarano M, Miller FA Jr, Schaff HV. Is the anterior intertrigonal distance increased in patients with mitral regurgitation due to leaflet prolapse? *Ann Thorac Surg*. 2009;88:1202-8.
27. Veronesi F, Corsi C, Sugeng L, Mor-Avi V, Caiani EG, Weinert L, Lamberti C, Lang RM. A study of functional anatomy of aortic-mitral valve coupling using 3D matrix transesophageal echocardiography. *Circ Cardiovasc Imaging*. 2009;2:24-31.

28. Veronesi F, Caiani EG, Sugeng L, Fusini L, Tamborini G, Alamanni F, Pepi M, Lang RM. Effect of mitral valve repair on mitral-aortic coupling: a real-time three-dimensional transesophageal echocardiography study. *J Am Soc Echocardiogr.* 2012;25: 524-31.
29. Watanabe N, Ogasawara Y, Yamaura Y, Wada N, Kawamoto T, Toyota E, Akasaka T, Yoshida K. Mitral annulus flattens in ischemic mitral regurgitation: geometric differences between inferior and anterior myocardial infarction: a real-time 3-dimensional echocardiographic study. *Circulation.* 2005;112: I458-62.
30. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: A quantitative clinical study. *Circulation.* 2000;102:1400-6.
31. Yu HY, Su MY, Liao TY, Peng HH, Lin FY, Tseng WY. Functional mitral regurgitation in chronic ischemic coronary artery disease: analysis of geometric alterations of mitral apparatus with magnetic resonance imaging. *J Thorac Cardiovasc Surg.* 2004;128:543-51.
32. Mihalatos DG, Joseph S, Gopal A, Bercow N, Toole R, Passick M, Grimson R, Norales A, Reichel N. Mitral annular remodeling with varying degrees and mechanisms of chronic mitral regurgitation. *J Am Soc Echocardiogr.* 2007;20:397-404.
33. Kumanohoso T, Otsuji Y, Yoshifuku S, Matsukida K, Koriyama C, Kisanuki A, Minagoe S, Levine RA, Tei C. Mechanism of higher incidence of ischemic mitral regurgitation in patients with inferior myocardial infarction: quantitative analysis of left ventricular and mitral valve geometry in 103 patients with prior myocardial infarction. *J Thorac Cardiovasc Surg.* 2003;125: 135-43.

SUMMARY AND DISCUSSION

VI

SUMMARY

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Chapter 1 is a general introduction to the subject matter of this thesis, outlining the development of transcatheter heart valve (THV) technology. The specific aims and outline of this thesis are presented.

Chapter 2 introduces the reader to the basic anatomy of the aortic valvar complex, its constituent components, and surrounding support structures. The anatomical description is greatly enhanced by high-quality images and is specifically focused on describing aortic anatomy for physicians performing transcatheter aortic valve implantation (TAVI).

Chapter 3 describes the processes of patient selection for TAVI from the perspective of an interventional cardiologist. This review stresses the importance of multimodal pre-procedural imaging and the role of the institutional Heart Team in patient selection. This chapter outlines the relevant investigations that should be performed prior to TAVI, focuses on the selection of the vascular access route, and summarises THV-sizing with multislice computed tomography (MSCT).

Chapter 4 is based on a textbook chapter that details pre-procedural planning and the performance of transfemoral TAVI. It describes the two most commonly used THV platforms: the CoreValve (Medtronic, Dublin, Ireland) and the Edwards SAPIEN (Edwards Lifesciences, Irvine, California, U.S.) valve. In each case, a step-by-step guide to vascular access, delivery catheter positioning, and prosthesis deployment is provided. The aetiology, incidence, and treatment of TAVI-related complications are outlined; (1) Cardiac: paravalvular aortic regurgitation; conduction abnormalities; atrial and ventricular arrhythmias; coronary obstruction; cardiac perforation; aortic root rupture; prosthetic valve dysfunction; embolization; thrombosis; infective endocarditis; and mitral regurgitation and mitral valve injury; and (2) Non-cardiac: stroke; vascular injury; acute kidney injury. Furthermore, the initial results of the major randomized trials of TAVI are described.

In **Chapter 5** we demonstrated the importance of MSCT-based valve sizing in TAVI recipients. We found that annulus dimensions were significantly greater when measured with MSCT compared to transoesophageal echocardiography (TOE), and this difference reduced the expected THV-oversizing by half (20 to 10%). Consequently, one in two patients in this cohort received the wrong CoreValve size. Furthermore, we showed that achieving the manufacturer recommended level of oversizing with TOE was not associated with a lower incidence of post-implantation paravalvular leak. In contrast, achieving the manufacturer recommendations using MSCT was associated with reduced paravalvular leak. Finally, we provided minimal MSCT oversizing recommendations for the 26 and 29 mm CoreValve prostheses using receiver-operating characteristic curves.

PART II. TAVI CANDIDATES AND TECHNOLOGY ADOPTION

In **Chapter 6**, the disease prevalence of aortic stenosis is evaluated and the number of potential TAVI candidates in Europe and North America is modelled. This systematic review and meta-analysis yielded a pooled prevalence of severe aortic stenosis in the general population ≥ 75 years of age of 3.4%. Using a clinical decision making algorithm derived from published TAVI studies, we estimated that some 290,000 patients in Europe (190,000) and North America (100,000) would meet current TAVI indications. This figure yields an estimated 27,000 potential TAVI candidates per annum.

In **Chapter 7**, the adoption of TAVI is described among 12 Western European Nations. The study demonstrates significant heterogeneity in the use of TAVI technology; the number of TAVI implants per million individuals ranged from 6.1 in Portugal to 88.7 in Germany (33 ± 25). Using the estimated number of TAVI candidates described in Chapter 6, we described the penetration of TAVI in each nation: the weighted average TAVI penetration rate was low (17.9%), with significant variability between nations: Germany (36.2%) had the highest TAVI penetration while Portugal (3.4%) had the lowest. We correlated a variety of national financial and healthcare indices with TAVI utilization, and found that national economic indexes and reimbursement strategies were closely linked with TAVI use and largely explain the observed inequitable adoption of TAVI technology across Europe.

In **Chapter 8**, we review the processes of THV and surgical heart valve approval in Europe and in the U.S. We describe the potential for the introduction of objective performance criteria (OPC) for approval of new-generation THVs for use in high- and extreme-risk patient populations in the US. We recommend that the approval of THV devices for use in low- and intermediate-risk patients or for new indications should provisionally be considered only with data from RCTs. However, in the near future, data from specific RCTs (PARNTER II and SURTAVI) can form the basis for development of additional OPC for intermediate-risk patients. Development of these and future OPC should include considerations of technology maturity, short- and long-term data, specific events likely to be related to particular THV designs, patient risk profile, and statistical methods to produce OPC.

PART III. NOVEL APPLICATIONS OF TAVI TECHNOLOGY

Chapter 9 summarizes the initial evidence that was available for the innovative use of TAVI technology to treat failing surgical aortic bioprosthetic heart valves, the so-called TAV-in-SAV procedure. The basic construction of surgical bioprosthetic valves and their associated failure modes are described. The fluoroscopic identification of surgical bioprostheses and the salient procedural steps are outlined.

Chapter 10 builds on the early knowledge of TAV-in-SAV procedures described in Chapter 13. The discrepancy between the labelled valve size of surgical prostheses and the “real” internal stent diameter that is crucial for TAV-in-SAV procedural success is described. Clinical outcomes from large patient series undergoing these procedures are described. This review also describes the adaptation of TAVI technology to degenerative surgical mitral bioprosthetic valves.

Chapter 11 is derived from the Clinical Atlas of Transcatheter Aortic Valve Therapies. This unique interactive teaching tool aims to provide a highly visual aid for clinicians undertaking TAVI, and more specifically TAV-in-SAV procedures. High-quality images and videos of all current surgical bioprostheses are provided, along with a fluoroscopic identification guide, and sample TAV-in-SAV cases for reference.

In **Chapter 12** we perform the first propensity-matched comparison between TAV-in-SAV and redo surgery for patients with failing aortic bioprostheses. This analysis found that all-cause mortality was similar between groups at 30 days and 1 year (13.1% redo-SAVR vs. 12.3% TAV-in-SAV; $p = 0.80$). Similar incidences of stroke and pacemaker implantation were observed. The duration of ICU and hospital stay was reduced with TAV-in-SAV.

Chapter 13 describes the results of a large multinational registry detailing the procedural and clinical outcomes of patients with severe bicuspid aortic valve (BAV) disease treated with TAVI. The study includes 139 patients treated with the balloon-expandable ($n = 48$) or self-expandable ($n = 91$) TAVI systems. Most patients had BAV stenosis (66%) and BAV type 1 morphology (68%). The 30-day and 1-year mortality rates were 3.6% and 17.5%, respectively. We observed a high incidence of post-implantation aortic regurgitation grade ≥ 2 of 28.4%, though when patients with MSCT sizing were considered, aortic regurgitation \geq grade 2 was only prevalent in 17.4%. MSCT sizing was associated with reduced AR on multivariate analysis, and should be considered mandatory for patient with BAV disease undergoing TAVI. Further studies, evaluating the performance of novel TAVI systems in BAV morphology are required.

In **Chapter 14**, we report the technical specifications and first-in-human implant of a novel TAVI system. The CoreValve Evolut is deployed using the 14 Fr-equivalent EnVeo R delivery catheter that allows the valve to be recaptured and repositioned during deployment. The reduction in the diameter of the delivery catheter should increase the proportion of patients suitable for transfemoral TAVI, and the repositionability is intended to minimize the consequences of THV malposition. Large series with long-term follow-up are required to demonstrate the safety and efficacy of this device.

In **Chapter 15**, we performed a prospective multicentre observational study describing the feasibility and early safety of patients undergoing TAVI with transcarotid vascular access. This study includes 96 patients with unsuitable ilio-femoral vasculature that underwent transcarotid TAVI in French 3 sites between April 2009 and December 2013. Carotid access was achieved in all cases, without any significant vascular access complications. The 30-day

and 1-year mortality rates were 6.3% and 16.7%, respectively. In-hospital transient ischaemic attack occurred in 3.1%, increasing to 6.3% at 30-days. There were no cases of VARC-defined in-hospital stroke. These data provide the basis for larger studies to evaluate the safety and efficacy of this technique.

PART IV. TRANSCATHETER HEART VALVE FAILURE

Chapter 16 is a systematic review of all published cases of TAVI failure, including 87 individual cases of THV failure. Some TAVI failure modes were similar to surgical bioprosthetic heart valve failure: prosthetic valve endocarditis; structural valve failure; and THV thrombosis. Interestingly, the management of THV failure tended to differ to that historically described for surgical valve failure; most patients with THV thrombosis were treated with long-term anticoagulants rather than reoperation; and most cases of structural THV failure were treated with redo TAVI rather than proceeding to surgical valve replacement. Moreover, we identified two novel causes of TAVI failure: late embolization; and prosthesis compression. These failure modes have not been reported in the surgical literature. Our findings are expected to inform clinicians of the management of THV failure, and future iterations of consensus reporting guidelines.

PART V. TRANSCATHETER MITRAL VALVE IMPLANTATION

In **Chapter 17**, we provide an overview of emerging transcatheter mitral valve implantation (TMVI) devices. We outline the potential of these devices to treat a large number of patients with either primary or secondary mitral regurgitation that are very symptomatic and are refused surgical intervention due to excessive operative risk. Furthermore, we outline the importance of MSCT screening and the considerable hurdles associated with the development of this technology.

Chapters 18 and 19 we describe and present our experience with a systematic MSCT image analysis methodology for the assessment of candidates for transcatheter mitral valve implantation. We present results from 49 patients with heart failure and significant mitral regurgitation, in both systole and diastole, and for comparison we also report a metaanalysis of published works describing the mitral annular dimensions in patients without mitral regurgitation.

GENERAL DISCUSSION

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The aim of this thesis was to investigate the patient, procedural, and device-related factors that affect clinical outcomes in transcatheter aortic valve implantation (TAVI). In this chapter, the results of this body of research will be considered and contextualized to current clinical practice. Future developments in the field of transcatheter heart valves (THV) will be considered.

INTRODUCTION

Transcatheter aortic valve intervention has evolved greatly since Professor Alain Cribier performed the first balloon aortic valvuloplasty to treat severe aortic stenosis in 1986.¹ While the impressive acute hemodynamic result achieved with balloon valvuloplasty were diminished by valve restenosis and symptoms recurred within 6–8 months,² Cribier had demonstrated that transcatheter valvular intervention was feasible. Perhaps technique refinement could produce an effective durable treatment for the 30–60% of patients who are refused surgery?³

In 2002, some 15 years after the first balloon valvuloplasty, Cribier implanted a first generation 23mm bovine pericardial stent valve developed by Percutaneous Valve Technologies (Fort Lee, NJ).⁴ The recipient was a 57-year-old man with refractory cardiogenic shock secondary to severe aortic stenosis, who was denied traditional aortic valve surgery. The intervening decade has seen dramatic developments in transcatheter valve technology, and a wealth of knowledge has been acquired with respect to patient selection, procedural techniques, and post-procedure care. These refinements have greatly improved patient safety and procedural outcomes, and TAVI is now considered to be the standard of care for patients at high or excessive risk for conventional surgical aortic valve replacement.^{5–7}

Patient selection can be especially challenging for complex procedures such as TAVI, where the patient's expectations, the clinical situation, co-morbid medical conditions, peripheral and aortic vascular anatomy require careful consideration. In **Chapter 2**, we provide a comprehensive description of the anatomy of the aortic valvar complex from the point of view of the TAVI physician. This chapter is derived from an interactive iPad application specifically created to serve as a reference tool for institutional TAVI teams. This application provides a comprehensive visual interactive and dynamic tool for TAVI operators of all levels, and features in excess of 800 videos and figures. The anatomy chapter is illustrated with high quality images, detailed figure legends, and interactive videos with anatomist Professor Robert Anderson.

Careful, considered patient selection by a team of experienced interventional cardiologists, cardiac surgeons, anaesthetists, and imaging specialists (the institutional heart team) has been at the core of the TAVI success story (**Chapter 3**). Surgical risk has been quantified using the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), EuroSCORE II, and the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality score. However, these scores share important limitations in high-risk patient subsets, most notably

a limited predictive capacity and an inability to capture significant comorbid conditions in what is a heterogeneous patient group. The logistic EuroSCORE for example, has a low discriminatory power in TAVI patients (C statistics 0.61 to 0.64). As such, TAVI has fostered a new era of cooperation between a variety of hospital-based services, including cardiologists, cardiac surgeons, anaesthetists, elderly-medicine physicians, imaging specialists, and allied health professionals. Together, the institutional heart team can draw on a much greater pool of experience to determine (A) if TAVI is the most appropriate option for the patient, (B) if the anatomy is suitable, and (C) identify the optimal procedural technique.

Careful pre-operative multimodal imaging assessment is fundamental for optimizing TAVI outcomes (**Chapter 5**). Pre-procedural anatomical screening is of considerable importance for TAVI. In particular, appropriate THV sizing is recognized to be a key factor for optimizing patient outcomes: PVL is an independent risk factor for mortality and has been reported in 9% to 21% of CoreValve and 6% to 13.9% of Edwards SAPIEN recipients.^{8,9} Appropriate THV sizing involves achieving a predefined amount of prosthesis oversizing relative to the aortic annulus. Previous studies have demonstrated that failing to achieve a 1:1 ratio of the THV relative to the aortic annulus (cover index: $[\text{TAVR area/annular area} - 1] \times 100$) is associated with PVL.¹⁰ CT provides more accurate annular measurements than TOE does, and the use of CT for THV sizing has been associated with improved clinical outcomes.¹⁰ CT multiplanar reformatting allows accurate 3D reconstruction of the aortic annulus in its true plane. The superiority of this technique over 2D TOE is explained by the oval shape and variable orientation of the aortic annulus and the likelihood that 2D echocardiographic imaging will measure a short-axis tangent across the annulus. In **Chapter 5**, we confirmed that previous observations that CT-based aortic annular diameters are significantly larger than those obtained by 2D echocardiography. When these CT diameters were used to recalculate the oversizing relative to the TOE-selected CoreValve, the actual THV oversizing was reduced by 50%. Accordingly, the retrospective CT analysis suggested that up to 50% of patients did not achieve the manufacturer's recommended THV-oversizing criteria and therefore received an inappropriate CoreValve size. CT data also suggested that one-third of patients had annuli too large for available CoreValve sizes during the time of enrolment. Adherence to CT-based but not TOE-based oversizing was a predictor of reduced PVL. According to CT, significantly lower PVL rates were observed in those patients who received a correct CoreValve size than in those who did not. These data, combined with other studies, have resulted in MSCT being considered as the gold standard technique for THV-size determination.

PART II. TAVI CANDIDATES AND TECHNOLOGY ADOPTION

TAVI Candidates

There remain few studies reporting the prevalence of valvular heart disease, and in particular, aortic stenosis in the general population. We undertook a systematic review and meta-analysis on the prevalence of aortic stenosis in the elderly (≥ 75 years), and estimated a prevalence rate of 3.4% (**Chapter 6**). Using pooled estimates from studies reporting clinical decision-making in severe aortic stenosis, we projected the number of TAVI candidates in Europe and North America. In agreement with the Euro Heart Survey,¹¹ we found that up to 40.5% of all elderly patients with severe symptomatic aortic stenosis do not undergo surgical aortic valve replacement. While there were differences between studies, specifically related to the time period and the reporting of aortic stenosis severity and symptoms, this analysis was the first to assess these parameters across studies, and confirms the undertreatment of aortic stenosis in elderly patients.³

Using the clinical decision-making algorithm, we estimate that there are 190,000 TAVI candidates in Europe, and 100,000 in the United States. Furthermore, we calculated that there are 27,000 new TAVI candidates between these regions per annum. The heterogeneity of the underpinning studies yielded wide confidence intervals for these figures, and therefore they should be considered as estimates, however this study is the first to provide some guidance as to the potential of the TAVI market in Europe and North America.

TAVI Adoption

Disparate adoption of medical technology is pervasive and usually results in inequitable patient access. Regional differences in TAVI adoption are likely to have emerged because of variations in social, regulatory, economic, and political circumstances, as well as disease prevalence and longevity. However, the adoption kinetics of a novel medical technology such as TAVI and the factors influencing these variables have not been previously described. We investigated TAVI utilization in 11 Western European Nations and found significant variability in the use of TAVI among nations (**Chapter 7**): in 2011, the number of TAVI implants per million individuals ranged from 6.1 in Portugal to 88.7 in Germany (33 ± 25). Furthermore, we linked TAVI use to a number of national financial indices and healthcare parameters and found that two factors were strongly associated with TAVI adoption: national healthcare spending per capita correlated with TAVI use ($r = 0.80$; $p = 0.005$); and the presence of TAVI-specific reimbursement (as apposed to TAVI reimbursement from general hospital budget) was associated with greater TAVI implant rates (698 ± 232 vs. 213 ± 112 implants/million individuals ≥ 75 years; $p = 0.002$). When we applied the implant numbers to the estimated number of TAVI candidates identified in our earlier study, we found that TAVI penetration ($[\text{actual use} / \text{potential use}] \times 100$) across Europe was low (17.9%). Penetration rates ranged from 3.4% in Portugal to 36.2% in Germany.

Overall, these data suggest that TAVI is underutilized in Western Europe, particular in less affluent nations without specific reimbursement for THVs. Such disparity is axiomatic, and has been previously demonstrated for a variety of high-tech medical therapies.¹² The identification of such inequitable access to medical technologies is important because it generates discussion and initiatives to address inequalities and the corresponding impact on patient outcomes through payer- and physician-led programs. It is therefore encouraging to see the recently announced introduction of the Valve-For-Life program by the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Similar to the stent-for-life initiative, this program aims to improve the delivery of care and patient access to TAVI, thereby reducing mortality and morbidity in patients suffering with valvular heart disease.¹³

The process of approval for THVs is also an important subject considered in this thesis. In Europe, THVs and surgical prostheses share a common market approval process: the Conformité Européenne (CE) mark provides authorization for a manufacturer to sell a product in the European Economic Area by affirming that it complies with pre-specified legal requirements. Importantly, the level of scientific evidence required to achieve CE-mark requires a single-arm demonstration of short-term safety and efficacy in approximately 50 patients. In contrast, the approval process for new-generation surgical or transcatheter prostheses in the US is very different. For surgical prostheses, the development of objective performance criteria (OPC) by the Food and Drug Administration (FDA) has superseded the requirement to perform RCTs due to the maturity of the device field and the minimal changes in new iterations of previously approved valves (predicate devices). Up until recently, approval of THVs has required randomized comparisons to standard FDA-approved therapies since the technology is immature, device design significantly different and device development still iterating rapidly. However, similar to the development of surgical prostheses, the established efficacy of TAVI as shown in multiple RCTs of high-risk patients has potentially made the requirement for lengthy RCTs before introducing new THV devices unacceptable from a societal, patient and physician standpoint. It may place patients at unnecessary risk by delaying access to improved safer and more efficient technology. Therefore, alternative study approaches should be considered for new THV-device approval.

The FDA recently also approved several THVs based on single-arm studies, the first one being the CoreValve device that was tested in the CoreValve Extreme Risk Pivotal trial. Innovative trial designs, perhaps incorporating OPC, have been proposed but not formally introduced as alternatives to RCTs for new THV-device approval. **Chapter 8** provides an overview of OPC, considers the potential role of OPC for THV-device approval, and discusses the challenges associated with such an approach. Several recommendations for the future implementation of OPC for THV devices are provided.

PART III. NOVEL APPLICATIONS OF TAVI TECHNOLOGY

Transcatheter heart valve technology has already expanded well beyond the initial focus of Professor Cribier's endeavours. TAVI is now frequently applied to a variety of off-label clinical situations, including intermediate / low risk patients, bicuspid aortic valve morphology, and the development of alternate vascular access routes. Perhaps the most notable adaptation of this technology is the treatment of patients with failing surgical bioprosthetic valves (**Chapters 9, 10, 11, 12**). In 2007, Wenaweser and colleagues reported the implantation of a Medtronic CoreValve (Medtronic CV, Luxembourg S.a.r.l.) into a degenerated surgical aortic bioprosthesis.¹⁴ Since this first case, numerous transcatheter aortic valve in surgical aortic valve (TAV-in-SAV) procedures have been performed and experienced physicians are adapting current THVs for treatment of failing surgical atrioventricular and pulmonary bioprostheses. Optimal results for valve-in-valve or valve-in-ring procedures require a thorough knowledge of surgical bioprosthesis construction or ring morphology. In these chapters, we provide detailed descriptions of the construction of surgical bioprostheses and their failure modes and outline the importance of pre-procedural imaging for TAV-in-SAV procedures. Furthermore, we provide a comprehensive step-by-step guide for THV sizing and procedural planning for TAVI practitioners undertaking these procedures. As for the anatomy section described above, **Chapter 11** is derived from the interactive TAVI Atlas that provides the clinician with a high-quality and interactive guide to TAV-in-SAV procedures. Numerous videos are included in this iPad application demonstrating the specific implantation technique required for each TAV-in-SAV procedure.

As it is unlikely that a randomized trial will be conducted to formally compare redo surgery and TAV-in-SAV treatment strategies, we conducted a propensity-matched analysis comparing these treatments (**Chapter 12**). We found that 30-day and 1-year mortality, stroke, and a host of other hard endpoints were comparable between groups. Hospital stay was however shorter in the TAV-in-SAV cohort. Thus, current data support the treatment of patients with failing surgical bioprostheses at high operative risk using THV technology in specialised centres. Longer-term data is of course required to validate this approach, particularly in younger patients, but it is possible that these innovative procedures will become the standard of care for surgical bioprosthetic valve dysfunction.¹⁵

Bicuspid aortic valve (BAV) is a heritable disease affecting 0.5% to 2% of the general population, with a strong male predilection. BAV stenosis and/or regurgitation is the most common indication for SAVR in patients <70 years of age. BAV morphology was been excluded from the landmark TAVI trials involving as abnormal cusp fusion, pronounced asymmetry of the valve orifice and annulus, heavily calcified and fibrotic leaflets, and calcified raphe could adversely affect the expansion of transcatheter valves and lead to paravalvular aortic regurgitation and poor haemodynamic function. We therefore undertook a multicenter study to assess the safety and efficacy of TAVI in BAV in a large group of patients, and to assess hae-

modynamic, echocardiographic, and clinical outcomes (**Chapter 13**).¹⁶ We studied 139 elderly patients with BAV undergoing TAVI across 12 European and Canadian centres. We found that the application of TAVI to BAV morphology was associated with similar clinical outcomes to patients with tricuspid aortic valve stenosis, though with \geq grade 2 post-implantation paravalvular leak in 28% of cases at 30-days. Underscoring the importance of MSCT-based valve sizing in these patients, this figure fell to 17.4% in among patients undergoing MSCT-sizing. Nevertheless, this study demonstrated for the first time that results of TAVI were suboptimal in patients with BAV morphology, and thus that it should be used reservedly. There is the potential for novel THV devices that are repositionable and/or have sealing cuffs to mitigate the higher rates of PVL. Nevertheless, it is important to state that in patients with BAV disease, SAVR should continue to be considered the first line therapy, unless patients are considered by the institutional heart team to be at high-surgical risk or indeed inoperable. As TAVI expands into lower risk populations, the question of equivalent efficacy to SAVR in patients with BAV will become more acute, as BAV is highly represented in these younger cohorts. Physicians, medical societies, the medical device industry, and other stakeholders have a responsibility to ensure TAVI technology is appropriately tested in randomized controlled trials in such patients.

Transcatheter valve technology is evolving rapidly. New-generation devices require smaller vascular access sheaths for valve delivery, are recapturable and repositionable and have sealing skirts to reduce paravalvular leak, and deflectable delivery catheters allowing the operator to attempt more challenging anatomy. The Medtronic Evolut R with in-line sheath technology is a novel THV device described within these pages (**Chapter 14**). We reported the first human case using this recapturable, repositionable, retrievable device in a patient with a severely stenotic failing aortic bioprosthesis.¹⁷ This newly designed delivery catheter is a 14 Fr-equivalent system. Given that major vascular complications are associated with considerable morbidity and mortality, and that the ratio of the outer diameter of the delivery sheath to the femoral artery (SFAR) is a strong predictor of these complications,¹⁸ the 4 Fr reduction in sheath size compared to the system predecessor is likely to extend the potential and safety of transfemoral TAVI. Applying the SFAR ratio to the EnVeo R system, transfemoral TAVI can be safely performed in patients with iliofemoral diameters as small as 5.4mm. Indeed, if the 20% oversizing ratio between the introducer sheath (18 Fr: outer diameter 7.2 mm) and the minimal femoral artery diameter (6 mm) is maintained, then femoral anatomy as small as 5 mm could be navigated with the EnVeo R delivery catheter. Such advancements are of course related to the ever-decreasing morbidity and mortality associated with TAVI.

Despite the reduction in the size of the vascular sheaths required for TAVI, transfemoral procedures are challenging or impossible in up to one-quarter of TAVI candidates. In such cases, a variety of alternate vascular access routes have been described: transapical, transaxillary, direct aortic, and transcaval. Each of these alternative strategies may be undesirable in certain clinical and anatomical situations, and each may be associated with adverse clinical

consequences, including greater invasiveness, post-procedural pain, delayed mobility and patient discharge, and perhaps, increased mortality in the case of the transapical route. Herein, we described the largest series of patients undergoing TAVI using a transcarotid vascular access route (**Chapter 15**).¹⁹ Among 96 patients treated at 3 French sites, successful vascular access was achieved in all cases, without any access site vascular complications. The 30-day and 1-year mortality rates were 6.3 and 16.7%, respectively, and procedural success and efficacy were similar to other alternate vascular access series. Stroke was an endpoint of particular importance, as high rates of cerebrovascular complications could significantly limit the application of the technique. Gratifyingly, at 30-days we observed no stroke and only 6 TIA. It is interesting to note that many of these TIA events were contralateral to the carotid vascular access site. Thus, there may be several potential stroke mechanisms during transcarotid TAVI: 1) embolization of carotid artery plaque due to arterial puncture and instrumentation; 2) access site trauma providing a nidus for thrombosis with subsequent embolization; 3) inadequate collateral perfusion through the circle of Willis; and 4) embolization of debris during balloon valvuloplasty or THV implantation. The low rate of stroke observed in this study may be attributed to careful patient selection (common carotid artery minimal lumen diameter >7.0 mm), mandatory pre-treatment with dual antiplatelet agents, and adequate intraoperative anticoagulation (activated clotting time >250 s). We also limited the duration of antegrade ischaemia by placing the large bore introducer sheath only when necessary. Nevertheless, there remains the potential to further reduce the risk of cerebral ischaemia by limiting THV postdilation, using embolic protection devices, and by further refining the anatomical selection criteria for transcarotid TAVI. These data support the feasibility of transcarotid arterial access for TAVI and encouraging short- and medium-term clinical outcomes.

PART IV. TRANSCATHETER HEART VALVE FAILURE

Ever-improving procedural safety and promising medium-term clinical efficacy have encouraged the application of THV technology to lower risk patients. Indeed, two randomized trials of TAVI in intermediate-risk patients are expected to report in the next year, and the US FDA has granted permission for randomized TAVI trials in low-risk patients. In this context, understanding the modes of THV failure and exploring valve durability and long-term clinical efficacy are of vital importance (**Chapter 16**). A variety of failure modes have been described for surgical bioprostheses, including infective endocarditis (IE), thrombosis, and structural valve failure (SVF). Surgical bioprosthetic failure has been clearly described and quantified, while in contrast, a systematic description of THV failure has not been performed. We performed a systemic review of all published cases of THV failure to address this knowledge gap.²⁰ Among 70 publications, we identified 87 individual cases of THV failure. Similar to surgical bioprosthetic heart valve failure, we observed cases of prosthetic valve endocarditis (PVE),

structural valve failure, and THV thrombosis. The microbiological profile of THV PVE was similar to surgical PVE, though one-quarter had satellite mitral valve endocarditis, and surgical intervention was required in 40%. Structural valve failure occurred most frequently due to leaflet calcification and was predominantly treated by redo-THV. Transcatheter heart valve thrombosis occurred at a mean 9 ± 7 months post-implantation and was successfully treated by prolonged anticoagulation in most cases. No thromboembolic events were attributed to THV thrombosis. Two novel causes of THV failure were identified: late THV embolization and THV compression following cardiopulmonary resuscitation. These failure modes have not been reported in the surgical literature. Potential risk factors for late THV embolization include low prosthesis implantation, THV undersizing/underexpansion, bicuspid, and non-calcified anatomy. Transcatheter heart valve embolization mandated surgery in 80% of patients. Transcatheter heart valve compression was noted at post-mortem in most cases. Late embolization and THV compression represent complications previously unreported in the surgical literature. Of course, this study is has limitations inherent to all systematic reviews, and the included studies were either case reports or small series, precluding comparison with the entire TAVI population at risk. Accurate estimation of the true incident rates of each THV failure mode was therefore not possible, and the likely underreporting of adverse events would be expected to result in a significant underestimation of event rates. Nevertheless, the identification and description of failure modes, and moreover the account of management strategies of these events provides both a reference for physicians and a foundation on which further studies can build.

PART V. TRANSCATHETER MITRAL VALVE IMPLANTATION

One of the aims of this thesis was to draw on experience gained in the TAVI field to explore some basic principles of transcatheter mitral valve implantation (TMVI). As the prevalence of mitral valve disease is almost three times that of aortic valve disease,²⁵ this technique offers the potential to treat a great number of elderly and/or high-risk patients with severe mitral regurgitation (MR). Indeed, the Euro Heart Survey suggested that half of all patients hospitalised with symptomatic severe MR do not undergo potentially curative surgical repair/replacement due to advanced age, comorbid illnesses, and left ventricular dysfunction.^{11, 26} There remains a great deal to learn about which patients could benefit from TMVI. Dr Elliot C. Cutler performed the first surgical mitral valve repair in 1939, yet the mode of repair/replacement and the timing of the intervention still remain topics of some debate. As with TAVI, patient selection is determined by anatomical and clinical criteria. Both involve complex decision matrices which require much clarification. Anatomically, TMVI is a veritable minefield: a large, non-circular, saddle-shaped, highly dynamic, non-calcified annulus without the ability for radial anchoring which is tethered to a complex, highly individualised, subvalvular

apparatus, and intimately related to the left ventricular outflow tract (LVOT), the coronary sinus, and the left circumflex coronary artery. Detailed MSCT analysis will be imperative for patient selection and preoperative procedural planning as this novel technology emerges in the next decade.

In **Chapter 17**, we describe recent developments in TVMI technology, outlining the design principles, construction, and available evidence for TMVI devices in early phase clinical trials. To date, five transcatheter mitral valve systems have been implanted in humans: CardiaQ valve system (CardiaQ Valve Technologies, Inc.); Tiara™ valve (Neovasc Inc., Richmond, Canada); FORTIS valve (Edwards Lifesciences, Irvine, CA, USA); Tendyne valve (Tendyne Inc., Roseville, MN, USA); and Twelve valve (Twelve, Inc., Redwood City, CA, USA). These devices share common features: nitinol self-expanding frames, trileaflet valves, bovine pericardial leaflets (Tendyne is porcine), fabric sealing skirt (CardiaQ is pericardial), and trans-apical delivery (CardiaQ also transseptal). Each of these systems, and those in preclinical development (Medtronic Mitral15 [Medtronic, Minneapolis MN, USA]; HighLife [HighLife Inc., Paris, France]), offer innovative design solutions to overcome the challenging anatomy of the mitral valve complex. TMVI systems must be flexible to deal with the complex and variable anatomy, provide large effective orifice areas, and deal with high transvalvular gradients. They must anchor without reliance on radial force (axial sealing), accommodate significant dislodgement forces, and avoid LVOT obstruction. Given these obstacles, additional areas of concern include stent fatigue and fracture, valve thrombosis, embolization, leaflet durability, and paravalvular leak with resultant haemolysis.

In the final chapters of this thesis (**Chapters 18 and 19**), we describe and evaluate a systematic MSCT image analysis methodology that provides measurements relevant for TMVI. A systematic step-by-step measurement methodology using a dedicated software package (3mensio Structural Heart 6.1 [Pie Medical Imaging BV, Maastricht, The Netherlands]) is described for structures of the mitral valvular complex including: the mitral valve annulus, left ventricle, left atrium, papillary muscles, and left ventricular outflow tract. This information is of relevance for those involved in the design and development of these novel transcatheter devices, and will be of importance in determining patient suitability in the future. Previous literature on mitral valve MSCT focused on establishing diagnosis and characterizing pathological states. Furthermore, the measurement methodology and nomenclature are heterogeneous among different authors. The systematic methodology presented here has the potential to facilitate the comparison of studies and the communication of results.

We applied this methodology to the MSCT data collected from a cohort of patients with severe functional mitral regurgitation recruited for the PTOLEMY-2 (NCT00787293) and PTOLEMY2Canada (NCT00815386) clinical trials of the Viacor percutaneous transvenous mitral annuloplasty system (Viacor, Inc., Wilmington, MA, USA). Herein, two independent observers measured 25 different geometrical properties of the mitral valve apparatus using the above-described methodology. The inter-observer difference (<10%) and the intra-class

correlation suggested excellent inter-observer agreement for most measurements. Among the patient population studied (N=32), the mean mitral annulus intercommissural and aorto-mural diameters were, respectively, 41.5 ± 5.2 mm and 38.7 ± 5.9 mm in systole. The obstacle-free zone below the mitral annulus averaged more than 20.0 mm and varied by less than 1 mm between systole and diastole.

These data have implications for the design of transcatheter mitral valves. The demonstration that, in patients with FMR, the mitral annulus is nearly symmetrical between its two major axes and contracts <2% in systole may alleviate concerns regarding excessive stress on the prosthetic valve frame. However, left ventricle immediately below the mitral annulus is highly dynamic and may substantially stress a device. The frame of a transcatheter valve may protrude on either aspect of the mitral annulus. In particular, the papillary muscles can represent an obstacle to the deployment of a transcatheter device. Our data however, demonstrates that the projected distance between the mitral plane and the heads of papillary muscles (the axial obstacle-free zone for the prosthesis) is approximately 20 mm and is constant during the cardiac cycle.

CONCLUSIONS

The past decade has seen a revolution in the management of valvular heart disease, and in particular severe aortic stenosis. The emergence of transcatheter heart valve technology has the potential to change forever the way we treat patients with valvular heart disease. The appropriate selection of patients for TAVI by a multidisciplinary institutional heart team is of utmost importance for the individual patient, and indeed for the future of the therapy itself. In this thesis, we have provided important information on the anatomic, 3-D imaging, and clinical criteria used for patient selection.

TAVI technology continues to evolve at an astonishing pace and is being applied in new and innovative ways to treat patients. Application of this therapy to those with failing aortic and mitral bioprostheses and bicuspid aortic valve morphology represent important technical milestones. Continued scientific rigor is however required to ensure comparative efficacy with alternate treatment modalities. This is of particular relevance as the management of valvular heart disease will have an increasing impact on public health and health care resource consumption as the global population ages. Physicians, medical societies, and other stakeholders have a responsibility to ensure the appropriate use and sensible dispersion of this innovative technology.

The extension of TAVI technology to younger and lower-risk patient populations is imminent. This paradigm shift will be evidence-based with clear demonstration of transcatheter valve safety and durability in these patient groups.

Transcatheter mitral valve implantation has the potential to greatly impact patient care. The success of this technology will depend on innovative valve design, rigorous patient selection, and rigorous clinical evidence.

REFERENCES

1. Cribier A, Savin T, Saoudi N, Rocha P, Berland J and Letac B. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? *Lancet*. 1986;1:63-7.
2. Serruys PW, Luijten HE, Beatt KJ, Di Mario C, de Feyter PJ, Essed CE, Roelandt JR and van den Brand M. Percutaneous balloon valvuloplasty for calcific aortic stenosis. A treatment 'sine cure'? *Eur Heart J*. 1988;9:782-94.
3. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, Gohlke-Barwolf C, Boersma E, Ravaud P and Vahanian A. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J*. 2005;26:2714-20.
4. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F and Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation*. 2002;106:3006-8.
5. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, Webb JG, Mack MJ, Douglas PS, Thourani VH, Babaliaros VC, Herrmann HC, Szeto WY, Pichard AD, Williams MR, Fontana GP, Miller DC, Anderson WN, Smith CR, Akin JJ and Davidson MJ. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2485-91.
6. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Davidson MJ, Svensson LG and Akin J. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2477-84.
7. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Jr., Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S and Oh JK. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790-8.
8. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetché D, Carrie D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E and Laskar M. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med*. 2012;366:1705-15.
9. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN and Leon MB. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2012;366:1686-95.
10. Hayashida K, Lefevre T, Chevalier B, Hovasse T, Romano M, Garot P, Bouvier E, Farge A, Donzeau-Gouge P, Cormier B and Morice MC. Impact of post-procedural aortic regurgitation on mortality after transcatheter aortic valve implantation. *JACC Cardiovascular interventions*. 2012;5:1247-56.
11. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P and Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24:1231-43.

12. Lubinski A, Bissinger A, Boersma L, Leenhardt A, Merkely B, Oto A, Proclemer A, Brugada J, Vardas PE and Wolpert C. Determinants of geographic variations in implantation of cardiac defibrillators in the European Society of Cardiology member countries--data from the European Heart Rhythm Association White Book. *Europace*. 2011;13:654-62.
13. Kristensen SD, Fajadet J, Di Mario C, Kaifoszova Z, Laut KG, Deleanu D, Gilard M, Guagliumi G, Goktekin O, Jorgova J, Kanakakis J, Ostojic M, Pereira H, Sabate M, Sobhy M, Vrints C, Wijns W and Widimsky P. Implementation of primary angioplasty in Europe: stent for life initiative progress report. *EuroIntervention*. 2012;8:35-42.
14. Wenaweser P, Buellesfeld L, Gerckens U and Grube E. Percutaneous aortic valve replacement for severe aortic regurgitation in degenerated bioprosthesis: the first valve in valve procedure using the Corevalve Revalving system. *Catheter Cardiovasc Interv*. 2007;70:760-4.
15. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, Barbanti M, Latib A, Schaefer U, Rodes-Cabau J, Treede H, Piazza N, Hildick-Smith D, Himbert D, Walther T, Hengstenberg C, Nissen H, Bekerredjian R, Presbitero P, Ferrari E, Segev A, de Weger A, Windecker S, Moat NE, Napodano M, Wilbring M, Cerillo AG, Brecker S, Tchetché D, Lefevre T, De Marco F, Fiorina C, Petronio AS, Teles RC, Testa L, Laborde JC, Leon MB and Kornowski R. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312:162-70.
16. Mylotte D, Lefevre T, Sondergaard L, Watanabe Y, Modine T, Dvir D, Bosmans J, Tchetché D, Kornowski R, Sinning JM, Theriault-Lauzier P, O'Sullivan CJ, Barbanti M, Debry N, Buithieu J, Codner P, Dorfmeister M, Martucci G, Nickenig G, Wenaweser P, Tamburino C, Grube E, Webb JG, Windecker S, Lange R and Piazza N. Transcatheter aortic valve replacement in bicuspid aortic valve disease. *J Am Coll Cardiol*. 2014;64:2330-9.
17. Piazza N, Martucci G, Lachapelle K, de Varennes B, Bilodeau L, Buithieu J and Mylotte D. First-in-human experience with the Medtronic CoreValve Evolut R. *EuroIntervention*. 2014;9:1260-3.
18. Hayashida K, Lefevre T, Chevalier B, Hovasse T, Romano M, Garot P, Mylotte D, Uribe J, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B and Morice MC. Transfemoral aortic valve implantation new criteria to predict vascular complications. *JACC Cardiovascular interventions*. 2011;4:851-8.
19. Mylotte D, Sudre A, Teiger E, Obadia JF, Lee M, Spence M, Khamis H, Al Nooryani A, Delhay C, Amr G, Koussa M, Debry N, Piazza N and Modine T. Transcatheter Aortic Valve Replacement: Feasibility and Safety. *JACC Cardiovascular interventions*. 2016;9:472-80.
20. Mylotte D, Andalib A, Theriault-Lauzier P, Dorfmeister M, Girgis M, Alharbi W, Chetrit M, Galatas C, Mamane S, Sebag I, Buithieu J, Bilodeau L, de Varennes B, Lachapelle K, Lange R, Martucci G, Virmani R and Piazza N. Transcatheter heart valve failure: a systematic review. *Eur Heart J*. 2015;36:1306-27.
21. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, de Backer O, Asch FM, Ruiz CE, Olsen NT, Trento A, Friedman J, Berman D, Cheng W, Kashif M, Jelnin V, Kliger CA, Guo H, Pichard AD, Weissman NJ, Kapadia S, Manasse E, Bhatt DL, Leon MB and Sondergaard L. Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves. *N Engl J Med*. 2015;373:2015-24.
22. Latib A, Naganuma T, Abdel-Wahab M, Danenberg H, Cota L, Barbanti M, Baumgartner H, Finkelstein A, Legrand V, de Lezo JS, Kefer J, Messika-Zeitoun D, Richardt G, Stabile E, Kaleschke G, Vahanian A, Laborde JC, Leon MB, Webb JG, Panoulas VF, Maisano F, Alfieri O and Colombo A. Treatment and clinical outcomes of transcatheter heart valve thrombosis. *Circ Cardiovasc Interv*. 2016;8. pii: e001779.
23. Leetmaa T, Hansson NC, Leipsic J, Jensen K, Poulsen SH, Andersen HR, Jensen JM, Webb J, Blanke P, Tang M and Norgaard BL. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. *Circ Cardiovasc Interv* 2016;8. pii: e001596.

24. Mylotte D and Piazza N. Transcatheter Aortic Valve Replacement Failure: Deja vu ou Jamais vu? *Circ Cardiovasc Interv* 2016;8. pii: e002531.
25. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG and Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005-11.
26. Mirabel M, Iung B, Baron G, Messika-Zeitoun D, Detaint D, Vanoverschelde JL, Butchart EG, Ravaud P and Vahanian A. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J*. 2007;28:1358-65.

**NEDERLANDSTALIGE
SAMENVATTING**

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Hoofdstuk 1 is een algemene inleiding tot het onderwerp van dit proefschrift, waarin de ontwikkeling van transkatheterhartklep (THV) -technologie wordt beschreven. De specifieke doelen en hoofdlijnen van dit proefschrift worden gepresenteerd.

Hoofdstuk 2 introduceert de lezer in de basisanatomie van de aortawortel, de onderdelen waaruit die uit is opgebouwd en de omliggende ondersteuningsstructuren. De anatomische beschrijving is rijkelijk voorzien van afbeeldingen en is specifiek gericht op het beschrijven van de anatomie van de aorta voor artsen die Transcatheter Aortic Valve Implantation - uitvoeren (TAVI).

Hoofdstuk 3 beschrijft patiënten die geselecteerd worden voor TAVI vanuit het perspectief van de interventiecardioloog. Deze review benadrukt het belang van multimodale pre-procedurele beeldvorming en de rol van het “Hart Team” bij de selectie van patiënten. Dit hoofdstuk geeft een overzicht van de relevante onderzoeken die voorafgaand aan een TAVI moeten worden uitgevoerd, richt zich op de selectie van de vasculaire toegangsroute en beschrijft hoe de juiste klepmaat wordt bepaald door middel van multislice computertomografie (MSCT).

Hoofdstuk 4 is gebaseerd op een hoofdstuk uit een leerboek dat de pre-procedurele planning en de uitvoering van een transfemorale TAVI beschrijft. Het beschrijft de twee meest gebruikte THV-platforms: de CoreValve (Medtronic, Dublin, Ierland) en de Edwards SAPIEN (Edwards Lifesciences, Irvine, California, U.S.) -klep. In beide gevallen wordt stapsgewijs de procedure voor vasculaire toegang, plaatsingspositie van de katheter en plaatsing van de prothese beschreven. De etiologie, incidentie en behandeling van aan TAVI gerelateerde complicaties worden geschetst; (1) Cardiaal: paravalvulaire regurgitatie van de aortaklep; geleidingsafwijkingen; atriale en ventriculaire aritmieën; coronaire obstructie; hartperforatie; aortawortelruptuur; kunstklepdysfunctie; embolisatie; trombose; infectieuze endocarditis; mitralisinsufficiëntie, en mitralisklep letsel; en (2) niet-cardiaal: beroerte; vaatletsel; acuut nierinsufficiëntie. Verder worden de eerste resultaten van de grote gerandomiseerde studies met TAVI beschreven.

In **Hoofdstuk 5** hebben we het belang aangetoond van op MSCT-gebaseerde klepafmetingen in TAVI-ontvangers. We vonden dat de dimensie van de annulus significant groter was wanneer deze gemeten werd met MSCT vergeleken met transoesophageale echocardiografie (TOE). Dit verschil verklaart de onjuiste maatvoering met als gevolg dat één op de twee patiënten een verkeerde maat CoreValve klep ontving wanneer deze gemeten werd op basis van TOE. Wanneer de keuze van de klepmaat gebaseerd was op basis van de CT-scan resulteerde dit in een lagere incidentie van paravalvulaire lekkage na implantatie. Tenslotte geven we, op basis van receiver-operating characteristic curves van MSCT, aanbevelingen om bij de klepmaten 26 en 29 mm van de CoreValve prothese een iets grotere klepmaat te kiezen.

DEEL II. TAVI KANDIDATEN EN TECHNOLOGIE ADOPTIE

In **Hoofdstuk 6** wordt de prevalentie van aortastenose onderzocht en wordt het aantal mogelijke TAVI-kandidaten in Europa en Noord-Amerika in kaart gebracht. Deze systematische review en meta-analyse leverden een gepoolde prevalentie op van 3,4% ernstige aortastenose in de algemene bevolking ≥ 75 jaar oud. Met behulp van een klinisch beslissingsalgoritme, dat is afgeleid van gepubliceerde TAVI-onderzoeken, schatten we dat ongeveer 290.000 patiënten in Europa (190.000) en Noord-Amerika (100.000) zouden voldoen aan de huidige TAVI-indicaties. Dit cijfer levert naar schatting 27.000 potentiële TAVI-kandidaten per jaar op.

In **hoofdstuk 7** wordt de acceptatie van TAVI beschreven in 12 West-Europese landen. De studie toont significante heterogeniteit in het gebruik van de TAVI-technologie; het aantal TAVI-implantaten per miljoen personen varieert van 6,1 in Portugal tot 88,7 in Duitsland (33 ± 25). Gebruikmakend van het geschatte aantal TAVI-kandidaten beschreven in Hoofdstuk 6, beschrijven we de penetratie van TAVI in elk land: de gewogen gemiddelde TAVI-penetratiegraad is laag (17,9%), met aanzienlijke variabiliteit tussen landen: Duitsland (36,2%) heeft de hoogste TAVI penetratie, terwijl Portugal (3,4%) de laagste heeft. We onderzoeken het verband tussen de verschillende financiële en gezondheidszorgindexen in diverse landen en de penetratie van TAVI. De nationale economische index- en de verschillende vergoedingen zijn nauw verbonden met het gebruik van TAVI in Europa.

In **hoofdstuk 8** bespreken we de processen van goedkeuring van THV en chirurgische hartkleppen in Europa en de VS. We beschrijven de mogelijkheid om objectieve prestatiecriteria (OPC te gebruiken) voor de goedkeuring van nieuwe THV's voor gebruik bij hoog risico patiënten. Wij adviseren dat de goedkeuring van THV's voor gebruik bij patiënten met een laag en gemiddeld risico of voor nieuwe indicaties voorlopig alleen met gegevens van gerandomiseerde studies (RCT) moet gebeuren. In de nabije toekomst kunnen gegevens uit specifieke RCT's (PARNTER II en SURTAVI) echter de basis vormen voor de ontwikkeling van OPC's voor patiënten met een gemiddeld risico. Bij de ontwikkeling van deze en toekomstige OPC's moet rekening worden gehouden met volwassenheid van de technologie, resultaten op de korte en lange termijn, specifieke gebeurtenissen die verband houden met bepaalde THV-ontwerpen, risicoprofiel van de patiënt en statistische methoden voor tot stand komen van OPC's.

DEEL III. NIEUWE TOEPASSINGEN VAN TAVI-TECHNOLOGIE

Hoofdstuk 9 vat het bewijs samen dat beschikbaar is voor het innovatieve gebruik van de TAVI-technologie om falende chirurgische aorta bioprothesen te behandelen, de zoge-

naamde TAV-in-SAV-procedure. De basisconstructie van chirurgische bioprotheses en de bijbehorende faalmodi worden beschreven. De fluoroscopische identificatie van chirurgische bioprotheses en de meest kenmerkende procedurele stappen worden beschreven.

Hoofdstuk 10 bouwt voort op de vroege kennis van TAV-in-SAV-procedures beschreven in hoofdstuk 10. De discrepantie tussen de gelabelde klepmaat van chirurgische prothesen en de “echte” interne stentdiameter, die cruciaal is voor het procedurele succes van TAV-in-SAV, wordt beschreven. Klinische uitkomsten van grote aantallen patiënten die deze procedure ondergaan, worden beschreven. Deze review beschrijft ook de aanpassing van de TAVI-technologie om degeneratieve chirurgische mitralis bioprothesen te kunnen behandelen.

Hoofdstuk 11 is afgeleid van de Clinical Atlas of Transcatheter Aortic Valve Therapies. Deze unieke interactieve leermethode is bedoeld als een visueel hulpmiddel voor klinici die TAVI uitvoeren, en meer specifiek voor TAV-in-SAV-procedures. Hoogwaardige afbeeldingen en video's van alle huidige chirurgische bioprothesen worden verstrekt, samen met een beschrijving van fluoroscopie en voorbeelden van TAV-in-SAV behandelingen ter referentie.

In **Hoofdstuk 12** voeren we de eerste “propensity matched” vergelijking uit tussen, TAV-in-SAV behandeling en reoperatie voor patiënten met falende aortaklep bioprothesen. Uit deze analyse bleek dat het sterfterisico vergelijkbaar was tussen groepen na 30 dagen en 1 jaar (13,1% redo-SAVR versus 12,3% TAV-in-SAV; $p = 0,80$). Gelijke incidentie van een herseninfarct en pacemaker werden ook waargenomen. De duur van ICU en ziekenhuisverblijf was verminderd na een TAV-in-SAV.

Hoofdstuk 13 beschrijft de resultaten van een grote multinationale studie, waarin patiënten met ernstige Bicuspide Aortaklep (BAV) behandeld worden met TAVI. De studie omvat 139 patiënten behandeld met de ballon-expandeerbare klep ($n = 48$) of zelf-expandeerbare ($n = 91$) TAVI-systemen. De meeste patiënten hadden BAV stenose (66%) en BAV type 1 morfologie (68%). De sterftecijfers na 30 dagen en 1 jaar waren respectievelijk 3,6% en 17,5%. We zagen een hoge incidentie van 28,4%, post-implantatie aortaklep regurgitatie graad ≥ 2 . Wanneer de klepmaat bepaald was door middel van MSCT, was de incidentie van aortaklepregulatie \geq graad 2 lager, namelijk 17,4%. MSCT-sizing was geassocieerd met verminderde AR bij multivariate analyse en moet als verplicht hulpmiddel worden beschouwd voor patiënten met een BAV-ziekte die TAVI ondergaan. Vervolgstudies en het evalueren van de uitkomsten van nieuwe TAVI-systemen bij patiënten met BAV zijn vereist.

In **hoofdstuk 14** vermelden we de technische specificaties en het eerste gebruik in de mens, van een nieuw TAVI-systeem. De CoreValve Evolut wordt geïmplanterd met behulp van de 14 Fr-equivalente EnVeo R-inbrengkatheter. De reductie in diameter van de katheter

zou het aantal patiënten dat geschikt is voor transfemorale TAVI moeten vergroten, en de herplaatsbaarheid is tevens bedoeld om de complicaties van THV implantatie te verminderen. Uitgebreide series met langdurige follow-up zijn vereist om de veiligheid en werkzaamheid van deze klep aan te tonen.

In **Hoofdstuk 15** beschrijven we een prospectieve, observationele studie in meerdere centra, waarin de haalbaarheid en vroege veiligheid van patiënten die TAVI ondergaan via de a. carotis. Deze studie omvat 96 patiënten met ongeschikte ilio-femorale vaten, die transcathetische TAVI ondergingen in 3 Franse centra, tussen april 2009 en december 2013. Carotis-toegang was in alle gevallen mogelijk, zonder significante complicaties. De sterftcijfers na 30 dagen en 1 jaar waren respectievelijk 6,3% en 16,7%. Transiënte ischemische aanval in het ziekenhuis vond plaats in 3,1%, en nam toe tot 6,3% na 30 dagen. Er waren geen gevallen van een VARC-gedefinieerde herseninfarct tijdens ziekenhuisopname. Deze gegevens vormen de basis voor grotere onderzoeken om de veiligheid en werkzaamheid van deze techniek te evalueren.

DEEL IV. TRANSKATHETER HARTKLEP DEFECT

Hoofdstuk 16 is een systematische review van alle gepubliceerde gevallen van TAVI-falen, waaronder 87 individuele gevallen van THV-falen. Het tekortschieten van sommige THV's is vergelijkbaar met chirurgisch hartklepfalen: kunstklep endocarditis; structurele degeneratie en THV-trombose. Interessant was dat de behandeling van het falen van de THV vaak anders lijkt te zijn dan die wordt beschreven voor het falen van chirurgische kleppen. De meeste patiënten met THV-trombose werden behandeld met langdurige anticoagulantia in plaats van reoperatie. De meeste gevallen van structureel THV-falen werden behandeld met opnieuw een TAVI, in plaats van chirurgische klepvervanging. Bovendien identificeerden we twee nieuwe oorzaken van falende TAVI: late embolisatie; en compressie van de prothese. Deze faalwijzen zijn niet in de chirurgische literatuur vermeld. Van onze bevindingen wordt verwacht dat zij klinici informeren over de behandeling van THV-falen. Tevens dient de nieuwe manier van klepfalen te worden opgenomen in de richtlijnen voor consensusrapportage.

DEEL V. TRANSKATHETER MITRALISKLEPIMPLANTATIE

In **hoofdstuk 17** geven we een overzicht van opkomende Transcatheter Mitralis Valve Implantation (TMVI) prothesen. We beschrijven het potentieel van deze procedures om een groot aantal patiënten met primaire of secundaire mitralisstenose of regurgitatie te behandelen die symptomatisch zijn en waar chirurgisch ingrijpen niet mogelijk is vanwege overmatig opera-

tierisico. Verder schetsen we het belang van MSCT-screening en de aanzienlijke hindernissen die gepaard gaan met de ontwikkeling van deze technologie.

Hoofdstukken 18 en 19 beschrijven we onze ervaring met een systematische MSCT-beeldanalysemethode voor de beoordeling van kandidaten voor Transcatheter-Mitralis klp implantatie. We presenteren resultaten van 49 patiënten met hartfalen en significante mitralisklep insufficiëntie, zowel in systole als diastole, en ter vergelijking rapporteren we ook een meta-analyse van gepubliceerde artikelen die de annulus dimensies beschrijven bij patiënten zonder mitralisklep insufficiëntie.

LIST OF PUBLICATIONS

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1. **Mylotte D**, Martucci G, Piazza N. Patient selection for transcatheter aortic valve implantation: An interventional cardiology perspective. *Ann Cardiothorac Surg.* 2012;1:206-15.
2. **Mylotte D**, Dorfmeister M, Elhmidi Y, Mazzitelli D, Bleiziffer S, Wagner A, Noterdaeme T, Lange R, Piazza N. Erroneous Measurement of the Aortic Annular Diameter Using 2-Dimensional Echocardiography Resulting in Inappropriate CoreValve Size Selection: A Retrospective Comparison With Multislice Computed Tomography. *JACC Cardiovasc Interv.* 2014;7:652-61.
3. **Mylotte D**, Osnabrugge RL, Windecker S, Lefevre T, de Jaegere P, Jeger R, Wenaweser P, Maisano F, Moat N, Sondergaard L, Bosmans J, Teles RC, Martucci G, Manoharan G, Garcia E, Van Mieghem NM, Kappetein AP, Serruys PW, Lange R, Piazza N. Transcatheter aortic valve replacement in europe: adoption trends and factors influencing device utilization. *J Am Coll Cardiol.* 2013;62:210-9.
4. **Mylotte D**, Lange R, Martucci G, Piazza N. Transcatheter heart valve implantation for failing surgical bioprostheses: technical considerations and evidence for valve-in-valve procedures. *Heart.* 2013;99:960-7.
5. **Mylotte D**, Osnabrugge RL, Martucci G, Lange R, Kappetein AP, Piazza N. Failing surgical bioprosthesis in aortic and mitral position. *EuroIntervention.* 2013;9 Suppl:S77-83.
6. **Mylotte D**, Lefevre T, Sondergaard L, Watanabe Y, Modine T, Dvir D, Bosmans J, Tchetché D, Kornowski R, Sinning JM, Theriault-Lauzier P, O'Sullivan CJ, Barbanti M, Debry N, Buithieu J, Codner P, Dorfmeister M, Martucci G, Nickenig G, Wenaweser P, Tamburino C, Grube E, Webb JG, Windecker S, Lange R, Piazza N. Transcatheter aortic valve replacement in bicuspid aortic valve disease. *J Am Coll Cardiol.* 2014;64:2330-9.
7. **Mylotte D**, Piazza N. Transcatheter Aortic Valve Replacement Failure: Deja vu ou Jamais vu? *Circ Cardiovasc Interv.* 2015; 8:4.
8. **Mylotte D**, Andalib A, Theriault-Lauzier P, Dorfmeister M, Girgis M, Alharbi W, Chetrit M, Galatas C, Mamane S, Sebag I, Buithieu J, Bilodeau L, de Varennes B, Lachapelle K, Lange R, Martucci G, Virmani R, Piazza N. Transcatheter heart valve failure: a systematic review. *Eur Heart J.* 2014. 36:1306-27.
9. **Mylotte D**, Pilote L, Ionescu-Ittu R, Abrahamowicz M, Khairy P, Therrien J, Mackie AS, Marelli A. Specialized adult congenital heart disease care: the impact of policy on mortality. *Circulation.* 2014;129:1804-12.
10. **Mylotte D**, Martucci G, Piazza N, McElhinney D. Percutaneous options for heart failure in adults with congenital heart disease. *Heart Fail Clin.* 2014;10:179-96.
11. **Mylotte D**, Quenneville SP, Kotowycz MA, Xie X, Brophy JM, Ionescu-Ittu R, Martucci G, Pilote L, Therrien J, Marelli AJ. Long-term cost-effectiveness of transcatheter versus surgical closure of secundum atrial septal defect in adults. *Int J Cardiol.* 2014;172:109-14.
12. **Mylotte D**, Routledge H, Harb T, Garot P, Hovasse T, Benamer H, Untersee H, Chevalier B, Morice MC, Louvard Y, Lefevre T. Provisional side branch-stenting for coronary bifurca-

- tion lesions: Evidence of improving procedural and clinical outcomes with contemporary techniques. *Catheter Cardiovasc Interv.* 2013;82:437-45.
13. **Mylotte D**, Morice MC, Eltchaninoff H, Garot J, Louvard Y, Lefevre T, Garot P. Reply: Challenges in retrospective analysis of PCI data in critically ill patients. *JACC Cardiovasc Interv.* 2013;6:986-7.
14. **Mylotte D**, Morice MC, Eltchaninoff H, Garot J, Louvard Y, Lefevre T, Garot P. Primary percutaneous coronary intervention in patients with acute myocardial infarction, resuscitated cardiac arrest, and cardiogenic shock: the role of primary multivessel revascularization. *JACC Cardiovasc Interv.* 2013;6:115-25.
15. **Mylotte D**, Sheahan RG, Nolan PN, Neylon MA, McArdle B, Constant O, Diffley A, Keane D, Nash PJ, Crowley J, Daly K. The implantable defibrillator and return to operation of vehicles study. *Europace.* 2012;15:212-8.
16. **Mylotte D**, Meftout B, Moynagh A, Vaquerizo B, Darremont O, Silvestri M, Louvard Y, Leymarie JL, Morice MC, Lefevre T, Garot P. Unprotected left main stenting in the real world: five-year outcomes of the French Left Main Taxus registry. *EuroIntervention.* 2012;8:970-81.
17. **Mylotte D**, Kavanagh GF, Peace AJ, Tedesco AF, Carmody D, O'Reilly M, Foley DP, Thompson CJ, Agha A, Smith D, Kenny D. Platelet reactivity in type 2 diabetes mellitus: a comparative analysis with survivors of myocardial infarction and the role of glycaemic control. *Platelets.* 2012;23:439-46.
18. **Mylotte D**, Hovasse T, Ziani A, Lefevre T, Dumonteil N, Louvard Y, Carrie D. Non-compliant balloons for final kissing inflation in coronary bifurcation lesions treated with provisional side branch stenting: a pilot study. *EuroIntervention.* 2012;7:1162-9.
19. **Mylotte D**, Peace AJ, Tedesco AT, Mangiacapra F, Dicker P, Kenny D, Foley DP. Clopidogrel discontinuation and platelet reactivity following coronary stenting. *J Thromb Haemost.* 2011;9:24-32.
20. **Mylotte D**, Foley D, Kenny D. Platelet function testing: methods of assessment and clinical utility. *Cardiovasc Hematol Agents Med Chem.* 2011;9:14-24.
21. **Mylotte D**, O'Regan A. Images in clinical medicine. What lies beneath? *New Engl J Med.* 2008;359:1822.
22. **Mylotte D**, Byrne RA, Iijima R, Kastrati A. Multivessel percutaneous coronary intervention: a review of the literature and fallacies in its interpretation. *Minerva Cardioangiol.* 2008;56:493-510.
23. **Mylotte D**, Sudre A, Teiger E, Obadia J, Spence M, Khamis H, Delhay C, Koussa M, Debry N, Piazza N, Modine T. Transcarotid Transcatheter Aortic Valve Replacement: Feasibility and Safety. *J Am Coll Cardiol.* 2016;9:472-80.
24. **Mylotte D**, Osnabrugge RL, Martucci G, Lange R, Kappetein AP, Piazza N. Adoption Of Transcatheter Aortic Valve Implantation In Western Europe. *Intervent Cardiol Rev.* 2013;9:37-40.

25. Piazza N, Martucci G, Lachapelle K, de Varennes B, Bilodeau L, Buithieu J, **Mylotte D**. First-in-human experience with the Medtronic CoreValve Evolut R. *EuroIntervention*. 2014;9:1260-3.
26. McHugh F, Ahmed K, Neylon A, Sharif F, Mylotte D. Antithrombotic management after transcatheter aortic valve implantation. *J Thorac Dis* 2018. In Press.
27. Osnabrugge RL, **Mylotte D**, Head SJ, Van Mieghem NM, Nkomo VT, Lereun8CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol*. 2013;62:1002-12.
28. Hovasse T, **Mylotte D**, Garot P, Salvatella N, Morice MC, Chevalier B, Pichard A, Lefevre T. Duration of balloon inflation for optimal stent deployment: Five Seconds Is Not Enough. *Catheter Cardiovasc Interv*. 2013;81:446-53.
29. Byrne RA, **Mylotte D**, Nolan P, Nash P. Migration of inferior vena cava stent into right ventricle: two- and three-dimensional echocardiographic imaging. *Eur J Echocardiogr*. 2009;10:370-1.
30. Benamer H, **Mylotte D**, Garcia-Alonso C, Untersee T, Garot P, Louvard Y, Lefevre T, Morice MC. Renal denervation a treatment for resistant hypertension: A French experience. *Ann Cardiol Angeiol*. 2013;62:384-91.
31. Tzikas A, **Mylotte D**, Bergman M. Real world outcomes of Left Atrial Appendage Occlusion. *Intervent Cardiol Rev*. 2016; 2016;10:109-111.
32. Sherlock M, **Mylotte D**, Mac Mahon J, Moore KB, Thompson CJ. Lipid lowering targets are easier to attain than those for treatment of hypertension in type 2 diabetes. *Ir J Med Sci*. 2006;175:36-41.
33. Agha A, Rogers B, **Mylotte D**, Taleb F, Tormey W, Phillips J, Thompson CJ. Neuroendocrine dysfunction in the acute phase of traumatic brain injury. *Clin Endocrinol*. 2004;60:584-91.
34. Theriault-Lauzier P, Andalib A, Martucci G, **Mylotte D**, Cecere R, Lange R, Tchetche D, Modine T, van Mieghem N, Windecker S, Buithieu J, Piazza N. Fluoroscopic anatomy of left-sided heart structures for transcatheter interventions: insight from multislice computed tomography. *JACC Cardiovasc Interv*. 2014;7:947-57.
35. Andalib A, Mamane S, Schiller I, Zakem A, **Mylotte D**, Martucci G, Lauzier P, Alharbi W, Cecere R, Dorfmeister M, Lange R, Brophy J, Piazza N. A systematic review and meta-analysis of surgical outcomes following mitral valve surgery in octogenarians: implications for transcatheter mitral valve interventions. *EuroIntervention*. 2014;9:1225-34.
36. Dvir D, Webb JG, Piazza N, Blanke P, Barbanti M, Bleiziffer S, Wood DA, **Mylotte D**, Wilson AB, Tan J, Stub D, Tamburino C, Lange R, Leipsic J. Multicenter Evaluation of Transcatheter Aortic Valve Replacement Using either SAPIEN XT or CoreValve: Degree of Device Oversizing by Computed-Tomography and Clinical Outcomes. *Catheter Cardiovasc Interv*. 2015; 86:508-15.

37. Hayashida K, Lefevre T, Chevalier B, Hovasse T, Romano M, Garot P, **Mylotte D**, Uribe J, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B, Morice MC. True percutaneous approach for transfemoral aortic valve implantation using the Prostar XL device: impact of learning curve on vascular complications. *JACC Cardiovasc Interv.* 2012;5:207-14.
38. Hayashida K, Lefevre T, Chevalier B, Hovasse T, Romano M, Garot P, **Mylotte D**, Uribe J, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B, Morice MC. Transfemoral aortic valve implantation new criteria to predict vascular complications. *JACC Cardiovasc Interv.* 2011;4:851-8.
39. Hayashida K, Bouvier E, Lefevre T, Hovasse T, Morice MC, Chevalier B, Romano M, Garot P, **Mylotte D**, Farge A, Donzeau-Gouge P, Cormier B. Impact of CT-guided valve sizing on post-procedural aortic regurgitation in transcatheter aortic valve implantation. *EuroIntervention.* 2012;8:546-55.
40. Seitz J, Horvilleur J, Lacotte J, D OHI, Mouhoub Y, Maltret A, Salerno F, **Mylotte D**, Monchi M, Garot J. Correlation between AF substrate ablation difficulty and left atrial fibrosis quantified by delayed-enhancement cardiac magnetic resonance. *Pacing Clin Electrophysiol.* 2011;34:1267-77.
41. Piazza N, Lauzier P, **Mylotte D**. Transcatheter aortic valve replacement and new conduction abnormalities/permanent pacemaker: Can we achieve the intended implant depth? *JACC Cardiovasc Interv.* 2016. 9:255-8.
42. **Mylotte D**, Piazza N, Serruys PW. TAVI adoption in Germany: onwards and upwards. *EuroIntervention.* 2016;11:968-70.
43. Vaquerizo B, Spaziano M, Alali J, **Mylotte D**, Theriault-Lauzier P, Alfagih R, Martucci G, Buithieu J, Piazza N. Three-dimensional echocardiography vs. computed tomography for transcatheter aortic valve replacement sizing. *Eur Heart J Cardiovasc Imaging.* 2016. 17:15-23.
44. Theriault-Lauzier P, **Mylotte D**, Dorfmeister M, Spaziano M, Andalib A, Mamane S, Chetrit M, Blanke P, Cecere R, Buithieu J, Martucci G, Tchetché D, Modine T, van Mieghem N, Lange R, Windecker S, Bilodeau L, Leipsic J, Piazza N. Quantitative multi-slice computed tomography assessment of the mitral valvular complex for transcatheter mitral valve interventions part 1: systematic measurement methodology and inter-observer variability. *EuroIntervention* 2016;12:e1011-e1020.
45. Theriault-Lauzier PP, Dorfmeister M, **Mylotte D**, Andalib A, Spaziano M, Blanke P, Martucci G, Lange R, Leipsic J, Bilodeau L, Piazza N. Quantitative multi-slice computed tomography assessment of the mitral valvular complex for transcatheter mitral valve interventions part 2: geometrical measurements in patients with functional mitral regurgitation. *EuroIntervention.* 2016;12:e1021-e1030.
46. **Mylotte D**, Piazza N. Transcatheter mitral valve implantation: a brief review. *EuroIntervention* 2015;11 Suppl W:W67-70.

47. O'Connor S, Piazza N, **Mylotte D**. Tailoring TAVI in Asia: insights from MSCT. *AsiaIntervention*. 2016;4:122-125.
48. Head SJ, **Mylotte D**, Mack MJ, Piazza N, van Mieghem N, Leon MB, Kappetein AP, Holmes Jr DR. Considerations and Recommendations for the Introduction of Objective Performance Criteria for Transcatheter Aortic Heart Valve Device Approval. *Circulation*. 2016 ;133:2086-93.
49. **Mylotte D**, Piazza N. Patient selection for transcatheter or surgical intervention: the Heart Team TRUMPS the STS. *EuroIntervention*. 2016;12:1439-1440.
50. Debry N, Delhay C, Azmoun A, Ramadan R, Fradi S, Brenot P, Sudre A, Moussa MD, Tchetché D, Ghostine S, **Mylotte D**, Modine T. Transcatheter Aortic Valve Replacement: General or Local Anesthesia. Impact of Renal Dysfunction on Results of Transcatheter Aortic Valve Replacement Outcomes in a Large Multicenter Cohort. *JACC Cardiovasc Interv*. 2016;9:2113-2120.
51. Codner P, Levi A, Gargiulo G, Praz F, Hayashida K, Watanabe Y, **Mylotte D**, Debry N, Barbanti M, Lefèvre T, Modine T, Bosmans J, Windecker S, Barbash I, Sinning JM, Nickenig G, Barsheshet A, Kornowski R. *Am J Cardiol*. 2016;118:1888-1896.
52. Sawaya FJ, Deutsch MA, Seiffert M, Yoon SH, Codner P, Wickramarachchi U, Latib A, Petronio AS, Rodés-Cabau J, Taramasso M, Spaziano M, Bosmans J, Biasco L, **Mylotte D**, Savontaus M, Gheeraert P, Chan J, Jørgensen TH, Sievert H, Mocetti M, Lefèvre T, Maisano F, Mangieri A, Hildick-Smith D, Kornowski R, Makkar R, Bleiziffer S, Søndergaard L, De Backer O. Safety and Efficacy of Transcatheter Aortic Valve Replacement in the Treatment of Pure Aortic Regurgitation in Native Valves and Failing Surgical Bioprostheses: Results From an International Registry Study. *JACC Cardiovasc Interv*. 2017;10:1048-1056.
53. **Mylotte D**. Structural heart disease training: time for structure. *EuroIntervention*. 2017;12:e2161-e2162.
54. Kalra SS, Firoozi S, Yeh J, Blackman DJ, Rashid S, Davies S, Moat N, Dalby M, Kabir T, Khogali SS, Anderson RA, Groves PH, **Mylotte D**, Hildick-Smith D, Rampat R, Kovac J, Gunarathne A, Laborde JC, Brecker SJ. Initial Experience of a Second-Generation Self-Expanding Transcatheter Aortic Valve: The UK & Ireland Evolut R Implanters' Registry. *JACC Cardiovasc Interv*. 2017;10:276-282.
55. **Mylotte D**. The forgotten valve no more. *EuroIntervention*. 2017;12:e1799-e1801.
56. Coughlan JJ, Kiernan T, **Mylotte D**, Arnous S. Annular Rupture During Transcatheter Aortic Valve Implantation: Predictors, Management and Outcomes. *Interv Cardiol*. 2018;13:140-144.
57. Dowling C, Firoozi S, Doyle N, Blackman DJ, Malkin CJ, Cunningham MS, Saraf S, Buch MH, Levy R, Chowdhary S, Spence MS, Manoharan G, Owens CG, Brennan PF, Roberts D, More R, Wiper A, Abdelaziz HK, **Mylotte D**, Neylon A, Martin N, Mercanti F, Dorman S, Panoulas V, Dalby M, Kashyap MN, Kabir T, Kovac J, Kontoprias K, Malik IS, Ghada MW, Sen S, Ruparelia N, Demir OM, Frame A, Uren NG, Anderson R, Rajathurai T, Tapp

- L, Deegan L, Grech E, Hall I, Neville M, Rampat R, Hildick-Smith D, Mullen M, Kennon S, Chandrala P, Doshi S, Brecker SJ. Initial experience of a large, self-expanding, and fully recapturable transcatheter aortic valve: The UK & Ireland Implanters' registry. *Catheter Cardiovasc Interv*. 2018. In Press
57. **Mylotte D**. MITRA-FR: speed bump or end of the road for percutaneous mitral repair in secondary mitral regurgitation? *EuroIntervention*. 2018;14:841-842.
58. Holm NR, Andreasen LN, Walsh S, Kajander OA, Witt N, Eek C, Knaapen P, Koltowski L, Gutiérrez-Chico JL, Burzotta F, Kockman J, Ormiston J, Santos-Pardo I, Laanmets P, **Mylotte D**, Madsen M, Hjort J, Kumsars I, Råmunddal T, Christiansen EH Rational and design of the European randomized Optical Coherence Tomography Optimized Bifurcation Event Reduction Trial (OCTOBER). *Am Heart J*. 2018;205:97-109.
59. Kotronias RA, Teitelbaum M, Webb JG, **Mylotte D**, Barbanti M, Wood DA, Ballantyne B, Osborne A, Solo K, Kwok CS, Mamas MA, Bagur R. Early Versus Standard Discharge After Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. *JACC Cardiovasc Interv*. 2018;11:1759-1771.
60. Dvir D, Khan J, Kornowski R, Komatsu I, Chatriwalla A, Mackenson GB, Simonato M, Ribeiro H, Wood D, Leipsic J, Webb J, **Mylotte D**. Novel strategies in aortic valve-in-valve therapy including bioprosthetic valve fracture and BASILICA. *EuroIntervention*. 2018;14:AB74-AB82.
61. **Mylotte D**. TAVI: a country for old men. Is this durable? *EuroIntervention*. 2018;14:e247-e249.
62. Walsh SJ, Hanratty CG, Watkins S, Oldroyd KG, Mulvihill NT, Hensey M, Chase A, Smith D, Cruden N, Spratt JC, **Mylotte D**, Johnson T, Hill J, Hussein HM, Bogaerts K, Morice MC, Foley DP. Culotte stenting for coronary bifurcation lesions with 2nd and 3rd generation everolimus-eluting stents: the CELTIC Bifurcation Study. *EuroIntervention*. 2018;14:e318-e324.
63. Overtchouk P, Sudre A, Delhay C, Juthier F, Van Belle E, Coisne A, Koussa M, **Mylotte D**, Modine T. Advanced image processing with fusion and calcification enhancement in transcatheter aortic valve implantation: impact on radiation exposure. *Interact Cardiovasc Thorac Surg*. 2018;27:512-519.
64. **Mylotte D**. The humble case report: bottom of the evidence-based medical pyramid or the foundation of clinical research? *EuroIntervention*. 2018;13:e2097-e2098.
65. Durko AP, Osnabrugge RL, Van Mieghem NM, Milojevic M, **Mylotte D**, Nkomo VT, Pieter Kappetein A. Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections. *Eur Heart J*. 2018;39:2635-2642.
66. Fennelly E, Lee M, Da Costa M, Sultan S, Sharif F, **Mylotte D**. Transcatheter Aortic Valve Implantation in a Nonagenarian with Aortic Aneurysm: Futility or Utility? *Case Rep Cardiol*. 2018;5434953.
67. Neylon A, **Mylotte D**. Who you gonna call? *EuroIntervention*. 2018;13:e1735-e1737.

68. Eggebrecht H, Vaquerizo B, Moris C, Bossone E, Lämmer J, Czerny M, Zierer A, Schröfel H, Kim WK, Walther T, Scholtz S, Rudolph T, Hengstenberg C, Kempfert J, Spaziano M, Lefevre T, Bleiziffer S, Schofer J, Mehili J, Seiffert M, Naber C, Biancari F, Eckner D, Cornet C, Lhermusier T, Philippart R, Siljander A, Giuseppe Cerillo A, Blackman D, Chieffo A, Kahlert P, Czerwinska-Jelonkiewicz K, Szymanski P, Landes U, Kornowski R, D'Onofrio A, Kaulfersch C, Søndergaard L, **Mylotte D**, Mehta RH, De Backer O. Incidence and outcomes of emergent cardiac surgery during transfemoral transcatheter aortic valve implantation (TAVI): insights from the European Registry on Emergent Cardiac Surgery during TAVI (EuRECS-TAVI).; European Registry on Emergent Cardiac Surgery during TAVI (EuRECS-TAVI). *Eur Heart J*. 2018;39:676-684.
69. Kolte D, Sardar P, Khera S, Zeymer U, Thiele H, Hochadel M, Radovanovic D, Erne P, Hambraeus K, James S, Claessen BE, Henriques JPS, **Mylotte D**, Garot P, Aronow WS, Owan T, Jain D, Panza JA, Frishman WH, Fonarow GC, Bhatt DL, Aronow HD, Abbott JD. Culprit Vessel-Only Versus Multivessel Percutaneous Coronary Intervention in Patients With Cardiogenic Shock Complicating ST-Segment-Elevation Myocardial Infarction: A Collaborative Meta-Analysis. *Circ Cardiovasc Interv*. 2017. In Press.
70. **Mylotte D**, Rushani D, Therrien J, Guo L, Liu A, Guo K, Martucci G, Mackie AS, Kaufman JS, Marelli A. Incidence, Predictors, and Mortality of Infective Endocarditis in Adults With Congenital Heart Disease Without Prosthetic Valves. *Am J Cardiol*. 2017;120:2278-2283.
71. Gaudino M, Alexander JH, Bakaeen FG, Ballman K, Barili F, Calafiore AM, Davierwala P, Goldman S, Kappetein P, Lorusso R, **Mylotte D**, Pagano D, Ruel M, Schwann T, Suma H, Taggart DP, Tranbaugh RF, Fremes S. Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol. *Eur J Cardiothorac Surg*. 2017;52:1031-1040.
72. Xiong TY, Feng Y, Liao YB, Li YJ, Zhao ZG, Wei X, Xu YN, Wei JF, Peng Y, Piazza N, **Mylotte D**, Chen M. Transcatheter aortic valve replacement in patients with non-calcific aortic stenosis. *EuroIntervention*. 2018;13:e1756-e1763.
73. **Mylotte D**. Transcatheter mitral valve replacement: looking beyond the implant. *EuroIntervention*. 2017;13:e1011-e1012.
74. Levi A, Codner P, Masalha A, Gargiulo G, Praz F, Hayashida K, Watanabe Y, **Mylotte D**, Debry N, Barbanti M, Lefèvre T, Modine T, Bosmans J, Windecker S, Barbash I, Sinning JM, Nickenig G, Barsheshet A, Kornowski R. Predictors of 1-Year Mortality After Transcatheter Aortic Valve Implantation in Patients With and Without Advanced Chronic Kidney Disease. *Am J Cardiol*. 2017;120:2025-2030.
75. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-2791.

76. Byrne RA, Capodanno D, **Mylotte D**, Serruys PW. State of the art: 40 years of percutaneous cardiac intervention. *EuroIntervention*. 2017;13:621-624.
77. **Mylotte D**, Byrne RA. EuroPCR 2017, late-breaking clinical trials and EuroIntervention. *EuroIntervention*. 2017;13:e499-e502.
78. Spaziano M, **Mylotte D**, Thériault-Lauzier P, De Backer O, Søndergaard L, Bosmans J, Debry N, Modine T, Barbanti M, Tamburino C, Sinning JM, Grube E, Nickenig G, Mellert F, Bleiziffer S, Lange R, de Varennes B, Lachapelle K, Martucci G, Piazza N. Transcatheter aortic valve implantation versus redo surgery for failing surgical aortic bioprostheses: a multicentre propensity score analysis. *EuroIntervention*. 2017;13:1149-1156.
79. Hameed A, Zafar H, **Mylotte D**, Sharif F. Recent Trends in Clot Retrieval Devices: A Review. *Cardiol Ther*. 2017 Dec;6(2):193-202.
80. Khamis R, **Mylotte D**. An old dichotomy in the space(r) age. *EuroIntervention*. 2017 Jun 20;13(3):259-261.

BOOK CHAPTERS

1. Endovascular and Hybrid Therapies for Structural Heart and Aortic Disease, 1st Edition. Edited by Jacques Kpodonu, Raoul Bonan. Transfemoral transcatheter aortic valve replacement. **Darren Mylotte**, Giuseppe Martucci, Rudiger Lange, Nicolo Piazza. 2013
2. Heart Valves, 1st Edition. Transcatheter Aortic Valves: **Darren Mylotte**, Giuseppe Martucci, Nicolo Piazza. 2013.
3. Transcatheter Heart Valve Replacement: An Illustrated Atlas. Informa Healthcare. Partick Serruys, Stephan Windeker, Martyn Thomas, Nicolo Piazza, **Darren Mylotte**, Nicolas van Meighem, Christos Bourantas, Stephan Stortecky. 1st Edition.

PHD-PORTFOLIO

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 Erasmus MC department: Cardio-Thoracic Surgery
 Promotor: Prof.dr. A.P. Kappetein

Academic Education

1995-2001 BCh BAO LRCPI (Hons) Royal College of Surgeons, Dublin, Republic of Ireland
2004 Membership Royal College of Physicians in Ireland
2004-2012 Irish Specialist Registrar Training Program
2006 US Medical Licensing Examinations
2011 Doctor of Medicine, Royal College of Surgeons in Ireland
2012 Health Service Management Diploma, Irish Institute of Commercial Management

PhD training	Year	ECTS
Oral presentations (21.6)		
EuroPCR (Paris, France)	2011	2.4
Transcatheter Cardiovascular Therapeutics (San Francisco, California, USA)	2011	1.2
Irish Cardiac Society, Killarney, Ireland	2011	1.2
American Heart Association (Orlando, Florida, USA)	2011	0.6
American College of Cardiology (Chicago, Illinois, USA)	2012	0.6
EuroPCR (Paris, France)	2012	0.6
Leipzig Intervention Course (Leipzig, Germany)	2013	0.6
European Society of Cardiology (Amsterdam, Netherlands)	2013	0.6
Irish Cardiac Society (Killarney, Ireland)	2013	1.2
EuroPCR (Paris, France)	2013	1.2
American College of Cardiology (San Francisco, California, USA)	2013	1.2
PCR London Valves (London, UK)	2014	0.6
American College of Cardiology (Washington, DC, USA)	2014	1.2
EuroPCR (Paris, France)	2014	1.2
European Society of Cardiology (Barcelona, Spain)	2014	0.6
Irish Cardiac Society (Athlone, Ireland)	2014	0.6
EuroPCR (Paris, France)	2015	2.4
PCR London Valve (Berlin, Germany)	2015	1.8
PCR CIT China Valve (Chengdu, China)	2015	1.8
Poster presentations (4.8)		
Transcatheter Cardiovascular Therapeutics (San Francisco, California, USA)	2011	0.6
American Heart Association (Orlando, Florida, USA)	2011	0.6
EuroPCR (Paris, France)	2012	0.6

American College of Cardiology (Chicago, Illinois, USA)	2012	0.6
European Society of Cardiology (Amsterdam, Netherlands)	2013	0.6
EuroPCR (Paris, France)	2013	1.2
American College of Cardiology (San Francisco, California, USA)	2013	0.6
European Society of Cardiology (Barcelona, Spain)	2014	0.6
Conferences (8.7)		
EuroPCR (Paris, France)	2011-2015	1.2
European Society of Cardiology	2011-2014	2.7
American College of Cardiology	2012-2014	1.5
American Heart Association	2011	0.9
Transcatheter Cardiovascular Therapeutics	2011-2014	1.2
PCR London Valves	2012-2015	1.2
In-depth courses (0.6)		
VITAL Presentation Training (Europa Publishing, Paris)	2014	0.6
Courses, seminars and meetings (3.3)		
PCR CIT Chengdu Valve Board Meeting (Berlin, Germany)	2012	0.3
Local scientific meetings of Dept. of Interventional Cardiology (McGill University Health Centre, Montreal, Canada)	2012-2014	3.0
Local scientific meetings of Dept. of Interventional Cardiology (Institut Cardiovasculaire de Paris, Paris, France)	2010-2012	2.0
Teaching (2.0)		
Supervising students and clinical researchers	2012-2016	2.0
Academic positions (7.0)		
Associate Editor Interventional Cardiology Review	2014-present	2.0
Associate editor Eurointervention (Rotterdam, Netherlands)	2013-present	2.0
Honorary Clinical Lecturer (University Hospital Galway)	2013-present	2.0
Course Co-Director PCR CIT Chengdu Valve	2015-present	1.0
Peer reviewer international scientific journals (4.0)		
European Heart Journal	2013-present	0.5
EuroIntervention	2013-present	0.5
JACC Cardiovascular Interventions	2014-present	0.5
American Heart Journal	2013-present	0.5
American Journal of Cardiology	2013-present	0.5
Catheterization and Cardiovascular Interventions	2014-present	0.5
British Journal of Cardiology	2014-present	0.5
Circulation Cardiovascular Intervention	2015-present	0.5

**DANKWOORD
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Late night Skype interviews with Dr Judith Therrien and Dr Giuseppe Martucci sealed a move to Montreal for a congenital and structural interventional fellowship. On this transatlantic voyage we were accompanied by our beautiful Parisian daughter Amélie. It was an honour to work with the amazing team at the Maude Unit in the Victoria Hospital (Montecarlos, Joanne, Lizzy, Johanne, Kathleen, Serge, and Lara), at the Jewish General Hospital, and the Montreal Children's Hospital. I am forever indebted to the family of Beth Raby whose generous support enabled me to learn from the stellar congenital team at the McGill University Health Care Centre. A huge thank you to Dr Judith Therrien, the most intelligent, compassionate, and practical physician I have met. I am so grateful to Professor Ariane Marelli who *tried* to teach me the art of clinical research and gave me amazing datasets with which to work. Dr Jean Buithieu, Dr Adrian Dancea, Dr Nathalie Bottega, Dr Renee Schiff, and my co-fellow Dr Ken Guo were constant supports. Dr Joe Martucci (Hey Joe!), from whom I learned congenital and

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In Galway, we were so happy to welcome “baby” Archie into our family. How lucky I am to have three amazing children who I love more than life itself. Amélie-boo, Evie-bun, and “baby” Archie, I will do all I can to give you all the love and opportunity that I was afforded.

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ABOUT THE AUTHOR

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Darren Mylotte was born on November 13, 1976, in Birmingham, the United Kingdom. His father, a native of County Mayo, on the west coast of Ireland, moved the family to Galway in 1981. Darren attended St. Patricks' national school and St. Josephs' secondary school in Galway.

In 1995, Darren started his medical undergraduate education at the Royal College of Surgeons in Dublin, Ireland. He graduated with honours in 2001, having been elected as President of the Student's Union and Sports Union during his tenure. Darren commenced work as a junior doctor (Medical Intern) and subsequently enrolled on the medical senior house officer-training scheme, during which he completed membership of the Royal College of Physicians in Ireland.

Darren started his general cardiology training in 2005, and undertook a Doctor of Medicine Degree in the field of cardiovascular platelet biology in 2007 under the guidance of Professor Dermot Kenny, at the Royal College of Surgeons. He then undertook fellowship training in interventional cardiology at the Institut Cardiovasculaire, in Paris, France in 2010. In 2012, he was awarded the European Society of Cardiology, Clinical Young Investigator of the Year and subsequently the Young Author Achievement Award from the Journal of the American College of Cardiology, Cardiovascular Interventions. In 2012, Darren commenced a clinical / interventional congenital and structural heart disease fellowship under the supervision of Dr.s Nicolo Piazza, Giuseppe Martucci, and Judith Therrien at the McGill University Health Centre, in Montreal, Quebec, Canada. In 2012, he started his Ph.D. research at the department of Cardio-Thoracic Surgery, Erasmus University Medical Center, under the supervision of Professor A.P. Kappetein. His work focuses on the evolution of transcatheter heart valve interventions. He is a deputy editor of *EuroIntervention*, is the structural heart disease editor of *Interventional Cardiology Review* and is an associate editor of *Frontiers in Interventional Cardiology*. Darren is a consultant cardiologist at the University Hospital and a senior lecturer at the National University of Ireland, Galway, in Ireland. He lives in Galway his beloved wife Joanna, two beautiful daughters, Amélie and Evie, and his "baby-boy" Archie.

