A novel Trans-Catheter Heart Valve System for Low- to Middle-Income Countries: Need assessment, Surgical Feasibility and Preclinical Translation

By

Assoc. Prof. Jacques Scherman
MBChB (Pret); DipOccMed (Stell); FC Cardio (SA); MMed (Uct)
Student number : SCHJAC015

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Supervisor: Professor Peter Zilla
Emeritus Chris Barnard Professor, Division of Cardiothoracic Surgery
University of Cape Town

As the candidate's supervisor I have approved this thesis for submission.

Signed: **Date:** 26 September 2023

Professor Peter Zilla
Emeritus Chris Barnard Professor, Division of Cardiothoracic Surgery
University of Cape Town
South Africa

DECLARATION

I, **A/Prof.Dr. Jacques Scherman** declare that

i. The research reported in this dissertation, except where otherwise indicated, and is my original work.
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1. **Scherman J**, Zilla P. Poorly Suited Heart valve prostheses heighten the plight of patients with rheumatic heart disease. Int J Cardiol. 2020; 318: 104-114.
2. **Scherman J**, Manganyi R, Human P, Pennel T, Brooks A, Brink J, Zilla P. Isolated Mechanical Aortic Valve Replacement in Rheumatic Patients in a Low- To Middle-Income Country. J Thoracic Cardiovasc Surg. 2019; 157(3): 886-893.
3. **Scherman J**, Van Breda B, Appa H, Van Heerden C, Ofoegbu C, Bezuidenhout D, Zilla P. Transcatheter Valve with Hollow-Balloon for Aortic valve Incompetence. Multimed Man Cardiothorac Surg. 2018, Feb 26.
4. **Scherman J**, Bezuidenhout D, Ofoegbu C, Williams DF, Zilla P. TAVI for low to middle income countries. Eur Heart J. 2017; 38(16): 1182-1184.
5. **Scherman J**, Ofoegbu C, Myburgh A, Swanevelder J, Van Breda B, Appa H, Human P, Williams D, Bezuidenhout D, Zilla P. Preclinical Evaluation of a Transcatheter Aortic Valve Replacement System for Patients with Rheumatic Heart Disease. EuroIntervention. 2019 Dec 6;15(11):e975-e982.

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Student number: SCHJAC015

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DEDICATION

In dedication to my parents, my children, my family and friends who have always encouraged and stimulated my academic pursuit in search of knowledge.

'Every Wall is a Door"
W.Clement Stone

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LIST OF ABBREVIATIONS

3D TOE:	3-dimensional transoesophageal echocardiography
AEC:	Animal Ethics Committee
AF:	atrial fibrillation
AR:	aortic regurgitation
ARF:	acute rheumatic fever
AS:	aortic stenosis
AV block:	atrio-ventricular block
AVR:	aortic valve replacement
BPTHV:	bioprosthetic transcatheter heart valve
BRICS:	Brazil, Russia, India, China, South-Africa
Co-Cr:	cobalt chromium
CPB:	cardiopulmonary bypass
CT:	computed tomography
CMR:	cardiovascular magnetic resonance
CVE:	cerebrovascular events
ECM:	extracellular matrix
EF:	ejection fraction
EOA:	effective orifice area
FHS:	Faculty of Health Sciences
FHS AEC:	Faculty of Health Sciences Animal Ethics Committee
GA:	glutaraldehyde
HICs:	high-income countries
INR:	international normalised ratio
ISO:	International Organization for Standardization
LICs:	low income countries
LMICs:	low- to middle-income countries
LVOT:	left ventricular outflow tract
MAVRE:	major adverse valve-related event
MICs:	middle income countries
MSCT:	multi-slice computed tomography
MVR:	mitral valve replacement
NHLS:	National Health Laboratory Service
NOAC:	new oral anticoagulant
Ops/mio:	operations per million
PPM:	permanent pacemaker
PTHV:	polymeric transcatheter heart valve
PVL:	para-valvular leak
R&D:	research and development
RHD:	rheumatic heart disease
SAT:	Strait Access Technologies
SAHPRA:	South African Health Products Regulatory Authority
SAVR:	surgical aortic valve replacement
SOV:	sinus of Valsalva
STJ:	sino-tubular junction
STS:	American Society of Thoracic Surgeons
SVD:	structural valve deterioration
TAVI:	transcatheter aortic valve implantation
TMVR:	transcatheter mitral valve replacement

TOE:	transoesophageal echocardiography
TTE:	transthoracic echocardiography
UCT:	University of Cape Town
VARC:	Valve Academic Research Consortium
VIV:	valve-in-valve
WHO:	World Health Organisation

PUBLICATIONS ARISING FROM THIS RESEARCH:

(1) PEER REVIEWED FULL PAPERS

i. **Scherman J**, Zilla P. Poorly Suited Heart valve prostheses heighten the plight of patients with rheumatic heart disease. Int J Cardiol. 2020; 318: 104-114.
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(2) INTERNATIONAL CONFERENCE PRESENTATIONS

i. *66th Annual Conference of the Israel Heart Society, Tel Aviv, Israel (April 2019).*
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Scherman J, Ofoegbu C, Geldenhuys G, Haw P, Gildenhuys F, Van Breda B, Nelson G, Zilla P.

vii. *63rd Annual Conference of the Israel Heart Society, Tel Aviv, Israel (April 2016).*
Isolated Aortic Valve Replacement in a Rheumatic Population.
Scherman J, Manganyi R, Human P, Zilla P.

(3) NATIONAL CONFERENCE PRESENTATIONS

i. *19th Annual SA Heart Congress, October 2018. Sun City, South Africa. (by invitation)*
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ABSTRACT/EXECUTIVE SUMMARY

My thesis covers the clinical translation of a unique initiative at a South African tertiary institution towards a comprehensive, tailor-made African answer to a global health problem affecting millions of indigent patients outside the industrial world.

At the core lies the inability of low- to middle-income countries (LMICs) to offer life-saving open heart surgery to hundreds of thousands of patients in need. Ironically, this unmet need for heart surgery persists at a time when open heart surgery has increasingly been replaced by trans-catheter interventions in the industrialized world. The overwhelming underlying condition of these patients is 'Rheumatic Heart Disease' (RHD). It is typically a disease of poverty, leading to different levels of destruction of the patients' heart valves in an estimated 33 million patients of LMICs globally. Heart valve surgery is often the only lifesaving remedy. While abundantly available to patients in industrialized countries it is largely absent in developing countries and seriously underprovided in middle income countries. Moreover, heart valve prostheses replacing the patient's diseased own valves were developed for the degenerative pathologies prevailing in high-income countries (HICs) with their sophisticated medical systems. As such, even the small proportion of patients in low-income countries who have access to heart valve surgery have to cope with poorly suited replacement valves. As systematic studies hardly exist in the affected countries, knowledge is anecdotal.

As a clinician at the interface of the developing and the developed world, I dedicated the first part of my thesis to establishing the shortcomings of contemporary replacement heart valves in patients with RHD. This part included one of the rare follow-up studies in indigent patients confirming the need for a radically different concept for these patients.

Providing the clinical end-goals to an engineering endeavor at the University of Cape Town (UCT) to develop a replacement heart valve for rheumatic patients who have no access to open heart surgery, the second phase of my PhD focused on the in-vivo translation of this concept. In the absence of an established animal model for such a trans-catheter solution for patients with RHD, the extensive implant series I performed achieved two goals: an optimization of the devices in close interaction with the engineers and the establishment of anatomical inclusion and exclusion criteria in both the sheep and the pig model.

On the basis of these accomplishments, I worked out an optimal implantation technique addressing the specific socioeconomic circumstances and the prevailing pathology of Developing Countries. Together with a drastically underdeveloped health care system, the leaking rheumatic heart valves of these patients justified a trans-apical approach at a time when industrialized countries had long adopted trans-femoral interventions for their much older patients with calcified, stenotic valves.

I then demonstrated the game-changing short and long-term performance of the heart valve devices developed at UCT in appropriate animal models that I also had to establish first.

Having successfully provided all the preclinical data required for 'first in humans' implants to the regulatory authorities, I used a statistical analysis approach to extrapolate clinical and pre-clinical data towards size predictions for the replacement valves expected to be needed in the upcoming clinical trial while defining anatomical exclusion criteria to further strengthen the safety criteria for these implants.

I trust that a most comprehensive clinical and laboratory-based PhD thesis that systematically progressed through the clinical translation process of a novel UCT-based development from the establishment of the clinical background framework conditions to the readiness to commence clinical trials complies with the high standards defining this highest of all postgraduate degrees.

CHAPTER 1

INTRODUCTION AND MOTIVATION FOR RESEARCH

1. OBJECTIVES OF THE THESIS

My thesis deals with the surgical treatment of rheumatic heart disease (RHD), a major health problem specifically affecting the heart valves of young to middle-aged patients in low- to middle-income countries (LMICs). If untreated, symptomatic RHD leads to death in a significant proportion of these patients. Still, each year hundreds of thousands of patients with rheumatic heart disease either have no access to heart surgery [1, 2] or receive replacement valves which are poorly suited for their pathologies and socio-economic circumstances [3].

As this detrimental dualism hardly affects patients from industrialised countries while being a major cause of mortality in LMICs, solutions need to be found that address the specific requirements of the patients of the developing world suffering from RHD.

Over the past two decades, the University of Cape Town (UCT) has evolved into a global centre of gravity for RHD research with regards to epidemiology and prophylaxis on the one hand [4-11] and access to cardiac surgery on the other [1, 2, 12-14]. While this research revealed a shocking gap between patients in need of heart valve surgery and the actually provided level of open heart surgery, the sub-optimal surgical choices available for the treatment of the few who have access to surgery continued to persist. For one, replacement valves were developed by high income countries (HICs) for their aging population and their sophisticated medical system. Similarly, guidelines for their most efficacious use were derived from huge data bases like that of STS (American Society of Thoracic Surgeons) or the European Society of Cardiothoracic Surgery.

In the absence of adequate data from patients of LMICs with RHD insufficient evidence existed to develop alternative guidelines. Furthermore, in the absence of local technological capabilities, tailor-made prostheses could not be contemplated.

In recent years , such technological capabilities did emerge at UCT in the wake of its overall focus on RHD research. The goal of this was developing tailor-made solutions that addresses both the limited access to open heart surgery in LMICs and the socioeconomic limitations to anticoagulation. The concept of simplifying trans-catheter technologies to allow heart valve implantations under the often non-sophisticated circumstances of LMICs and thereby avoiding the need for open heart surgery promised to increase access to life-saving heart valve surgery for millions of indigent patients. Combining this locally developed technology with the fruits of decades of UCT research into more resilient heart valve materials [15-42] added hope that these replacement valves will not only briefly improve the quality of life of indigent patients with RHD but add many years of life expectancy.

As a long-standing senior surgeon of UCT's Chris Barnard Department of Cardiothoracic surgery, my thesis provides the surgical input to this unique undertaking. Analyzing the specific clinical situation of patients needing heart valve surgery for RHD and providing follow-up data on the performance of contemporary heart valve prostheses in these patients established the baseline of insight into the actual surgical needs a tailor-made solution must address. At the same time, my experimental surgical studies towards establishing an animal model for the evolving development of UCT's trans-catheter valve provided crucial surgical feedback to the engineering team. After having proven the long-term performance of this trans-catheter valve in the sheep model, I used additional acute implant data from my pig experiments to define the anatomical exclusion criteria and predict valve sizes thereby carrying the concept from benchtop all the way through to clinical translation.

2. BACK GROUND

2.A. SURGICAL CHALLENGES OF RHEUMATIC HEART DISEASE

Rheumatic heart disease (RHD) remains one of the largest preventable burdens of disease in the world. It is perceived as a disease of childhood as it is acquired by streptococcal throat infection leading to an inflammatory reaction that involves many organs, including the heart. However, acute cases in children of 5-14 years represent only a minority of all cases [(43)]. The majority of patients only present later in life with the chronic form of the disease which affects patients between late adolescence and middle age [(8)].

2.A.1. Global Prevalence of RHD

In recent years, prophylaxis of RHD had attracted regional and international attention leading to awareness campaigns of world bodies like the WHO. The WHO now fully recognizes the global significance of rheumatic fever and RHD. On May 25th 2018, the World Health Assembly in Geneva adopted a resolution calling for resolute steps towards the global prevention and treatment of RHD. A recent Global Burden of Disease study has estimated the burden of RHD at 33 million [(9, 44, 45)], practically the same as the worldwide HIV infection rate (WHO Global Health Observatory data 2017). The latest studies suggest that 4440 per million population suffer from 'non-silent' RHD in endemic areas [(9)].

As the causative link between acute rheumatic fever (ARF) and chronic RHD had been a firmly established medical fact, societies and governments drew the conclusion from vanishing incidences of ARF that RHD had lost its health political significance. Yet, hundreds of thousands of patients in LMICs still end up with chronic RHD requiring surgery, many of those without a history of ARF, leading to a situation whereby symptomatic RHD became one of the most underappreciated causes of death both in low- (LICs) and middle-income countries (MICs) often without any adequate therapeutic options available.

Clinical evidence and the epidemiological literature show a clear correlation between RHD prevalence and poverty, poor housing, overcrowding and under-funded primary healthcare facilities. With the vast majority of these patients living in low- to middle-income countries rheumatic heart disease (RHD) affects more patients globally than degenerative valve disease. Contrary to the widely held view that RHD primarily affects low-income countries while middle income countries have near eradicated the disease, the latter still claim a significant proportion of the global burden of deaths caused by RHD. The 2015 share of the world-wide burden of RHD was still 21% for upper MICs such as China (23% of global RHD deaths) compared to the 47% (43% of global RHD deaths) for lower MICs such as India and Pakistan. Together, these three MICs comprised 70% of worldwide cases, countering the perception that RHD is restricted to Sub-Saharan Africa and has been largely eradicated elsewhere [(9)].

The poorly understood increase of patients with RHD who cannot recall a history of acute rheumatic fever (ARF) is partly to blame for this disparity of perception, as ARF has been taken as the official benchmark for RHD for decades. The Maghreb region is not the only example where the officially suggested eradication of ARF is paralleled by a continuous high incidence of patients needing heart valve surgery for RHD that cannot only be explained with a clinical lag-phase [(46)]. Results from many parts of the world, especially countries in Africa, demonstrate the clinical and economic burden of RHD and the urgent need for different tools to tackle the problem. Branco *et al* emphasized the neglected and underdiagnosed nature of rheumatic fever in South America in a 2016 paper [(47)]. In Asia, the treatment options for RHD has been discussed in relation to experience in India [(48)], Bangladesh [(49)], Nepal [(50)] and China [(51)]. Demina *et al*, using data from a major hospital in Moscow, Russia, reported that RHD was very

significant, causing significant mortality [52]. The majority of individuals in Australia and New Zealand do not have a high risk for rheumatic fever, but those of indigenous origin do have a high incidence of RHD [53, 54]. This also arises within many islands in the South Pacific [55].
Africa, especially but not exclusively sub-Sahara regions, is the major point for discussions about rheumatic fever and RHD. Unfortunately, very little data is available in the public domain about prevalence in northern Africa countries, but where information is available, for example Egypt [56], Nigeria [57] and Cote D'Ivoire [58] there appears to be a declining prevalence but with remaining significant problems. In the east of the continent, RHD constitutes the major cause of cardiovascular disease in Ethiopia [59] and, although there are facilities for open-heart surgery, the management of these patients is problematic. However, the recent establishment of local capabilities [1] could well be favourable for the introduction of less expensive therapies [60]. In Uganda, it was reported in 2015 that a high proportion of patients with severe RHD require surgical treatment but cannot access treatment due the lack of facilities and local expertise; the need for percutaneous intervention was highlighted [61]. In Harare, Zimbabwe, children usually present late with established RHD and cardiac failure, and secondary prophylaxis is suboptimal in a very poor setting that is unable to offer any valve replacement surgery [62]. In many southern African countries, the prevalence of RHD is unknown. The significance of the problem is only just becoming recognized in other countries such as Madagascar [63].

Paradoxically, in some countries of sub-Sahara Africa, much is known about RHD data, and efforts are in place to improve the infrastructure in order to deal with the prevailing conditions. For example, RHD remains endemic in Tanzania but health care utilization patterns have been altered to improve their infrastructure [64]. Rwanda is well organized; there is a collaboration between the Ministry of Health, the Rwanda Heart Foundation and a humanitarian cardiac program; using local skills, open-heart surgery is available in the country, with good results [65]. This situation should be very receptive to the introduction of less-expensive technology such as that developed at UCT/SAT. South Africa provides a significant amount of epidemiological data on RHD. A 2015 paper by Zuhlke *et al* concluded that the incidence of symptomatic RHD in adults and the prevalence of asymptomatic RHD in children are high, with a high rate of mortality [66].

2.A.2. Patients in need of Cardiac Surgery

Due to the limited availability of cardiac surgery in the affected regions, and therefore the lack of an endpoint of referral in many endemic areas, few hard data are available from which to extrapolate the proportion of patients with RHD who will eventually need surgery. Sliwa et al showed that 22% of patients reach this point within 30 months of becoming symptomatic [5]. Zhang and Okello reported an even worse situation in newly diagnosed RHD in Uganda. In this cohort, 72% required valvular surgery at presentation [67, 68]. Cannon et al recently described a very elegant multi-state model that confirmed the poor prognosis for those aged 5-24 at the time of diagnosis, even in Australia. Of those diagnosed as mild, almost 30% did show progression over 10 years with 11% progressing to severe disease, half of these needing surgery. Even more concerning was the fact that 50% of those with severe RHD at the time of diagnosis required surgery within 2 years and 10 % were dead within 6 years of diagnosis [2, 69].

Emerging echocardiographic screening-studies [70-77] leave the conclusions open as to how many patients will need surgery. Low detection rates by inadequate primary health care structures suggest a low priority for cardiac surgery to governments. Without a referral endpoint, the referral system is discouraged from sending patients for cardiac surgery even if they were successfully identified on the primary health care level [1].

Young patients with symptomatic RHD typically have the mitral valve affected. However, notwithstanding the fact that mitral valve disease remains the major indication for surgery in RHD [5, 59, 78-83], the aortic valve becomes increasingly affected as patients get older in the course of the epidemiologic transition in MICs [1, 2]. As such, the mean age of patients needing surgery has gradually increased as a consequence of urbanisation and affluence [in South Africa from 22 in the early 1980s [84] and 31 in the 1990s [85] to 41 in the late 2000s [5]; in Brazil's to 44 [79] and in Korea to 52 years [86]. As a reflection of this trend, today's largely urban patients of MICs are well into their fourties when they need heart valve replacements for RHD [5, 79]. Our own most recent 10-year cohort (2008-2018) at Groote Schuur Hospital/University of Cape Town (mean age 45±14 years) confirms the trend from a mitral valve predominance to one of the aortic valve: mitral valve surgery was still required in 78% of all patients with RHD but aortic valve replacement (AVR)/AV-repair occurred in 50% (more than half of them needing double valve replacement). The vast majority of the patients needing aortic valve replacement need it for aortic regurgitation (AR). While AR is the almost exclusive clinical presentation of aortic valve disease in low-income countries, RHD still causes four times more patients to be affected by non-calcific AR than calcific AS in middle-income countries. It is estimated that 56% of all patients requiring single aortic valve replacement (AVR) in MICs still need it for rheumatic AR. As this percentage represents a mean value between a Westernizing urban population and a rural majority, a large proportion of patients requiring an AVR outside the reach of metropolitan centres continues to need it for RHD. As AR poses both a diastolic as well as a systolic volume overload, it causes early irremediable damage [87]. The timing of surgery is therefore challenging as the morbidity and mortality associated with aortic valve replacement needs to be weighed against the disease progressing to the point from which onwards a recovery of left ventricular function and improved survival can no longer be achieved [88]. Cut-off points for prognostically meaningful surgery have been >55 mm for end-systolic left ventricular diameter and 25-35 percent for ejection fraction [88, 89]. (see chapter 2).

2.A.3. Surgery for RHD

Once RHD becomes clinically symptomatic, surgery remains the only life-extending therapy. Tragically, access to cardiac surgery is largely absent or very limited [1, 2, 12]. Moreover, even if cardiac surgery is available, prosthetic valves perform poorly in these patients given their young age, the high incidence of multi-valve disease, late diagnoses and often challenging socio-economic circumstances. With open heart surgery hopelessly underprovided in the regions most affected by RHD and replacement valves being poorly suited for such patients, surgical solutions therefore need to address both the means to implant replacement valves under the prevailing conditions as well as their ability to safely function under poorly monitored anticoagulation (see Chapter 2).

As much as patients under these circumstances would benefit from repairs rather than replacement, skills are largely not established and the often severely fibrosed rheumatic valves are not amenable to repairs in a significant proportion of patients. As such, although valve sparing operations even in the presence of severe fibrosis [90] have significantly expanded the spectrum of mitral repairs [81, 91-95] and recently also aortic valve repairs [96] in the hands of a state of the art cardiac centre a significant proportion of patients in low- to middle-income countries will continue to rely on valve replacements. The lack of repair skills in frontline low-volume centres [1] and the high incidences of endocarditis [97] are only two of the reasons. Unfortunately, contemporary replacement heart valves were developed for the patients of industrialised countries with their advanced medical systems. There, complication rates are kept within an acceptable range by providing reliable anti-coagulation monitoring to prevent clotting of the hinge mechanism of mechanical valves and by ensuring that bioprosthetic or so

called ‘tissue valves’ which do not need anticoagulation go preferentially into older patients as they tend to prematurely degenerate in younger patients. Both these preconditions are insufficiently met in low- to middle-income countries (LMICs) where the dominant valve pathology is rheumatic rather than degenerative [1, 2, 8, 58, 80, 81, 98-104].

By being in average 30 years younger than Western patients with degenerative diseases, rheumatic patients are largely deemed to not qualify for contemporary tissue valves due to their accelerated degeneration in this age group. At the same time, socioeconomic circumstances prevailing in areas endemic for RHD concur with poor anticoagulation compliance in patients with mechanical heart valves. Furthermore, co-morbidities like atrial fibrillation affecting a significant proportion of young patients with RHD aggravate the consequences of unreliable compliance with anticoagulation. As such - independent of prostheses related challenges - patients needing surgery for RHD have a significantly higher risk of prosthetic valve failure than those with degenerative or congenital valve disease.

2.A.4. Unmet needs of Cardiac Surgery in LMICs

All of the above evidence demonstrates that many countries that are either of low-income, or have significant low to middle-income regions, or have susceptible indigenous populations, may have a high prevalence of RHD. In these regions, the infrastructure is usually inadequate to provide open-heart surgery, the only established successful therapy . The awareness of RHD has improved following the Drakensburg Declaration [105] and the recent pronouncements of the WHO; preventive schemes are also beginning to have some beneficial effect. However, a very large number of individuals in these countries are still significantly affected by RHD, and are in need of new innovative technologies for the relief of valve dysfunction. In Africa alone, there are 15 million individuals living with RHD and 100,000 per year may need a heart valve intervention at some point in their lives [8].

Yet, capacities for open heart surgery in LMICs fall far short of the demand. With current capacities of LICs like Mozambique, Zimbabwe or Zambia in the region of 1.5 to 4 operations per million (Ops/mio) they under-deliver at least by a factor 50 to 100. In MICs, capacity needs grew 5 to 8 times since the establishment of first independent cardiac surgical outposts in the 1970s leaving them still with only a fraction of the population having access to heart surgery. In China, only 17 patients/million undergo heart valve surgery for RHD although population needs are in the region of 55/million. In India, the under-delivery of heart valve surgery for RHD is by a factor 10. As such, annually, almost 80,000 patients in China and 130,000 in India suffering from symptomatic RHD are not receiving surgery [2].

The biggest service discrepancies, however, do not occur between different countries but emerge between the public and the private sector within a country. At the extreme end is South Africa, where those 17% of the population with access to private medicine receive 12-times more operations per million population than those 83% who depend on the public sector [2]. Differently looked at, one private hospital cares for 300,000 cardiac surgical patients compared to 6.1 million patients per centre in the public sector. Similarly, 7.1 cardiac surgeons provide surgery per million private patients as opposed by 0.7 in public hospitals [2].

Given the fact that a large number of indigent patients would require heart valve surgery while at the same time cardiac surgery is one of the most resource intensive and expensive surgical disciplines a radically different solution will be required for the replacement or repair of rheumatic heart valves for years to come. If adapted to the needs of patients with rheumatic valve disease, transcatheter replacement valves may offer such a radically different solution.

2.B. THE CONCEPT OF TRANSCATHETER HEART VALVE REPLACEMENT

2.B.1. Minimally Invasive, Transcatheter, Heart Valve Procedures

Conventional surgical methods for replacement or repair of diseased heart valves are very successful, but an increasing number of patients, especially elderly patients, present with serious co-morbidities and are poor candidates for open-heart surgery. For a significant percentage of these patients, techniques have been developed where the heart is approached via a catheter, which is threaded through a blood vessel, most commonly along the femoral artery, which is accessed in the groin.

Referred to as TAVI, transcatheter aortic valve implantation, this type of technique is largely directed towards the treatment of severe aortic valve stenosis, being first introduced clinically in 2002 [(106)]. TAVI has evolved to become the standard procedure world-wide [(107)] and can be performed with only moderate sedation instead of general anaesthesia [(108)]. Europe has seen the most widespread adoption of the TAVI concept and several medical device companies have received CE Mark regulatory approval for TAVI valves. These include the original Sapien valve of Edwards Life Sciences [(109)], a balloon-expandable TAVI, and its various modifications [(110)]. The Medtronic CoreValve prosthesis is self-expanding [(111)] as is the St Jude Medical TAVI device, the Portico valve, which can be repositioned [(112)]. Other products are the Direct Flow Medical transcatheter system [(113)], the Symetis Acurate self-expanding valve of Boston Scientific [(114)] and the transapical Jena valve [(115)].

Transcatheter procedures for the treatment of some other conditions of the heart were introduced before those for valve implantation, for example in the closure of atrial septal defects, and their clinical success was already being seen by 2002/2003 [(116)]. At that time, numerous animal studies demonstrating the technical aspects of the TAVI concept were published [(117)]. The technical challenges associated with the use of percutaneous transcatheter methods for the treatment of end-stage inoperable patients with calcific aortic stenosis were discussed by Cribier and his colleagues in 2004 [(118)]. The early development work was performed within a company, Percutaneous Valve Technologies Inc. The first devices used three bovine pericardial leaflets mounted within a 14 mm stainless steel balloon-expandable stent, which achieved a maximum diameter of 23 mm after inflation. All patients reported in the study had severe co-morbidities. Procedures were performed under local anesthesia and mild sedation and an anterograde trans-septal approach was used, performed from the right femoral vein, using a 24F sheath. While the clinical results were mixed due to the very poor state of health of these patients, the technique was shown to be clearly effective. In two of the patients, rapid cardiac pacing was necessary in order to decrease aortic blood flow and reduce the risk of valve migration during balloon inflation. The animal model used to evaluate the procedure was noted to be difficult since sheep have limited space between the coronary ostia and the mitral valve.

The first case of a retrograde transcatheter aortic valve implantation technique was published in 2005 [(119)]. An introducer was advanced into the abdominal aorta *via* the right femoral artery and a valvuloplasty balloon pre-dilated the stenotic aortic valve; a balloon-expandable frame delivered the bioprosthetic valve. Webb *et al* further discussed the need for rapid pacing to facilitate implantation, which was becoming a significant clinical issue [(120)].

Clinical experiences were increasing rapidly, with extensive discussions about the route of implantation. Initially, the transapical route dominated, showing good early results in high risk patients, but with the acknowledgement that longer-term valve performance needed to be extensively studied [(121)]. Improvements in the outcome of trans-arterial valve replacement were also noted, with benefit to mitral regurgitation and left ventricular ejection fraction [(122)].

The position with respect to implantation route, and especially the role of transapical implantation, was discussed by Beyersdorf in 2007 [(123)]. The antegrade femoral venous route was considered to have the advantage of allowing the passage of large profile valved stents across the aortic valve. The long and tortuous route from the femoral vein to the valve, and the necessity of crossing and dilating the atrial septum and the need to cross the mitral valve were all major disadvantages. At the time, the retrograde arterial approach was associated with significant vascular trauma. Beyersdorf therefore considered that the transapical approach had much to offer, permitting a shorter and stiffer delivery system for precise positioning and placement of a stented prosthesis.

At that time and against the background of fundamentally different circumstances and pathologies, UCT's "Strait Access Technologies" was formed with the specific objective of developing a transapical transcatheter system for the implantation of valves that are durable when implanted in the typically young patients with RHD. Apart from the lack of sophisticated imaging facilities that are the backbone of modern trans-femoral deployment in industrialised countries, this transapical system aimed at easy and tactile valve-location and the stabilization of the typically hyperdynamic hearts without needing rapid ventricular pacing.

In industrialised countries, transcatheter aortic valve replacement for degenerative, calcific aortic stenosis continued to evolve towards its primacy today. In 2008, a position statement was issued by the European Association of Cardio-Thoracic Surgery, the European Society of Cardiology and the European Association of Percutaneous Cardiovascular Interventions [(124)]. This indicated that transcatheter aortic valve implantation may offer an alternative to conventional surgery for high-risk patients, but questions remained about safety and long-term durability; the technique should therefore be restricted to high-risk patients with contraindications for surgery, but could be extended to lower-risk patients if early results were confirmed. A major technical problem related to aortic valve malposition, especially giving embolization to the ascending aorta when the final position was supravalvular; at least one publication referred to this as a preventable complication [(125)].

Survival, and clinical complications, associated with both transapical and transfemoral aortic valve implantation were analysed by Bleiziffer *et al* [(126)]. Thirty-day and six-month survivals were 88.8% and 80.1% after transfemoral procedures, and 91.7% and 73.4% after transapical, the differences not being significant. Acute access site complications can occur in both techniques; peripheral vessel rupture, occlusion or bleeding occurs with the transfemoral approach, whilst post-operative thoracic bleeding may occur in transapical patients. It was also suggested that the incidence of neurological events is reduced with the transapical approach.

Results from clinical trials and implantation registries appeared during the 2010-2014 period. The PARTNER trial assessed the performance of the balloon-expandable bovine pericardial valve of Edwards Lifesciences, who had acquired Percutaneous Valve Technologies, and further developed the Sapien Valve [(127)]. This valve was compared to therapies such as balloon valvuloplasty, in a randomized trial involving 358 patients with severe aortic stenosis. Mortality at one year was 30.7% with the TAVI and 50.7% with standard therapy, and death or re-hospitalization was 42.5% with TAVI and 71.6% with standard therapy. With survivors at one year, the rate of cardiac symptoms was lower with TAVI, but TAVI patients were associated with a higher incidence of stroke.

A national transcatheter aortic valve registry was established in France, information from which was published in 2012 [(128)]; this showed that 3195 patients were implanted with either Edwards Sapien (66.9%) or Medtronic CoreValve (33.1%) devices, with a procedural success rate of 96.9%. Rates of death were 9.7% at 30 days and 24.0% at one year; the incidence of stroke at 1 year was 4.1% and of periprosthetic aortic regurgitation, 64.5% (two thirds of it

being mild or less) , with a higher risk in the transapical patients. A Valve Academic Research Consortium (VARC) was established, which provided a detailed discussion about performance [(129)].

A major review of the status of transcatheter aortic valve implantation was published, in two parts, by a multinational group in 2014 [(130, 131)]. These collective observations were made on the basis of over 100,000 TAVI patients who were primarily of geriatric nature, with stenotic, calcified, valves. The following general points were made:

- Existing scoring methods for evaluating risks of surgical and transcatheter procedures, guiding patient selection were suboptimal and needed to be refined.
- Adequate assessment of the aortic annulus was important for prosthesis sizing; undersizing may lead to regurgitation and oversizing may lead to annular rupture.
- Left ventricular function is important for outcomes after TAVI, but prediction of reversibility of this remained difficult.
- Moderate to severe mitral regurgitation is present in a significant number of aortic stenosis patients, which may be improved acutely after TAVI.
- An important complication of TAVI was the occurrence of paravalvular aortic regurgitation.
- Conduction disturbance and the need for permanent pacemaker implantation was also a concern.
- Early cerebrovascular events (CVE) after TAVI were considered to be related to manipulation of the calcified native valve during implantation, late CVE being associated with atrial fibrillation.
- Dual antiplatelet therapy was considered to be the standard of care, but alternative anti-coagulation therapies needed evaluation.
- Durability of the bioprostheses in use had been demonstrated at five years.

Clearly some of these factors are still relevant to the use of TAVI in young patients with RHD.

A systematic review of TAVI versus surgical valve replacement (SAVR) was carried out by an Italian group [(132)]. It was shown that, compared with SAVR, TAVI may have similar or reduced early and midterm all-cause mortality outcomes in patients with high and low-to-intermediate risk. Transfemoral TAVI provides mortality benefits over SAVR, reducing early myocardial infarction but benefits related to early cardiovascular death were unclear. A similar group investigated the performance of the CoreValve prosthesis over 5 years [(133)]. The all-cause mortality rates at 1,2,3,4 and 5 years were 21%, 29%, 38%, 48% and 55%, with cardiovascular mortality rates being 10%, 14%, 19%, 23% and 28% respectively; the 5-year neurological event rate was 7.5%. Among all re-hospitalizations, acute heart failure was the most frequent, followed by the need for permanent pacemaker implantation.

In an assessment of the future of TAVI, Hamm *et al* [(107)] concluded that TAVI has become the treatment of choice for inoperable patients by 2016. SAVR remains the gold standard for patients of low or intermediate operative risk but with an increasing trend towards using TAVI in intermediate-risk patients. Outstanding issues with TAVI included paravalvular leaks, stroke, pacemaker requirements and durability.

Since these early days, major significant clinical studies have first successively shown that TAVI are equivalent to SAVR even in low-risk patients [(134, 135)]. Moreover, continual improvements to both the implant techniques and the devices themselves have reduced the complications listed in the following chapter. By 2023, the only remaining group of patients with aortic stenosis remained young, low-risk patients where TAVI were recommended to be only undertaken with caution and guidance by a multidisciplinary heart team [(136)].

2.B.2. Issues with TAVI Techniques in Elderly Patients with Severe Aortic Stenosis

TAVI procedures have improved markedly in recent years such that they are considered as the preferred modality for treating adult patients with severe aortic stenosis. However, in spite of significant improvements and refinements, they should not be considered perfect yet. This section deals with the major issues as they historically evolved [(137)].

- ***Paravalvular Leaks (PVL)***

In elderly patients with stenotic valves, the native leaflets are not removed with TAVI techniques. The prosthesis is deployed within the native annulus, compressing the native leaflets against the aortic wall; there is likely to be incomplete annular sealing because of the gaps between the prosthesis and the annulus. In the beginning, between 60 and 80% of patients had some degree of paravalvular leak [(138)]. Significant PVL may result from incomplete prosthesis apposition to the native annulus due to patterns and extent of calcification or annular eccentricity, undersizing of the device, and/or malpositioning of the valve. Larger and eccentric annuli were identified as predictors of PVL and most likely reflected inadequate sizing. The extent of calcification and asymmetrical distribution, as well as the location of calcium on the aortic wall, valve commissure, or valve landing zone, were also identified as predictors for PVL. Post-implantation balloon dilatation of the valve was shown to reduce PVL and considered as an initial option for patients with PVL [(139)]. Studies have shown that post-dilatation can be safely performed, with a reduction of the regurgitation in a majority of patients. Calcification of the valve significantly influenced the success of this. Implantation of the valve that was too low was associated with higher incidence of PVL. Repositioning to a higher implantation depth was seen to reduce PVL. It is anticipated that susceptibility to PVL will be different when TAVI procedures are applied to younger RHD patients in view of the very different pathological conditions in the annulus.

- ***Durability of Pericardium***

It has long been known, on the basis of the use of pericardial tissues in SAVR, that these tissues are susceptible to degradation and calcification over a period of time in vivo [(41, 139)]. The lack of long-term durability is a major factor in determining the longevity of valve replacement procedures. A major factor here is the role of the agents used for fixation of the animal-derived tissues; it is necessary for the purposes of achieving both sterility and non-immunogenicity that the tissue undergoes chemical fixation treatment, and for several decades the most common agent has been glutaraldehyde [(140)]. However, the fixation process also causes structural changes in the tissue, including calcification and degradation, which limit the in vivo durability of the material [(141)].

The mechanisms of pericardial calcification have been reviewed by Schoen and Gotlieb [(142)]. Structural bioprosthetic heart valve deterioration tissue calcification and noncalcific degeneration is promoted by specific chemical, mechanical, and morphological changes that occur during tissue valve preparation and insertion. These processes render the cells nonviable, produce cell and extracellular matrix (ECM) debris, and lock the collagen into a fixed geometrical configuration. Since active repair processes cannot occur, repair of the ECM by the cells endogenous to the transplanted pericardium is impossible, and damage to the ECM occurring during valve function is cumulative. Normal internal tissue rearrangements accompanying valvular function are inhibited, inducing tissue buckling. The fragments of the devitalized cells that remain in the tissue serve as nuclei for calcification.

Mineralization of bioprosthetic heart valves occurs initially at the cell membranes and other intercellular structures of the devitalized connective tissue cells high in phosphorus. Glutaraldehyde preservation disrupts the membrane pumps that normally force excess calcium ions out of cells and without these homeostatic processes, calcium can react with phosphates

of the devitalized cells to yield calcium phosphate crystals. Collagen and elastic fibers can also serve as nucleation sites for calcium phosphate mineral. Bioprosthetic valve mineralization is passive and dystrophic, but regulation occurs by a biochemical environment conducive to mineralization (including young recipient age), by implant structure and chemistry, and by mechanical factors.

Glutaraldehyde was introduced as a fixative / sterilant for bioprostheses several decades ago [(143)]. In order to reduce calcification, several methods have been developed for inclusion in the processing regimes for the pericardium treatment. The work of Vyavahare *et al* mentioned earlier [(43)] suggested that an ethanol pre-treatment may reduce or even prevent calcification. The actual characteristics of the cross-linking process are very important. It has been found that certain epoxide agents, such as triglycidyl amine (TGA), or TGA coupled with 2-mercaptoethylidene-1, 1-bisphosphonic acid can give better calcification resistance [(144)]. Moreover, as demonstrated by several of the SAT team, incorporation of lysine into the cross-linking process, along with varying the glutaraldehyde concentration, can also lead to improved performance [(32, 41)].

Biological treatments may also be used, by themselves or in combination with cross-linking. One such process involves decellularization of the pericardium, for example using sodium dodecyl sulfate [(145)]. Decellularization treatment is preferably accompanied by procedures to assess effectiveness by determining DNA / RNA levels and also the use of DNase / RNase solutions for removal of remaining DNA / RNA [(146)]. Alternatively, in view of the potential role of components of the immune system in pericardium degeneration, biological approaches to minimize responses to the α-Gal antigen have been proposed [(147)].

It is important to note that valve material durability does vary with valve characteristics, including pre-treatment methods and, even with established surgical bioprosthetic valves, clinically significant differences can be seen [(148)]. In 2016, Arsalan and Walther published a review of the issues concerning the durability of bioprostheses used for transcatheter valve implantation [(149)] followed by more contemporary reviews on improving tissue longevity by WF Williams in 2021 [(150)] and on immune mechanisms behind tissue degeneration by P Human in 2022 [(151)] and F. Naso in 2023 [(152)].

In view of the importance of maximizing the durability of the pericardium, manufacturers have concentrated efforts on perfecting the treatment methods. SAT has combined a number of procedures, including decellularization, DNase/RNase treatment, glutaraldehyde and L-lysine cross-linking, and final removal of imine and aldehyde groups, in order to optimize performance [(153)].

- ***Stroke and Cerebrovascular Accidents***

Ever since the first clinical applications of TAVI procedures, stroke has been the most feared complication; in the first reported series, rates of stroke within 30 days were usually in the range of 4 to 6% [(154)]; this compared to rates of around 1% with SAVR [(155)]. Neuro-imaging studies have now shown that TAVI is not only associated with such clinically apparent neurological events but also with a relatively high rate of clinically silent microembolic cerebral lesions [(156)]. Nombela-Franco *et al* reported in 2012, from a 5-center registry involving just over 1,000 TAVI patients, that there was a 5.1% rate of cerebrovascular events within 30 days, and a 3.3% late event rate over a 12-month follow up [(157)]. Stroke rates within this series were 4.2% and 2.1% respectively.

The risk of cerebrovascular accidents is inherently related to both patient-based and procedural-related risks [(158)]. Factors that increase risks of these effects include a history of stroke between 6 and 12 months prior to TAVI, and of prior history of cerebrovascular disease

in general, a high incidence of carotid artery stenosis and severe baseline aortic regurgitation. Initial balloon aortic valvuloplasty results in the fracture of valvular tissue leading to embolism of overlying calcium deposits and increased thrombogenic complications. Periprocedural neurological events are most likely associated with embolization of debris liberated from aortic arch atheroma or the heavily calcified aortic valve itself. The transfemoral approach involves advancement of catheters through the aortic arch, such manipulation of these tissues not being seen with the transapical approach. In addition, cerebral hypoperfusion during rapid right ventricular pacing may also play a role. Taking into account these risks, antithrombotic therapy has to be carefully considered with all conventional TAVI patients with calcified valves [(159)]. Modern cerebral embolic protection devices are promising [(160)]. In the light of these clinical observations, the risk of cerebrovascular accidents and strokes should be minimal with a transapical approach to TAVI in RHD patients, whose valves are not calcified and where rapid ventricular pacing is not required.

- ***Chronic Pacing***

Because of the close proximity of the atrioventricular bundle to the aortic valve complex, various forms of conduction disturbance can occur after aortic valve surgery. It has been reported that early permanent pacemakers are required in 3-8% of patients undergoing SAVR [(161)]; there have been several studies of such a need after TAVI use [(162)]. Godin *et al* [(163)] reported low permanent pacemaker requirement rates, from 4 to 11% with the balloon expandable Sapien valve, while the incidence with the self-expandable CoreValve prosthesis ranged from 16 to 39% according to Khawaja *et al* [(164)], and 22% of patients receiving the same valve developed complete atrioventricular (AV) block according to Kostopoulou *et al* [(165)]. While the need for permanent pacemakers (PPM) has come down over the years, the PPM rate is still higher for self-expanding TAVI than for balloon expanding ones [(153)].

- ***Perforations***

Annular rupture and perforation of either the right or left ventricles can occur during TAVI procedures, with an incidence in elderly patients of between 1 and 2% [(37)]. Most perforations are associated with the use of temporary pacing wires [(166)].

3. TAILOR-MADE SOLUTIONS FOR PATIENTS WITH RHD IN LMICs

3.A. THE POTENTIAL USE OF TAVI TECHNIQUES TO ADDRESS UNMET NEEDS

The previous sections outlined the challenges facing the international community in addressing the needs of young RHD patients in many countries of the world, where socio-economic and clinical factors constrain the use of those clinical techniques that have become established in the developed countries, for example in Europe and North America. I have also addressed the clinical factors associated with the introduction of the TAVI techniques that have become instrumental routine procedures extending and replacing surgical options for patients with heart valve conditions.

This section addresses the factors associated with the potential extension of TAVI technology to the young RHD patients in low and middle-income countries. As with the potential use of many innovative technologies in totally new areas of application, there is little direct hard evidence in the peer-reviewed literature to definitively confirm safety and efficacy within the target population. In my thesis I attempted to validate the need for technologies such as those of TAVI in these countries, together with validation of the relevance of different aspects of UCT's SAT TAVI in these intended patients.

3.B. TECHNOLOGICAL AND CLINICAL CHALLENGES FOR TAVI TECHNIQUES IN RHD

There is little published information about the specific challenges that face the introduction of new TAVI techniques for RHD patients, who present quite different anatomical and physiological features compared to traditional heart valve replacement patients in the developed world; moreover, these TAVI therapies will be used in parts of the world that have hitherto been unused to the relevant transcatheter techniques [(167)]. Again, initial reports in 2021 came from high-income countries and are based on rheumatic aortic stenosis rather than the prevailing aortic incompetence [(168)]. In many of these countries, the clinical infrastructure for TAVI procedures in general have been addressed, witnessed, for example, by guidelines published for TAVI in South Africa [(169)]. Watkins *et al* have discussed the cost-effectiveness of interventions for rheumatic fever and RHD control across Africa [(170)] and have concluded that traditional valve surgery is not cost-effective in typical low-income countries, implying that alternative, lower-cost interventional techniques that do not require standard open-heart surgery infrastructure, could significantly alter this balance. Arora *et al* used China and India as examples of 'emerging economies' to discuss the potential introduction of transcatheter techniques for heart valve disease, determining that health care policy, and especially the distribution of economic prosperity has to evolve to promote both preventive measures and the promotion of new technologies such as TAVI [(171)]. Minimally invasive techniques, using a mini-thoracotomy rather than TAVI, are already being used for mitral valve replacement in China [(172)]. The need for an effective approach to the introduction of new technologies to treat young patients with inoperable heart valve dysfunction has been anticipated by Majeed *et al*, who predicted in 2016 an increasing off-label use of the now common TAVI procedures in such patients [(173)].

In the experimental work underpinning this thesis, the anticipated contribution of UCT's SAT TAVI procedures [(153)] to the treatment of RHD in low to middle income countries has been tested in the acute porcine [(174)] and chronic ovine model [(175)]. Both series pointed to the value of avoiding tertiary cardiology support by means of a simplified, slow and non-occlusive deployment, with tactile feedback rather than highly sophisticated dependence on imaging technology. I addressed the potential risks associated with this very innovative technology by extensive pre-clinical studies directed towards the validation of these features. It is recognized that for traditional TAVI patients, the transfemoral route has proven to be superior to the transapical route [(176, 177)] especially because of lower early mortality; however, the use of the unique non-occlusive delivery system that is integral to the SAT transapical approach should address that issue.

It should be noted that the transapical route does require a procedure to close the left ventricular apex. The SAT approach utilizes purse string sutures for this closure. This method is well-established, with good outcomes reported over the last decade [(178-180)]. There are several other possible closure procedures, as reviewed by Ziegelmueller *et al* [(181)], and some of these may well be equally well-established in the future, but purse string sutures are fully justified at this stage.

The differing underlying pathology seen with young RHD individuals and typical elderly heart valve patients in the developed world, does present a number of challenges. First, in the latter patients, the degenerative calcific aortic valves provide a fluoroscopic footprint which facilitates positioning and placement of the TAVI valve. However, rheumatic aortic valve pathology is normally non-calcific so that fluoroscopy is less relevant. UCT's SAT approach involves a self-homing, non-occlusive deployment system, where evidence of safety and efficacy has been determined during pre-clinical evaluation. This non-occlusive helical balloon with self-locating retractable balloon trunks facilitates easy positioning and placement within

the aortic root, obviating the need for rapid ventricular pacing during implantation and allowing slower, controlled placement. The second point also concerns the lack of a calcific pathology, with compliant aortic roots, in relation to anchoring the device. Again, there is little guidance from the literature on this aspect; UCT's SAT technology involves a self-anchoring stent design, in which anchorage arms secure the positioning on the native aortic valve leaflets and a sealing skirt at the annular level eliminates potential paravalvular regurgitation [(153)].

4. INTRODUCTORY CONCLUSION

This introduction to my thesis has clearly established the immense need for a relatively low cost treatment regime that can be applied and adopted to save the lives of millions of young patients suffering from RHD who live in low and middle income regions of the world.

The extreme difficulty of employing resource-intensive open-heart surgery procedures in these regions suggests that minimally invasive technologies, and specifically TAVI procedures, have the potential to provide some resolution to this problem. However, the significant advances of TAVI technology that have been seen in recent years within developed countries, such as those of North America and Europe, are largely inapplicable in low and middle income regions, because of their different pathology (non-calcific AR instead of calcific AS); the need for significant infrastructure, especially with imaging equipment; the need for rapid ventricular pacing during implantation and the high associated costs.

CHAPTER 2

STRUCTURE OF THE THESIS

This thesis is presented in accordance with the thesis by manuscript format within the Faculty of Health Sciences at the University of Cape Town. The thesis also includes 5 peer-reviewed publications.

It addresses the technical and clinical issues associated with the development of a transcatheter heart valve intended for implantation, by a transapical route, in patients suffering from rheumatic heart disease (RHD). It focuses on the special needs of these patients, who are mostly young individuals living in low- and middle-income countries, where access to the very expensive and clinically-challenging open heart-surgery is difficult, and where the minimally invasive techniques for catheter-delivered replacement valves now available in industrialised countries, provide major economic and technical hurdles.

I first provide insight into the specific clinical and pathological manifestations of surgical RHD; the specific patho-physiological challenges for its surgical treatment; the consideration of socio-economic circumstances making contemporary replacement valves so poorly suited for LMICs and the need to offer solutions in the absence of open heart surgery in most of these regions. This in-depth assessment represents hitherto insufficiently analysed key aspects of surgery for RHD. Since they do not only affect the choices of replacement valves but also the pre-operative decision making process this analysis of ***chapter three*** was published in the *'International Journal of Cardiology'*.

In spite of the high number of patients needing heart valve surgery for RHD, studies investigating the actual performance of prosthetic valves in patients are scarce. I therefore conducted a clinical follow-up study at a teaching hospital of a low- and middle-income country like South Africa to highlight the catastrophic outcome after mechanical heart valve replacement under the given socioeconomic circumstances and in the absence of an alternative to American- and European prostheses that were developed for very different patients and against a distinctly different infrastructure- and educational background. This study represents ***chapter four*** of my thesis and was published in our most prestigious surgical journal, the *"Journal of Thoracic and Cardiovascular Surgery'.*

Over the past 10 years, transcatheter heart valve technologies were developed at UCT which promise to allow the replacement of diseased rheumatic heart valves in the absence of open heart surgery and under the often basic facilities of low-income countries. The clinical translation of this concept formed the core of my thesis. In ***chapter five*** this tailor-made trans-catheter replacement heart valve is being introduced. In the course of this PhD I had intense input into the design and R&D of the SAT TAVI on the basis of my clinical experience and the numerous animal experiments with it, conducted by me. The SAT valve does not only address the lack of open heart surgery in countries most affected by RHD but also the need for long lasting leaflet materials. The latter is a crucial sine-qua-non for any 'tailor-made' solution for patients with RHD given their young age and the known rapid degeneration of bioprosthetic valves in such patients.

As contemporary transcatheter aortic valve replacements (TAVI) were exclusively developed for the calcified, stiff aortic valves of the typically elderly patients of HICs with their degenerative stenotic valve disease, a TAVI valve developed for rheumatic patients with aortic regurgitation needed to be differently designed to also accommodate the soft, compliant aortic roots of young patients. As none of the contemporary TAVI valves addresses this indication, a first step towards the pre-clinical testing of this novel TAVI was the de-novo establishment of a new large animal model for transcatheter aortic valve replacement. It was a difficult journey to establish such a model in a species like the sheep which has a sinus of Valsalva anatomy that is much narrower than in humans or in a species like the pig that has similar challenges and

outgrows its implanted valves. At the end of large series of implants summarised in ***chapter six*** size guidelines for animal implants and anatomical exclusion criteria have been established.

Yet, once the process of establishing a model for TAVIs in compliant aortic roots has been concluded I published the surgical technique in a 'how-to-do' publication in the internet-based educational tool of the *European Journal of Cardio-Thoracic Surgery*. The summary of this publication represents ***chapter seven****.*

The implantation technique was verified in an acute sheep trial, using the transcatheter system together with a polymer leaflet version of the SAT TAVI. It was published in the European Heart Journal with its impact factor of 39 and represents ***chapter eight.*** There, I demonstrate the successful, completely non-occlusive, self-homing placement of this balloon expandable TAVI in sheep.

As the pericardial version of the TAVI system will be clinically tested first, long-term chronic sheep implants tested the bioprosthetic SAT TAVI system in ***chapter nine***. The 5-months sheep implants confirmed the complete tissue integration of the TAVI with no traces of leaflet calcification, an observation that had previously been demonstrated in subcutaneous rat studies [(15)]. Extensive surface endothelialisation was accompanied resulting in the absence of thrombotic appositions both on the leaflets themselves and the skirt. This pre-clinical study therefore confirmed the longevity of the decellularized and specially crosslinked bioprosthetic pericardium and the ability of the valve stent to firmly anchor in non calcified, compliant aortic roots. As this study represents the pre-clinical verification of a trans-apically inserted system, it was published in a high-impact interventional cardiology journal *(EuroIntervention).*

Chapter ten eventually draws dimensional and anatomical conclusions with regards to TAVI sizes expected in humans. Here, I correlate the size shift seen in conventional TAVIs for patients with aortic stenosis with that seen in the compliant roots of pigs and sheep to arrive at a rational prediction for the clinical implantations in patients with rheumatic aortic regurgitation.

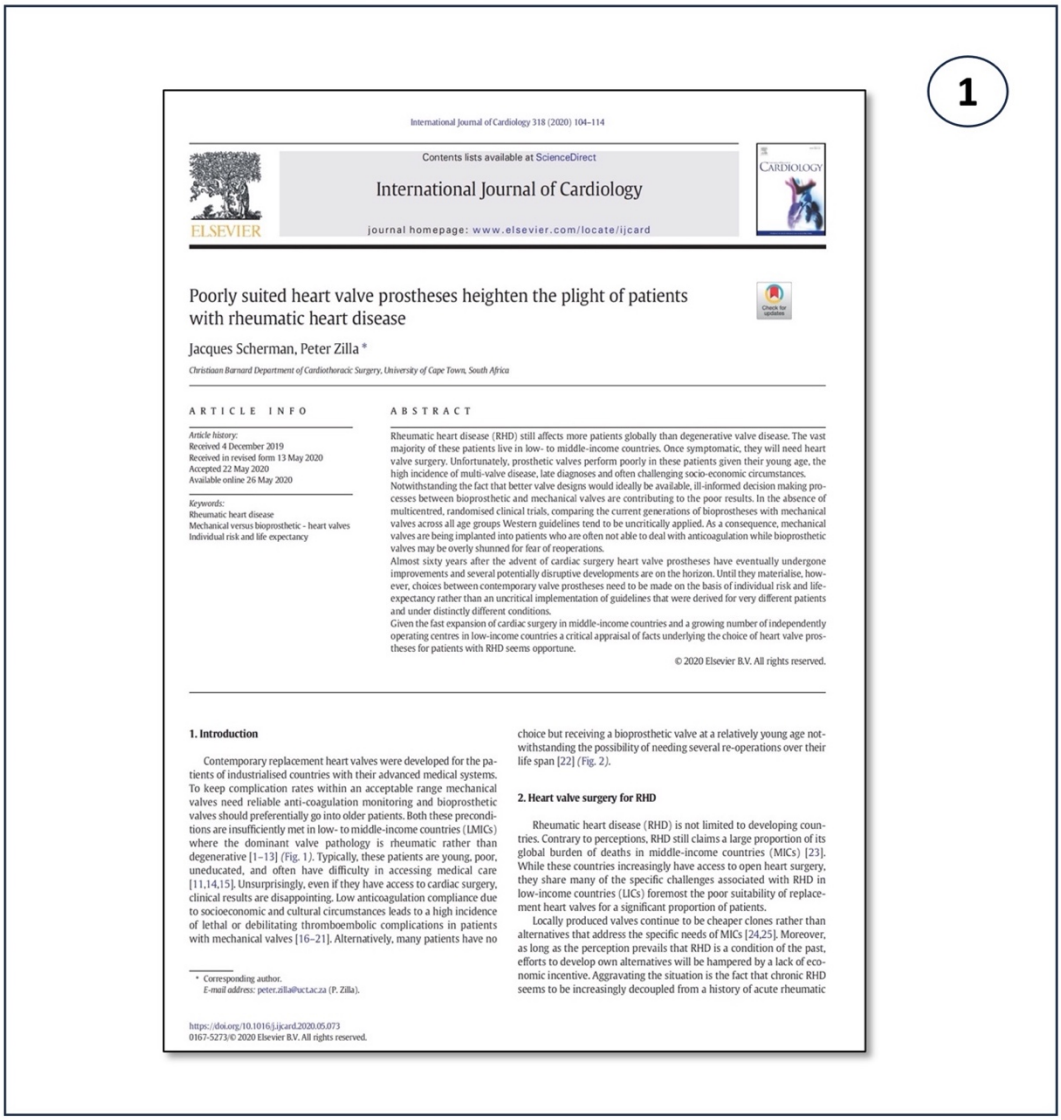
In the final ***chapter eleven***, I conclude the arc my thesis drew from providing the rationale for a tailor-made trans-catheter solution for patients with rheumatic heart disease in low- to middle-income countries to the de-novo establishment of meaningful animal models to the definition of anatomical exclusion criteria and the pre-clinical verification. At the end of this chapter, the key points of my thesis are synthesised into the selection criteria for patients as well as the expected impact of such a novel system on the patients in need.

On the basis of this PhD thesis, the ethics committee of the University of Cape Town and the national device regulatory authority (SAHPRA) has approved a first-in-man safety study with the SAT bioprosthetic TAVI at Groote Schuur Hospital (Appendix 2).

CHAPTER 3
CLINICAL AND SOCIO-ECONOMIC BACKGROUND

This Chapter provides the insight into the specific clinical and pathological manifestations of surgical RHD; the specific pathophysiological challenges for its surgical treatment; the additional unique adverse circumstances making contemporary replacement valves so poorly suited for LMICs and the need to offer solutions in the absence of open heart surgery in most of these regions.

This in-depth assessment represents hitherto insufficiently analysed key aspects of surgery for RHD. Since they do not only affect the choices of replacement valves but also the pre-operative decision making process this analysis was published in the 'International Journal of Cardiology'.



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Poorly suited heart valve prostheses heighten the plight of patients with rheumatic heart disease

Jacques Scherman, Peter Zilla *

Christiaan Barnard Department of Cardiothoracic Surgery, University of Cape Town, South Africa

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ABSTRACT

Rheumatic heart disease (RHD) still affects more patients globally than degenerative valve disease. The vast majority of these patients live in low- to middle-income countries. Once symptomatic, they will need heart valve surgery. Unfortunately, prosthetic valves perform poorly in these patients given their young age, the high incidence of multi-valve disease, late diagnoses and often challenging socio-economic circumstances.

Notwithstanding the fact that better valve designs would ideally be available, ill-informed decision making processes between bioprosthetic and mechanical valves are contributing to the poor results. In the absence of multicentred, randomised clinical trials, comparing the current generations of bioprostheses with mechanical valves across all age groups Western guidelines tend to be uncritically applied. As a consequence, mechanical valves are being implanted into patients who are often not able to deal with anticoagulation while bioprosthetic valves may be overly shunned for fear of reoperations.

Almost sixty years after the advent of cardiac surgery heart valve prostheses have eventually undergone improvements and several potentially disruptive developments are on the horizon. Until they materialise, however, choices between contemporary valve prostheses need to be made on the basis of individual risk and life-expectancy rather than an uncritical implementation of guidelines that were derived for very different patients and under distinctly different conditions.

Given the fast expansion of cardiac surgery in middle-income countries and a growing number of independently operating centres in low-income countries a critical appraisal of facts underlying the choice of heart valve prostheses for patients with RHD seems opportune.

1. Introduction

Contemporary replacement heart valves were developed for the patients of industrialised countries with their advanced medical systems. To keep complication rates within an acceptable range mechanical valves need reliable anti-coagulation monitoring and bioprosthetic valves should preferentially go into older patients. Both these preconditions are insufficiently met in low- to middle-income countries (LMICs) where the dominant valve pathology is rheumatic rather than degenerative [1–13] (Fig. 1). Typically, these patients are young, poor, uneducated, and often have difficulty in accessing medical care [11,14,15]. Unsurprisingly, even if they have access to cardiac surgery, clinical results are disappointing. Low anticoagulation compliance due to socioeconomic and cultural circumstances leads to a high incidence of lethal or debilitating thromboembolic complications in patients with mechanical valves [16–21]. Alternatively, many patients have no choice but receiving a bioprosthetic valve at a relatively young age notwithstanding the possibility of needing several re-operations over their life span [22] (Fig. 2).

2. Heart valve surgery for RHD

Rheumatic heart disease (RHD) is not limited to developing countries. Contrary to perceptions, RHD still claims a large proportion of its global burden of deaths in middle-income countries (MICs) [23]. While these countries increasingly have access to open heart surgery, they share many of the specific challenges associated with RHD in low-income countries (LICs) foremost the poor suitability of replacement heart valves for a significant proportion of patients.

Locally produced valves continue to be cheaper clones rather than alternatives that address the specific needs of MICs [24,25]. Moreover, as long as the perception prevails that RHD is a condition of the past, efforts to develop own alternatives will be hampered by a lack of economic incentive. Aggravating the situation is the fact that chronic RHD seems to be increasingly decoupled from a history of acute rheumatic

* Corresponding author.
E-mail address: peter.zilla@uct.ac.za (P. Zilla).

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POORLY SUITED HEART VALVE PROSTHESES HEIGHTEN THE PLIGHT OF PATIENTS WITH RHEUMATIC HEART DISEASE

Jacques Scherman and Peter Zilla

Christiaan Barnard Department of Cardiothoracic Surgery, University of Cape Town

ABSTRACT

Rheumatic heart disease (RHD) still affects more patients globally than degenerative valve disease. The vast majority of these patients live in low- to middle-income countries. Once symptomatic, they will need heart valve surgery. Unfortunately, prosthetic valves perform poorly in these patients given their young age, the high incidence of multi-valve disease, late diagnoses and often challenging socio-economic circumstances.

Notwithstanding the fact that better valve designs would ideally be available, ill-informed decision making processes between bioprosthetic and mechanical valves are contributing to the poor results. In the absence of multicentred, randomised clinical trials, comparing the current generations of bioprostheses with mechanical valves across all age groups Western guidelines tend to be uncritically applied. As a consequence, mechanical valves are being implanted into patients who are often not able to deal with anticoagulation while bioprosthetic valves may be overly shunned for fear of reoperations.

Almost sixty years after the advent of cardiac surgery heart valve prostheses have eventually undergone improvements and several potentially disruptive developments are on the horizon. Until they materialise, however, choices between contemporary valve prostheses need to be made on the basis of individual risk and life-expectancy rather than an uncritical implementation of guidelines that were derived for very different patients and under distinctly different conditions.

Given the fast expansion of cardiac surgery in middle-income countries and a growing number of independently operating centres in low-income countries a critical appraisal of facts underlying the choice of heart valve prostheses for patients with RHD seems opportune.

INTRODUCTION

Contemporary replacement heart valves were developed for the patients of industrialised countries with their advanced medical systems. To keep complication rates within an acceptable range mechanical valves need reliable anti-coagulation monitoring and bioprosthetic valves should preferentially go into older patients. Both these preconditions are insufficiently met in low- to middle-income countries (LMICs) where the dominant valve pathology is rheumatic rather than degenerative [1, 2, 8, 58, 80, 81, 98-104] *(Figure 2).*Typically, these patients are young, poor, uneducated, and often have difficulty in accessing medical care [1, 61, 182]. Unsurprisingly, even if they have access to cardiac surgery, clinical results are disappointing. Low anticoagulation compliance due to socioeconomic and cultural circumstances leads to a high incidence of lethal or debilitating thromboembolic complications in patients with mechanical valves [78, 83, 183-186]. Alternatively, many patients have no choice but receiving a bioprosthetic valve at a relatively young age notwithstanding the possibility of needing several re-operations over their life span [82] *(Figure 3)*.

HEART VALVE SURGERY FOR RHD

Rheumatic heart disease (RHD) is not limited to developing countries. Contrary to perceptions, RHD still claims a large proportion of its global burden of deaths in middle-income countries (MICs) [9]. While these countries increasingly have access to open heart surgery, they share many of the specific challenges associated with RHD in low-income countries (LICs) foremost the poor suitability of replacement heart valves for a significant proportion of patients. Locally produced valves continue to be cheaper clones rather than alternatives that address the specific needs of MICs [187, 188]. Moreover, as long as the perception prevails that RHD is a condition of the past, efforts to develop own alternatives will be hampered by a lack of economic incentive. Aggravating the situation is the fact that chronic RHD seems to be increasingly decoupled from a history of acute rheumatic fever (ARF) the prevailing benchmark for the disease. Predictably, governments interpreted the low incidences of ARF [189] as a sign of near eradication of RHD. Yet, the actual number of cases requiring surgery remains high [46, 79]. This decoupling is still poorly understood and cannot only be explained with a clinical lag-phase. In a recent Brazilian national survey, for instance, decades of declining incidence of acute rheumatic fever [189] were opposed by a continually large proportion of patients needing heart valve surgery for chronic RHD [2,79].

This increasingly diverse manifestation of RHD is also reflected in the time the inflammatory process needs to cause clinically symptomatic heart valve disease requiring surgery. As a consequence, the patient age at surgery – one of the main determinants of prosthetic performance - varies widely.

Differences to the typical patients of high-income countries (HICs) do not only apply to the suitability of valve prostheses but also to operative techniques from 'peeling' of excess fibrous leaflet tissue in mitral repairs [190] to the preservation of the sub-valvular apparatus (PSVA) in mitral valve replacements (MVRs) [191]. Similarly, predicted mortalities as reflected in the scoring system of large supra-continental databases like STS or EuroSCORE poorly apply. Inherently, they represent mean values of vast numbers of the largely elderly patients of HICs with predominantly degenerative or secondary valve disease. These calculated risk scores also reflect the advanced medical systems of these countries. As such, in the absence of own comparable databases, multicentre comparisons or even sufficiently available cardiac surgical services in the regions rife with RHD, decision making processes largely rely on sub-compatible North American and European prostheses and guidelines, often reluctantly carried over to LMICs in the absence of alternatives. Few will dispute the inadequacy of this compromise. The example of a HIC like Australia where the indigenous population had twice as high a mortality after valve replacement for RHD than predicted by EuroSCORE II [192] is a similar case in point as surgery for infective endocarditis in South Africa where actual results deviated significantly from EuroSCORE predictions [97]

Another fundamental difference between these two worlds is the predominance of single valve disease – often together with the need for revascularisation procedures - in the non-rheumatic patients of HICs as opposed to a high percentage of double- or even triple-valve disease in LMICs patients with RHD [5, 11, 79, 80, 82, 193]. This further complicates the choice of valve prosthesis as the different flow and stress conditions associated with the particular anatomical location of one valve may affect the valve choice for the other.

PATIENT CHARACTERISTICS

Even if future valve prostheses resolve key issues of prostheses-inherent failure modes, patient specific circumstances will still modulate their performance. The underlying pathology, socioeconomic embedding, or patient age create fundamentally different conditions for the longevity and performance of replacement valves. By being in average 30 years younger than

Western patients with degenerative diseases, rheumatic patients are largely deemed to not qualify for contemporary tissue valves due to their accelerated degeneration in this age group. On the other hand, socioeconomic circumstances prevailing in areas endemic for RHD concur with poor anticoagulation compliance in patients with mechanical heart valves. Furthermore, co-morbidities like atrial fibrillation affecting a significant proportion of young patients with RHD aggravate the consequences of unreliable compliance with anticoagulation. Last not least, both mechanical and tissue valves are exposed to distinctly different haemodynamic conditions in the aortic than in the mitral position making them more prone to fail in the latter. While bioprostheses degenerate there faster because of greater loading forces [194, 195] mechanical prostheses also thrombose 2-3 times more frequently in the mitral *(Figure 4)* than in the aortic position [196] due to more pro-thrombogenic fluid-dynamics. Even under the conditions of a high-income country like Canada, their 10 year cumulative stroke rate was twice as high after mitral valve replacements (MVRs) than after aortic valve replacement (AVR) [197]. As such - independent of prostheses related challenges - patients needing surgery for RHD have a significantly higher risk of prosthetic valve failure than those with degenerative or congenital valve disease.

UNDERLYING PATHOLOGY AND INFLUENCE OF GENDER

In exaggerated terms, symptomatic RHD preferentially affects the mitral valve of young to middle-aged females [59, 78, 82, 83, 192] while degenerative disease affects the aortic valve of elderly males [198-200]. In countries like Sweden where RHD affects less than 1% of valve patients the aortic valve accounted for 69% of all valve procedures. With the advent of TAVIs, this percentage increased to 79% in Germany in 2017 [200], the country with the highest TAVI rate globally [198, 199]. In contrast, the mitral valve was replaced or repaired in 71% of rheumatic patients in an urban South African study [5] and was in need of surgery in >96% of patients in the 'REMEDY' study, analysing symptomatic patients with RHD from 14 LMICs in Africa and Asia [11]. Coinciding with the high prevalence of the mitral valve in RHD is an overall female gender bias of between two thirds [59, 78, 83] and three quarters [82, 92]. Thus, as a natural consequence of a female predominance and their prevailing need for mitral valve surgery, one can conclude that female patients have a higher likelihood of experiencing early structural valve degeneration or thromboembolic events than males. As such, a significant baseline bias against female patients already exists even before one takes the conundrum into account that pregnancy presents for heart valve surgery.

To make things worse, women also have a higher incidence of rheumatic mitral valve stenosis [201-203] due to a more prominent and aggressive inflammatory process [204]. One possible implication of this may be a higher recurrence rate after mitral repairs [204]. A more aggressive inflammatory process may also augment intimal hyperplasia and as such pannus overgrowth [22] Pannus overgrowth can either lead to a narrowing of the orifice of mechanical valves *(Figure 4)* or to bioprosthetic leaflet immobilization and is estimated to be behind obstructive valve failure in between 31% [205] and 53% [206] of cases.

Notwithstanding the fact that mitral valve disease remains the major indication for surgery in RHD [5, 59, 78-83] the aortic valve becomes increasingly affected as patients get older in the course of the epidemiologic transition [1, 2]. Our own most recent 10-year cohort (2008-2018) at Groote Schuur Hospital/University of Cape Town (mean age 45±14 years) confirms this trend: mitral valve surgery was still required in 78% of all patients with RHD but aortic valve replacement (AVR)/AV-repair occurred in 50% (more than half of them needing double valve replacement). In contrast to degenerative disease, aortic regurgitation (AR) by far outweighs stenosis (AS) in RHD. AR poses both a diastolic as well as a systolic volume overload, thereby causing early irremediable damage [87]. The timing of surgery is challenging as the morbidity and mortality associated with aortic valve replacement in a LMIC needs to be weighed against

the disease progressing to the point from which onwards a recovery of LV function and improved survival can no longer be achieved [88]. Cut-off points for prognostically meaningful surgery have been >55 mm for end-systolic left ventricular diameter and 25-35 percent for ejection fraction [88, 89].

PATIENT AGE AND PREGNANCY

Patient age at the time of surgery – which is a crucial determinant for both bioprosthetic valve degeneration and compliance with anticoagulation [207, 208] – varies widely. A majority of the often rural patients of low-income countries (LICs) need surgery when they are still in their early twenties [78]. It is unfortunately in those regions where patients are youngest that socioeconomic conditions result in the lowest compliance with anticoagulation. The problem often starts with the regular availability of warfarin itself [78]. In an Indian study, only 44% of patients were in the therapeutic range and as few as 8% fully compliant [186]. Results from Turkey [209], Ethiopia [78], Kenya [210] and Cameroon [81] all reported similar anticoagulation-related bleeding events. Thomson-Mangnall et all found young age to be a risk factor for non-compliance [207] and Koshy et al found it significantly more often in males [208]. Yet, as much as maleness and being young are co-factors towards poor INR control, the female bias of RHD in this age group [59, 82] makes women in child bearing age particularly endangered by inadequate replacement valves [83, 211]. For them, inadequate anticoagulation control [78, 81, 186] (frequently aggravated by anti-retroviral medication) coincides with high birth rates and therefore with a higher probability of not being on contraception after heart valve replacement or even experiencing more than one pregnancy with a prosthetic valve [212]. Less than 5% of women with RHD of childbearing age in Uganda, for instance, are on contraceptions [213]. The fact that pregnancies happen 11 years earlier and fertility rates are >4 times higher even in countries where cardiac surgery has been established [58, 214, 215] seriously impacts the outcome of heart valve replacements. In a Bangladeshi comparative study 12% of patients showed thrombus formation on mechanical valves during pregnancy and 3% had warfarin embryopathies. Normal pregnancy-outcome was only achieved in 2 out of 3 women in the mechanical group versus almost all in the bioprosthetic group [216]. Together with other reasons for poor results such as high rates of infective endocarditis [5, 97] this age group is left with a particularly dire choice of heart valve prostheses [83, 217].
In MICs the mean age of these patients at the time of surgery has gradually increased as a consequence of urbanisation and affluence [in South Africa from 22 in the early 1980s [84] and 31 in the 1990s [85] to 41 in the late 2000s [5]; in Brazil's to 44 [79] and in Korea to 52 years [86]. As such, today's largely urban patients of MICs are well into their fourties when they need heart valve replacements for RHD [5, 79]. Although they are 10-20 years older than in LICs [59, 78, 82] these patients would still be 20 years too young to qualify for tissue valves under European and North American guidelines [218, 219] As older patients not only mean a slower degeneration of tissue valves but in the case of mitral valve disease, for instance, also a higher incidence of chronic atrial fibrillation, this dynamic shift of patient characteristics needs to be taken into account when it comes to valve choices and eventually guidelines.

ATRIAL FIBRILLATION (AF)

The incidence of new onset AF in RHD is 3.5% per year overall and 6.0% per year in patients with an enlarged left atrium (≥47mm) [220]. Its prevalence is particularly high in patients with advanced valvular disease [221] with 40% of RHD patients undergoing valve surgery having AF and another one-third of the remaining 60% developing AF after surgery [222]. It is also valvular AF that is associated with the highest risk of stroke [209] particularly in rheumatic patients [223]. It is estimated that at least 3-7.5% of new strokes each year worldwide are directly due to RHD,

representing 144,000-360,000 strokes and 108,000-269,000 stroke deaths per year and 640,000-1.6 million stroke survivors in less developed countries [224]. A hospital-based stroke registry in Iran found RHD in almost 45% of patients admitted with cardioembolic stroke [224] and 29% of cardioembolic strokes in India [225] were due to RHD.
Again, the highest risk group are females post MVR who are in chronic AF. In a 2014 study from Turkey initially screening > 2,000 patients, 74% of all patients with a prosthetic heart valve who were in AF had an MVR and 72% were female [209]. It were these patients – already at higher risk of thromboembolic incidences due to the specific mitral valve heamodynamics – who also had the poorest INR control (only 36% showed therapeutic levels) [209].
The key question in this context is whether a mechanical valve is less forgiving regarding INR fluctuations than AF. Non-warfarin anticoagulants (NOACs) for post-surgical anticoagulation won't be available for mechanical valve replacements in rheumatic patients and fixed-dose warfarin regimens were shown to lead to an increase in thromboembolic events [226]. Yet, in the clear absence of anticoagulation requirements for the replacement valve itself - as is the case in patients with tissue valves - NOACs may still affect the choice of prosthesis. One of the warfarin-controlled pivotal non-vitamin K oral anticoagulants trials in AF comprising more than 21,000 participants included patients with bioprosthetic valves [227]. A subgroup analysis showed that patients with low dose edoxaban had similar rates of stroke but lower rates of major bleeding compared with warfarin suggesting that edoxaban is a reasonable alternative to warfarin in patients with AF and a bioprosthetic valve [228]. In some young patients with RHD and AF whose life expectancy would make them potential candidates for a bioprosthetic valve a significantly lower bleeding risk may give further support to this option. Furthermore, even in Western patients with their largely degenerative valve diseases, AF is known to adversely influence ventricular function and survival [229, 230] - particularly after MVR [231]. In patients with RHD in LMICs this already reduced baseline survival often coincides with typical late presentation and an associated poor ventricular function. As the presence of NYHA functional class III/IV and AF at surgery was shown to further increase the ten-year mortality by 32% and 40%, respectively [232], the presence of chronic AF in patients needing valve replacement highlights more than any other co-morbidity how different and multifactorial the decision making process is when it comes to the choice between mechanical and bioprosthetic replacement valves in rheumatic patients of LMIC as opposed to the typical patients needing valve surgery in HICs.

VALVE FAILURES

As much as valve sparing operations even in the presence of severe fibrosis [90] have significantly expanded the spectrum of mitral repairs [81, 91-95] and aortic valve repairs [96] including the Ross operation [233] are beginning to be applied to patients with RHD [234] a significant proportion of patients will continue to rely on valve replacements. The lack of repair skills in frontline low-volume centres [1] and the high incidences of endocarditis [97] are only two of the reasons.

LACK OF GUIDELINES

Roughly generalising the caveat that needs to be observed when trying to employ Western guidelines to the rheumatic patients of LMICS: mechanical valve-failures are potentially catastrophic whereas tissue valve degeneration occurs over time. In a study from Turkey involving rheumatic patients with failing valve prostheses the re-operative mortality was 3 times higher in the mechanical group, not even taking those patients with clotted mechanical valves into consideration who died before reaching the hospital [234]. Yet, while the likelihood of a patient reaching hospital for re-intervention is significantly higher in bioprosthetic valves,

one needs to weigh this survival advantage against the rising mortality coming with each re-operation caused by a degenerated tissue valve. There is also an ethical predicament in offering multiple operations to one patient in a resource constrained environment. Normally, guidelines help in complex clinical decision-making processes. In HICs, extensive data underlie the guidelines for valve choices. Current North American and European guidelines recommend mechanical valves for patients younger than 60 with a grey-zone of either mechanical or tissue valves between age 60 to 65 and clear recommendations for tissue valves beyond 65 [235]. No such clear recommendations emerge from the often scanty data collected in LMICs with their predominantly rheumatic burden of valve disease.

MECHANICAL VALVES

In LICs like the Fijis the ten year mortality for mechanical heart valves (mean age 26yrs) was 24% with death occurring 3.2 years after surgery [83]. Similarly, in Cameroon (mean age 28yrs) the 6-year mortality with mechanical valves was 21% [81]. Maori and Pacific island women (mean age 25yrs) had a seven- to eight-fold relative risk of death after heart valve replacement, compared with European women [217]. Although rapid tissue valve degeneration in this age group led to an almost 3 times higher re-operation rate after bioprosthetic valve replacement at 10 years compared to mechanical valves the relative risk of death in the same time period was 2.2 times higher after mechanical valve replacement [217]. A similar trend was seen in children in Saudi Arabia where the 15 year survival with bioprosthetic valves was 92% as opposed to 76% with mechanical valves [236]. In a Pakistani study, 18% of children with mechanical valves had serious thromboembolic or haemorrhagic incidences within 10 years [237].

Similarly, the 10-year mortality for MVRs in a MIC like South Africa (mean age at implantation 41yrs) [238] was 20% and the 10-year mortality for rheumatic AVR (mean age 43yrs) was 15% [183]. Differently looked at these results, every one in four relatively young patient post mechanical AVR was either dead or had a major thromboembolic/haemorrhagic incident after 10 years [183]. In India, the actuarial 10-year death-rate in patients operated at a mean age of 16 years was 41% after mechanical MVR and 28% after mechanical AVR [239].

BIOPROSTHETIC ('TISSUE') VALVES

Given the disappointing results with mechanical valves in LMICs, it is remarkable that only one contemporary study offers data on bioprosthetic valves in the young rheumatic patients of these countries [240]. To the contrary, high re-operation rates in young patients in HICs [241-247] are being used to justify the near-complete avoidance of tissue valves in the rheumatic patients of LMICs [78, 81-83, 94, 183, 235, 248]. Ironically, a reverse trend emerged over the years: while LMICs increasingly followed the North American and European recommendation of mechanical valves for patients younger than sixty, the age-boundaries for tissue valves have continuously been downward-eroded in HICs [241-244, 246, 247, 249-254]. Between 1997 and 2014, for instance, the proportion of patients in California and New York State who received a tissue valve increased from 14% to 47% with a mean age of 43years [251]. Therefore, long-term data on tissue valves in young patients do exist, albeit from patient with degenerative disease in HICs and from 2nd rather than 4th generation prostheses. For early implants, mean-times to reoperations were 7.7 years in patients younger than 40, 12.9 years for age 40 to 60 [255], 16.6 years for age 60-70 [256] and 19.4 for patients older than 70 years [256]. Studies of the intervening period concluded for the 30-50yr age group that reinterventions reached 25-35% between 10 and 20 years of implantation [241] and 55-86% after 20 years [242, 244, 247, 250, 257]. In the middle-age group of 50-60 years, reintervention rates were not too different with 37% at 10 years [244] and 45-81% at 20 years [247, 257]. However, arguments why one should not uncritically extrapolate these data to

today's young rheumatic patients in LMICs are manifold. For one, patients, circumstances and prostheses have changed over time. Although all key studies were published between 2005 and 2018 their actual implants go back to the 1970s and 1980s [250, 254, 257]. Furthermore, although most of the recommendations coming out of the research of recent years have not been implemented in contemporary valves [22, 258-262] some of them have [263]. This is partially reflected in performance differences between different makes: a 3 year freedom from valve related failure of 18% in Mitroflow valves, for instance, was opposed by 100% in Edwards Perimount Magna valves [148] most likely on the grounds of alcohol-based lipid extraction in the Edwards valves not used in early Mitroflow models. Similarly, the long outstanding verdict on pericardial versus porcine valves seems to have come closer to a conclusion as pericardial valves saw a longer freedom from valve related failure than porcine prostheses (10.2 versus 5.7 years) [245] and a higher rate of freedom from reoperation in a most recent study [264].

CONSIDERATIONS FOR VALVE SELECTION

Fear of reoperations has deadlocked discussions around valve choices on the level of evidence rooted in the 1980s and 1990s. Overall cardiac surgical mortalities are different in today's era. As such, contemporary operative mortality rates of 4-5% for first time re-operations [265-268] may make re-interventions a costly inconvenience rather than a deterrent. In modern series analysing redo AVRs and MVRs separately, the operative mortality of the first re-operation lay in the 3-4% range for AVRs [269-271] and 4-8% for MVRs [272, 273]. For redo-AVRs, Turina et al [274] have even shown that mortalities can be brought down to 1.4% if only elective cases were considered. Less invasive operative techniques also had an impact in recent years. Schneider et al reported a decrease of the mortality of redo-AVRs from 9.3% to zero over the last decade [275]. Similarly, no mortality was also observed in redo-MVRs both using minimally invasive [276] and beating heart techniques [277].

In order for bioprosthetic valves to be considered for young patients, however, the morbidity and mortality associated with mechanical valves would need to outweigh the accumulated mortality and inconvenience of re-interventions for bioprosthetic valves. Several Western studies did conclude that there was no difference in long-term mortality between mechanical and tissue valves [251, 252, 278-283]. In patients with RHD in LMICs, the high rate of thromboembolic and haemorrhagic incidences in mechanical valves needs to be additionally taken into account. Importantly, the limited capacity of the health care systems to deal with acutely failing valves [183, 238] must also be considered. In a study from Turkey reporting on the re-operation of 700 patients who had a valve replacement mainly for RHD at a relatively young age, the mortality was three times higher in urgent (mostly mechanical valves) than in elective (mostly bioprosthetic) re-operations [234].

Against this background, the individual life expectancy of a patient needs to be the final determinant in the choice of the least detrimental valve prosthesis. In developing countries, patients from rural backgrounds and low socioeconomic status very often present with advanced disease. Hence, despite being young in age, the life expectancy of these patients is much lower than that of Western populations. As such, the assessment of life expectancy, based solely upon chronological age, is erroneous and age-related Western cut-offs are not valid [284]. Besides age, the cardiac condition of the patient, systemic illnesses and the socioeconomic status, life expectancy is also affected by the patient's gender and location (urban vs rural). In India, for instance, the life expectancy of a rural male (60.2 years) is much less than that of urban female (69.0 years) [284]. Life expectancy is also a direct reflection of an individual's socioeconomic and educational status [284]. Thus, the 11.9 years life expectancy of a 60-year-old patient receiving a bioprosthesis in India [285] is much shorter than the life expectancy of 22.6 years for 60-year-olds reported by the US National Centre for Health Statistics [284, 286]. On top of this, valve patients live shorter, even in HICs. Lindblom and

colleagues [287] have shown that the relative life expectancy was only 78% post AVR and 65% post MVR [287] and less in younger patients [287]. As patients with RHD often have advanced disease their life expectancy is even shorter as symptoms of heart failure and/or AF further reduce the expected survival [284]. The presence of aortic regurgitation and mitral regurgitation further contribute to excess mortality [232, 284, 287]. Therefore, it can be assumed that in a significant proportion of patients life expectancy will lie below the implant duration of the first tissue valve.
Overall, other considerations also need to come in like the potentially game-changing effect transcatheter therapies may have on valve choices. Ample evidence exists that by now valve-in-valve (VIV)-TAVI/TMVR is an established procedure that allows redo-AVRs [288-290] and MVRs [291] without re-opening of the chest. At its extreme it includes the possibility of insertion into a failing tissue valve during pregnancy [289]. Yet, there are limitations. In VIV-TMVRs, a known complication in every 50th 'Western' patient is left ventricular outflow tract (LVOT) obstruction [291]. Given the small ventricular cavity of patients with rheumatic mitral valve stenosis and as such of patients with stenosed bioprosthetic valves, the higher incidence of LVOT obstruction may be a limiting factor for this indication. Furthermore, costs are a prohibitive obstacle for valve-in-valve transcatheter solutions in LMICs but more affordable local makes have begun to emerge [292, 293]. Whether transcatheter VIV-procedures will further significantly lower re-operative mortality will need to be shown. In a 2019 meta-analysis a zero operative mortality in the VIV-TAVI group increased to 4% when the 30day mortality was assessed, matching that of surgical reoperations by the time of discharge.

In summary, in the absence of large, multicentred, randomised clinical trials, using the current generations of bioprostheses and mechanical valves across all age groups [284] valve choices will be least harmful if sensible and appropriate criteria rather than Western guidelines are being uncritically applied.
At the outset of such an approach must be an assessment of a patient's life expectancy taking his/her geographic, socioeconomic and medical background into consideration. Assessment criteria must be continually adjusted: overall life expectancies have increased (in India eg from 54 in 1980 to 70 in 2019 [294]); pericardial valves have emerged as more durable [240, 245, 264] and scientific insights into mechanisms of tissue degeneration or thrombus formation are beginning to be reflected in contemporary prostheses [263]. Other aspects such as whether a prosthesis is for the aortic or the mitral position should also be taken into account. As much as surgeons in LMICs have somehow considered these criteria in the past, the supremacy of the 'chronological age' of patients enshrined in the guidelines of HICs still dominates the decision making process in LMICs.

GLIMMERS OF HOPE

The quest for longer lasting tissue valves and anticoagulation-free mechanical valves of young patients of HICs who are eager to live an active life may add weight to the efforts of middle-income countries addressing the needs of their patients with RHD.

Low-thrombogenicity designs of mechanical valves have been a holy grail for decades but with tri-leaflet concepts [295] they may eventually be within reach. A novel design that placed the hinges of a tri-leaflet valve distinctly into the central systolic blood-flow, thereby eluding the adverse flow areas near the housing of the valve, showed very promising in-vitro results [296] and most recently also an in-vivo breakthrough (personal communication)(Fig 6).
Calcific bioprosthetic degeneration of tissue valves was shown to hinge on remnant immunogenicity [19]. Better immune-suppression through alternative crosslinking approaches [22, 23] and/or decellularization [260, 262] were shown to mitigate calcification. Alternatively, alpha-

gal receptor-depleted trans-genic pigs were suggested as tissue source [297]. As a first step towards clinical implementation, cell membrane extraction through alcohol-based lipid wash-out [258, 259, 261] was partially introduced to commercial valves [263]. Complete decellularization with the goal of extracting the main antigen carriers from the tissue was clinically successfully demonstrated in allografts [298]. Decellularization of xenografts tissue [260] was a logical next step. Non-crosslinked in order to allow tissue regeneration, such tissue was clinically tried with poor outcome [299] suggesting that unmasked/non-crosslinked extracellular matrix may still be sufficiently immunogenic to trigger an inflammatory xenograft response. While gentler decellularization may allow for non-crosslinked decellularization [300] either mildly [301] or conventionally crosslinked decellularized-pericardium [302] have been clinically successfully used for valve reconstruction patches [303]. Following two decades of conclusive research, decellularized tissue valves potentially combined with engineered crosslinking [15] will undoubtedly introduce a quantum leap into bioprosthetic heart valve developments. In its wake, one can expect a dramatic downward-shift of the age limit for tissue valves. Unsurprisingly, MICs like Brazil and South Africa [175] and HICs with a significant burden of RHD like Australia [301] are currently pioneering such prostheses.

Polymeric leaflet materials are immune-quiescent but had previously experienced calcific degeneration due to polymer degradation and imperfect production [304]. Daebritz and Jansen had shown the potential of polymer valves in the challenging calf model [305, 306] . Momentum has built up in recent years [31] culminating in first-in-man implants in 2019 [307].

Given the often very young age of patients with RHD, replacing diseased heart valves with living prostheses has been the ultimate goal of generations of researchers. Over the past decade, the focus of tissue engineering has shifted from in-vitro bio-reactor-based concepts [35, 308] to self-regenerating polymer-based approaches [34]. The recent failure of clinically implanted 'Xeltis' valves [309], after promising pre-clinical trials [310], however, demonstrated the complexity of the balance between degradation and regeneration.

Last not least, lack of cardiac surgical capacity is not only a big challenge for LICs but also for MICs outside the urban reach [1, 2, 12]. A combination of easy-to-place trans-catheter technologies tailor-made for non-sophisticated medical facilities (Figure 7) and suitable for the often compliant, non-calcified valves of patients with RHD with long-lasting leaflet material (Figure 8) may introduce replacement valves that eventually address the "needs of the many" [174, 175].

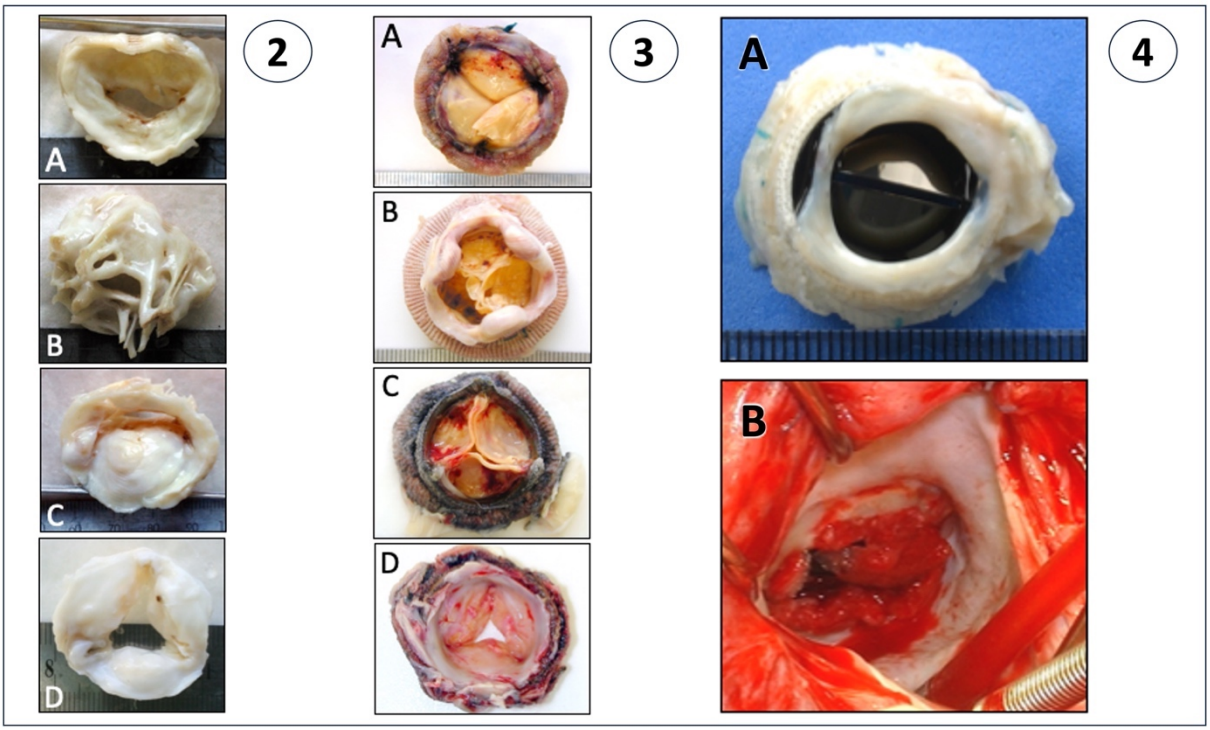

Figure 2: *Typical rheumatic heart valves needing replacement. (A) MS in 26 year old female; (B) MS in 30 year old female; (C) Mixed MV-disease 52 year old female and (D) mixed AV disease in 57 year old male.*

Figure 3: *Failed early-generation bioprosthetic heart valves implanted into patients with RHD in the 1990s. Most long-term studies are based on this second generation of tissue valves. (A) MVR with CE Porcine Valve implanted in a 39yr old patient deemed non-compliant for anticoagulation. Prosthetic endocarditis (Infected sewing ring) and ruptured leaflet at age 45; (B) AVR with Hancock I Porcine Valve at age 33 failed (calcified, ruptured) after 19 years at age 52; (C) MVR with St.Jude Pericardial valve in 36yr old woman after 2 blocked mechanical valves. Explant after 9yrs (stenosed, MV gradient 34mm); (D) Pericardial prosthesis of unknown make failing after 9yrs (primarily stenosed) at age 45 after 2 previous mechanical valves clotted.*

Figure 4: *The two primary failure modes of mechanical heart valves in the young patients of low- to middle-income countries with RHD: (A) vigorous infra-valvular pannus ingrowth seven years after AVR with Mira (Edwards) at age 25 and (B) clotted and sub-totally obstructed mitral valve (Reproduced from [(6)] with permission).*

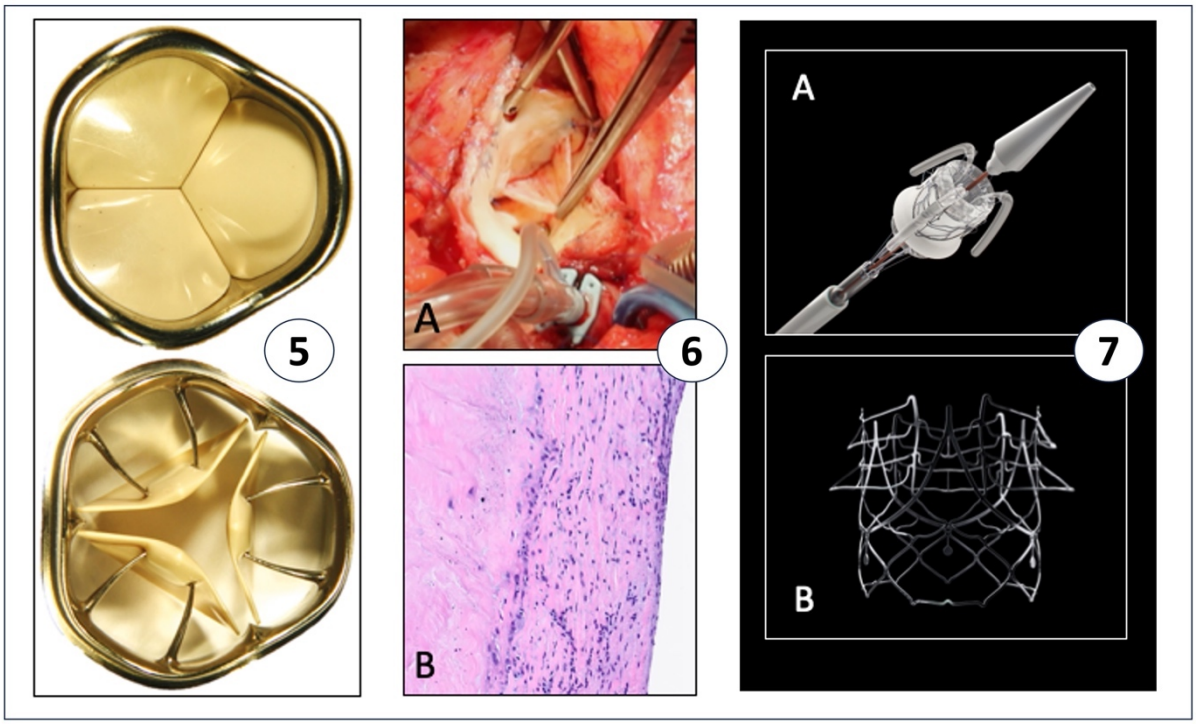

Figure 5: *Novel tri-leaflet mechanical heart valve: Main characteristics are zero back flow during diastole, pivoting completely in systolic flow, no contact of the leaflets with the valve ring in systole, antithrombotic material (titanium and PEEK), aerodynamically optimized leaflet configuration (similar to one wing aircraft) and ring design preventing suture pledgets from protruding into the blood-flow (Courtesy of H.Sievers with permission from* [(296)]*.*

Figure 6: *Decellularized xeno-pericardium as a promise for bioprosthetic longevity: (A)"Auto Tissue Berlin" Matrix Patch (decellularized equine pericardium)* [(175)] *5 years after replacing one cusp during aortic valve repair in a 7-year old child. The patch is still thin and pliable. Redo surgery was necessary because of the retraction of the two shaved native cusps. (Courtesy of Boulos Asfour, St. Augustin, Germany) (B) Hematoxylin & Eosin stain of the explanted patch. Pseudointima formation (right half of the image) covering the decellularized equine surgical patch (left half of the image) demonstrating sparse cell infiltration and no significant cellular inflammatory reaction. (Courtesy of Matthias Sigler, University of Göttingen, Germany)*

Figure 7: *Transcatheter system enabling the implantation of replacement valves under basic conditions. (A) Self-homing, non-occlusive delivery system for the deployment of balloon expandable TAVI s (reproduced with permission from* [(175)] *(B) TAVI-stent developed for the largely non-calcified, compliant aortic roots of patients with AR in low- to middle-income countries with RHD (with permission of Strait Access Technologies (SAT) / University of Cape Town).*

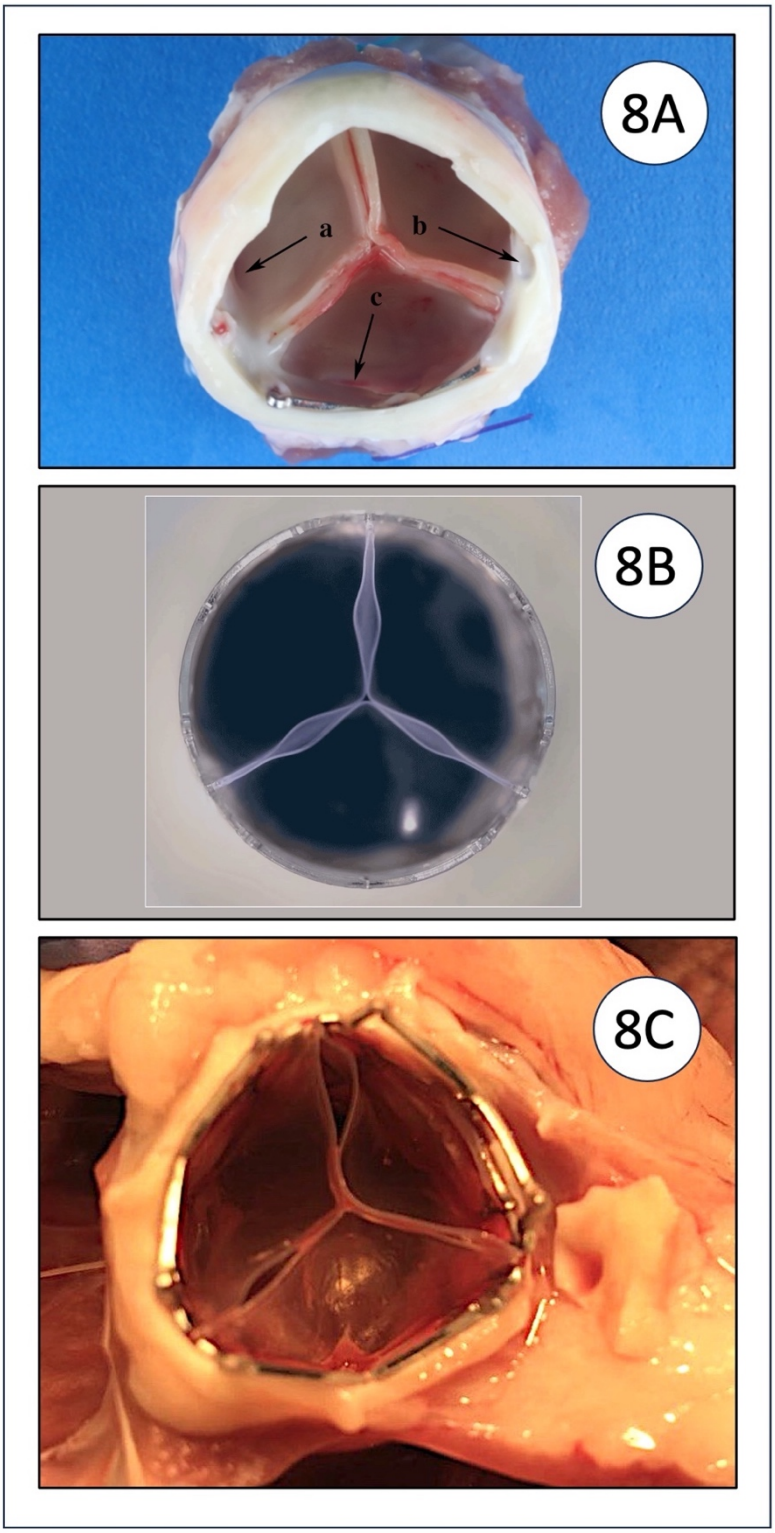

Figure 8: *SAT TAVIs (A) with decellularized bovine pericardial leaflets (reproduced from [175] with permission) after 5 months in sheep orthotopic position (B) with polymer leaflets in vitro and (C) polymer leaflets after 5 months in the sheep [311]. At explantation, both leaflet types (A,C) had no traces of calcification and were soft and pliable.*

CHAPTER 4

DEMONSTRATION OF POOR SUITABILITY OF CONTEMPORARY MECHANICAL HEART VALVES FOR PATIENTS WITH RHEUMATIC HEART DISEASE

I conducted a clinical study at a teaching hospital of a low- and middle-income country like South Africa to highlight the catastrophic outcome after mechanical heart valve replacement under the given socioeconomic circumstances and in the absence of an alternative to American- and European prostheses that were developed for very different patients and against a distinctly different infrastructure- and educational background. This work was published in our most prestigious surgical journal, the 'Journal of Thoracic and Cardiovascular Surgery'.

9

Adult: Aortic Valve — Scherman et al

Isolated mechanical aortic valve replacement in rheumatic patients in a low- to middle-income country

Check for updates

Jacques Scherman, MD, Rodgers Manganyi, MD, Paul Human, PhD, Timothy Pennel, MD, PhD, Andre Brooks, MD, Johan Brink, MD, and Peter Zilla, MD, PhD

ABSTRACT

Objective: Although the results of aortic valve replacement are well documented for industrialized countries, the outcome in patients with rheumatic aortic valve disease in low- to middle-income countries is less well explored. The aim of this study was to determine the long-term survival and clinical outcomes after isolated aortic valve replacement in patients with rheumatic heart disease in a Sub-Saharan country where follow-up of indigent patients is often challenging.

Methods: A retrospective review of 969 aortic valve replacements performed between 2003 and 2013 was conducted at Cape Town's Groote Schuur Hospital. Patients who underwent concomitant procedures (n = 664) or had nonrheumatic valve pathology (n = 185) were excluded. The mean age of the rheumatic cohort (n = 121) was 43.1 ± 11.6 years with a mean follow-up period of 6.14 ± 3.44 years. The primary end points were survival and valve-related complications.

Results: A 15% cardiac- or valve-related 10-year mortality after receiving a mechanical prosthesis corresponded with a significantly higher mortality rate than that of a matched population. Overall cumulative survival at 1, 5, and 10 years was 93.5% (87.0-96.9), 86.4% (78.4-91.8), and 78.1% (67.5-86.0), respectively, and the corresponding cumulative freedom from combined thromboembolism and bleeding was 94.4% (88.2-97.5), 87.4% (79.4-92.5), and 86.1% (77.9-91.6), respectively.

Conclusions: In low- to middle-income countries, with their unique mix of indigent and "First World" patients, rheumatic heart disease still accounts for a significant proportion of patients requiring isolated aortic valve replacement. Although mechanical prostheses are often selected in these young adults, survival remains suboptimal. Major bleeding and thromboembolic events account for the majority (77%) of the reported valve-related complications. (J Thorac Cardiovasc Surg 2019;157:886-93)

Freedom from major adverse valve-related events after mechanical AVR.

Central Message

In low- to middle-income countries, up to 1 of every 4 young rheumatic patients receiving a mechanical AVR have a major valve-related event within the first decade after valve replacement.

Perspective

None of the current heart valve prostheses offer a true lifelong solution. In young patients with RHD, compelling evidence is lacking to balance the risk of thromboembolic/bleeding events with mechanical valves against reoperative risk inherent to bioprostheses. Technological developments and evolving transcatheter solutions may together favor more liberal use of bioprostheses in these patients.

See Commentary on page 894.

In low- to middle-income countries, rheumatic heart disease (RHD) still accounts for the majority of patients in need of cardiac surgery. It is estimated that in Africa alone, there are 15 million patients living with RHD, of whom 100,000 per year may need valve surgery during some stage of their lives,[1] provided cardiac surgery is available. Because of the nature of the underlying disease, aortic valve repair options are limited, and as such, surgical aortic valve replacement (AVR) remains the treatment of choice for the majority of patients with symptomatic rheumatic aortic valve disease. Apart from access to open surgery, the choice of valve prosthesis presents a particular challenge given the socioeconomic circumstances of these patients. Yet, in the absence of local evidence-based recommendations, low- to middle-income countries largely apply First World guidelines when it comes to valve selection.[2-4] As such, the majority of patients still receive mechanical valves at

From the Chris Barnard Division of Cardiothoracic Surgery, University of Cape Town, Cape Town, South Africa.

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Address for reprints: Jacques Scherman, MD, Chris Barnard Division of Cardiothoracic Surgery, Groote Schuur Hospital, University of Cape Town, 7925 Observatory, Cape Town, South Africa (E-mail: jacques.scherman@uct.ac.za).

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Figure 9: ***<u>Scherman J</u>****, Manganyi R, Human P, Pennel T, Brooks A, Brink J, Zilla P. Isolated Mechanical Aortic Valve Replacement in Rheumatic Patients in a Low- To Middle-Income Country. J Thoracic Cardiovasc Surg. 2019; 157(3): 886-893.*

ISOLATED MECHANICAL AORTIC VALVE REPLACEMENT IN RHEUMATIC PATIENTS IN A LOW- TO MIDDLE-INCOME COUNTRY

Jacques Scherman, Rodgers Manganyi, Paul Human, Timothy Pennel, Andre Brooks, Johan Brink, Peter Zilla

Chris Barnard Division of Cardiothoracic Surgery, University of Cape Town

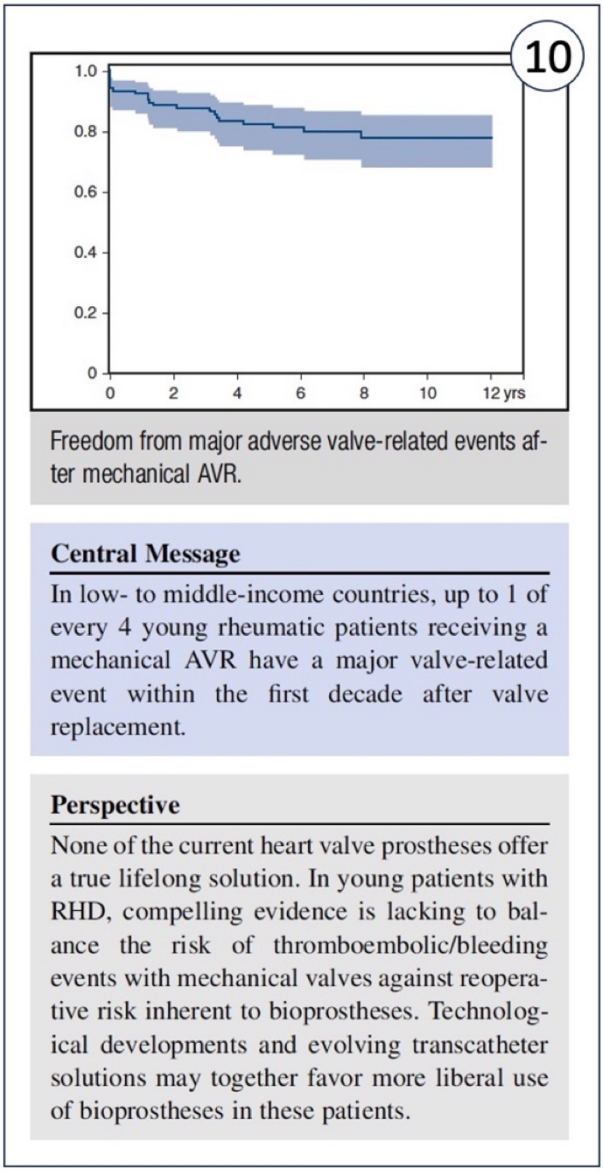
ABSTRACT *(Core Message:* ***Figure 10****)*

Objective: Although the results of aortic valve replacement (AVR) are well documented for industrialized countries, the outcome in patients with rheumatic aortic valve disease in low- to middle-income countries is less well explored. The aim of this study was to determine the long-term survival and clinical outcomes after isolated AVR in rheumatic heart disease (RHD) patients in a Sub-Saharan country where follow-up of indigent patients is often challenging.

Methods: A retrospective review of 969 aortic valve replacements done between 2003 and 2013 was conducted at Cape Town's Groote Schuur Hospital. Patients who underwent concomitant procedures (n=664) or had non-rheumatic valve pathology (n=185) were excluded. The mean age of the rheumatic cohort (n=121) was 43.1±11.6 years with a mean follow-up period of 6.14±3.44 years. The primary end points were survival and valve-related complications.

Results: A 15% cardiac- or valve-related 10-year mortality after receiving a mechanical prosthesis corresponded with a significant higher mortality rate than that of a matched population. Overall cumulative survival at 1, 5, and 10 years was 93.5% (87.0-96.9), 86.4% (78.4-91.8) and 78.1% (67.5-86.0) and the corresponding cumulative freedom from combined thromboembolism and bleeding was 94.4% (88.2-97.5), 87.4% (79.4-92.5) and 86.1% (77.9-91.6), respectively.

Conclusion: In low- to middle-income countries, with their unique mix of indigent and 'First World' patients, RHD still accounts for a significant proportion of patients requiring isolated AVR. Although mechanical prostheses are often selected in these young adults, survival remains suboptimal. Major bleeding- and thromboembolic events account for the majority (77%) of the reported valve-related complications.



Freedom from major adverse valve-related events after mechanical AVR.

Central Message

In low- to middle-income countries, up to 1 of every 4 young rheumatic patients receiving a mechanical AVR have a major valve-related event within the first decade after valve replacement.

Perspective

None of the current heart valve prostheses offer a true lifelong solution. In young patients with RHD, compelling evidence is lacking to balance the risk of thromboembolic/bleeding events with mechanical valves against reoperative risk inherent to bioprostheses. Technological developments and evolving transcatheter solutions may together favor more liberal use of bioprostheses in these patients.

INTRODUCTION

In low- to middle-income countries, rheumatic heart disease (RHD) still accounts for the majority of patients in need of cardiac surgery. It is estimated that in Africa alone there are 15 million patients living with RHD, of which 100 000 per year may need valve surgery during some stage of their lives [(8)] -provided cardiac surgery is available. Due to the nature of the underlying disease, aortic valve repair options are limited, and as such surgical AVR remains the treatment of choice for the majority of patients suffering from symptomatic rheumatic aortic valve disease. Apart from access to open-heart surgery, the choice of valve prosthesis presents a particular challenge given the socioeconomic circumstances of these patients. Yet, in the absence of local evidence-based recommendations, low- to middle-income countries largely apply first world guidelines when it comes to valve selection [(235, 312, 313)]. As such, the vast majority of patients still receive mechanical valves at a time when the collective experience of industrialized countries had long swung towards tissue valves due to their significantly older patient population. The de facto paradigm of this decision continues to be that the anticipation of premature tissue valve degeneration in young patients outweighs poverty-, culture-, and access-related adverse events associated with mechanical heart valves. Given this prevailing assumption, prospective comparative studies between the two valve types would be considered unethical although the true outcome of mechanical valve replacements remains unknown. A first step towards evidence-based decision-making would thus be to determine the long-term fate of mechanical valve replacements in the largely young rheumatic patients of a low- to middle-income country with reasonable access to cardiac surgery.

MATERIALS AND METHODS

The study was approved by the institutional review board (Human Research Ethics Committee: Approval Ref 344/2014; Faculty of Health Sciences, University of Cape Town. Institutional Review Board (IRB): IRB00001938).

Patients

All patients who underwent an AVR at Cape Town's Groote Schuur Hospital between January 2003 and December 2013 were followed-up retrospectively. A total of 969 patients were identified. Patients who underwent concomitant procedures, aortic root replacements, aortic valve repairs, transcatheter or redo-procedures were excluded (n=664 patients). We further excluded all patients who had underlying calcific degenerative disease, endocarditis, congenital aortic valve disease or any other non-rheumatic heart valve pathology (n=184 patients), leaving 121 patients who underwent an isolated first-time AVR for RHD. The majority of these patients (89%, n=108) received a mechanical prosthesis. The subgroup of patients who received a bioprosthesis was small (11%, n=13) and significantly older (mean age of 58.6±11.6 years) than the mechanical group and therefore not included in the subsequent analysis. The preoperative baseline characteristics are summarized in Table 1. The mean age of this rheumatic cohort was 43.1±11.6 years at the time of surgery with 63.8% (n=69) of the cohort being male. Pure aortic regurgitation occurred in 61% (n=66) of the patients, pure aortic stenosis in 8% (n=9), and 31% (n=33) had a mixed (predominantly regurgitant) aortic valve lesion. Atrial fibrillation was present in 8% (n=9) pre-operatively. The majority of patients (90%) presented in NYHA class II or III at the time of surgery. The mean calculated STS score (risk of mortality) of this rheumatic cohort was 0.7%±0.2%.

Operative Data and Prosthesis Selection

The mean cardiopulmonary bypass time was 114±26 minutes with a cross-clamp time of 78±21 minutes. All procedures were performed under moderate hypothermia using St Thomas crystalloid cardioplegic solution. The distribution of mechanical prostheses was as follows: St Jude Medical in 32 patients (26%), On-X in 30 patients (25%), Edwards MIRA in 23 patients (19%), Medtronic Advantage in 19 patients (16%) and Medtronic ATS in 4 patients (3%).

Anticoagulation and Post-operative Management

Anticoagulation therapy with Warfarin was routinely commenced on the first post-operative day in all patients who received a mechanical prosthesis. A low molecular weight Heparin was concomitantly used until a target international normalised ratio (INR) between 2 and 3 was reached. Following discharge from hospital all patients were referred to their closest medical clinic or facility where further INR testing and follow-up could be performed.

Data Collection and Outcomes

During the past decade the widespread use of pre-paid mobile phones as well as institutional and national laboratory databases introduced improved means for follow-up, hitherto unavailable, for a patient population with a significant rural component.
Data were retrospectively collected using the cardiac surgical database of the Chris Barnard Division of Cardiothoracic Surgery, University of Cape Town; as well as from hospital medical records, the metropolitan hospital-link database, the National Health Laboratory Service's (NHLS) database and telephonic interviews.

The follow-up period ended in October 2014. The mean follow-up period was 6.1±3.4 years and 100% complete. The primary outcomes were valve-related mortality and valve-related morbidity, which included prosthetic valve dysfunction, bleeding and embolic events, prosthetic valve endocarditis and the need for reintervention. The outcomes were reported as per guidelines for reporting mortality and morbidity after cardiac valve interventions [(314)].

Statistical Analysis

Statistical analysis was performed using the JMP® statistical software package (version 10.0.2, Cary; NC). All continuous numerical data were expressed as means ± standard deviation. Kaplan-Meier survival estimates were expressed as percentages and 95% confidence intervals. For comparison of mortality rates against that of the standard population, the method described by Finkelstein et al., using age- and sex-matched vital data, obtained for the Western Cape Province from Statistics South Africa ("Stats SA"), was employed [(315)]. Statistical comparison between standard population and cohort patient survival was performed using the one-sample Log-Rank test. For visual comparison, 95% pointwise confidence intervals were included. A significance level below 0.05 was considered statistically significant.

RESULTS

The main finding of this retrospective analysis was a significantly inferior long-term survival of the study group compared to an age and sex-matched comparable South African subpopulation (Fig. 11) with 39% (n=7) of late deaths being valve-related. Major bleeding- and thromboembolic events (n=17 events) accounted for the majority (77%) of the reported valve-related complications. One out of every four of these young rheumatic patients suffered a major adverse valve-related event (mortality or major morbidity) during the first decade after having received a mechanical aortic valve prosthesis.

Early Mortality and Complications

The in-hospital/thirty-day mortality for the rheumatic mechanical AVR cohort was 1.9% (n=2). The causes of early death were multi-organ failure (n=1) and a thromboembolic neurological event (n=1). New onset atrial fibrillation/flutter occurred in 4.6% (n=5) of patients. New onset atrio-ventricular block requiring a permanent pacemaker occurred in 1.9% (n=2). Bleeding requiring reoperation (<48 hours) occurred in 2.8% (n=3); late drainage of a pericardial effusion (< 30 days) in 1.9% (n=2); renal failure in 0.9% (n=1) and early stroke in 0.9% (n=1) of patients.

Late Mortality

Late mortality (all cause) occurred in 18 of 106 patients (17%) at a mean of 43±37 months after surgery. The majority of the late deaths were cardiac or valve related (89%, n=16). Table 2 summarises the causes of late deaths. Cumulative survival at 1, 5 and 10 years following mechanical AVR was 93.5% (87.0-96.9), 86.4% (78.4-91.8) and 78.1% (67.5-86.0), respectively. This was considerably lower than that of the age and sex-matched population in the Western Cape Province, South Africa, where this study was conducted, whose expected survival was 97.7% (97.0-98.4), 91.8% (90.2-93.4), and 86.6% (79.6-93.7), respectively (p<0.001) (Figure 11).

Valve-related Morbidity

Overall, nine major bleeding- and eight thromboembolic events occurred in 14 patients. Of the thromboembolic events, seven were strokes and one a transient ischemic event. The cumulative freedom from the composite of thromboembolism and bleeding following mechanical AVR was 94.4% (88.2-97.5), 87.4% (79.4-92.5) and 86.1% (77.9-91.6) at 1, 5 and 10 years, respectively (Figure 12).

Only 2 reoperations were performed during the follow-up period (6.14±3.44 years). The indications for re-intervention were valve thrombosis (n=1) and prosthetic valve endocarditis (n=1). As such, freedom from reoperation at 1, 5 and 10 years was 100%, 99.0% (93.0-99.9) and 96.9% (87.4-99.3), respectively.

Freedom from any valve-related event (i.e. prosthetic valve dysfunction, bleeding/thromboembolic events, prosthetic valve endocarditis, and the need for reintervention) at 1, 5 and 10 years was 94.4% (88.2-97.5), 87.4% (79.4-92.5) and 82.9% (73.5-89.4), respectively (Figure 13).

Major Adverse Valve-Related Events (MAVRE)

Freedom from MAVRE (i.e. valve-related mortality, valve-related morbidity and the need for a new pacemaker) at 1, 5 and 10 years was 92.6% (85.9-96.3), 82.6% (74.0-88.8) and 78.1% (68.4-85.5), respectively (Figure 14). A further sub-analysis comparing the different types of mechanical prosthesis used did not show any significant difference in terms of major adverse valve-related events (p=0.23).

DISCUSSION

With the often-remarkable growth of cardiac surgery in emerging economies where RHD still prevails, the reliance on first-world guidelines for the choice of replacement valves that do not take the specific pathology, patient age and socio-economic circumstances of the affected patients into account, may unintendedly result in poor outcomes.

Our cohort analysis of single mechanical AVR's in rheumatic patients showed a significantly higher ten-year mortality than their matched population counterparts. This sobering outcome was aggravated by the fact that the mean age of these patients was younger than 45 years. Together with low mortality rates for re-operations for degenerated tissue valves [267, 316, 317],

a 15% ten-year cardiac- or valve-related mortality after receiving a mechanical valve prosthesis justifies a critical appraisal of our current practise of prosthesis selection.

Recent renewed interest in RHD together with the increasing volumes of cardiac operations performed in the affected countries have led to a shift in focus from merely emulating First World standards towards recognition of the need to respond to a distinctly different pathology-, resource- and patient-baseline [8, 318]. Epidemiologic assessments of disease burdens countering the widely-held belief that RHD has been largely contained need to form the backbone of such a re-orientation. Validating this quest, Sliwa et al. found the incidence of RHD in >14-year-old South African patients as high as 24/100,000 per year, a stark contrast to the <1/100,000 in developed countries [5, 319]. More importantly, within 30 months of diagnosis 22% of these newly diagnosed patients needed heart valve surgery [5].

Challenges in Dealing with RHD Patients

In the relatively young patients with RHD compelling evidence is still lacking to balance the risk of anticoagulation-related bleeding and thromboembolism associated with a mechanical valve with the risk of structural valve deterioration (SVD) and potential reoperation inherent to bioprostheses [284]. Yet, observational studies have shown that major bleeding and thromboembolic complications in patients with mechanical valves are generally much higher in low- to middle-income than in high-income countries [320]. In the present study, the vast majority of patients did not complete secondary school education (84%) and 71% were unemployed. Infrastructure such as transportation and access to health facilities in low- to middle-income countries is often suboptimal for ensuring therapeutic anticoagulation [321]. In the current series major bleeding and thromboembolic events accounted for the majority (77%, n=17) of the reported valve-related complications.

Although the rate of structural valve degeneration of bioprostheses is inversely proportional to a patient's age [322], prosthesis durability; a patient's life expectancy; operative risk of a redo-procedure and the socioeconomic circumstances of typical rheumatic populations must be interpreted together. Even in industrialized countries the life expectancy of patients who underwent an AVR is substantially lower than that of the general population [232, 285]. In a large contemporary 'First World' series, Bouhout et al also reported suboptimal survival rates in young patients receiving mechanical prostheses. Of note, however, is their higher cumulative survival at 1,5, and 10 years of 98%±1%, 95%±1%, and 87%±1%, despite an 'older' mean age of 53±9 years compared to 43.1±11.6 years in our series [323]. Weighing the risk of anticoagulation-related events versus prosthesis-longevity therefore needs to be interpreted in the context of the even lower life expectancy of AVR patients in low- to middle-income countries. Thus, when several large series reported the operative mortality risk for re-operative AVR patients to be 5-7% [267, 316, 317] this relatively low risk must be compared to the lifetime risk of anticoagulation-related events in the poorly anti-coagulated communities of developing countries. During the follow-up in a Kenyan series, for instance, only 7% of mechanical valve recipients had adequate anticoagulation for more than 50% of the 5-year observation period [184].

Cardiac disease in pregnancy is associated with high morbidity and mortality rates [6, 8]. RHD is the most common underlying cardiac lesion in pregnant patients presenting at referral hospitals in South Africa and as such the incidence of AVRs in this age group is additionally much higher than in developed countries [324]. While the patient's young age would 'qualify' them for a mechanical valve, the detrimental effects of warfarin during the first and last trimesters of pregnancy have been well described. Our study underlined the magnitude of this most distinctive difference in patient populations: more than one-third (36.2%) of our

rheumatic mechanical AVR patients were female (mean age 44.3±11.5 years), and a significant proportion presented during their childbearing years or even during pregnancy.

Alternative Solutions for Low- to Middle-Income Countries

The use of new anticoagulants (NOACs), such as direct thrombin inhibitors is particularly attractive and shown to be an effective alternative to Warfarin in patients with atrial fibrillation. Its use in patients with mechanical heart valves has however been associated with increased rates of thromboembolic and bleeding complications [(325)]. In view of this excess risk, Warfarin remains the drug of choice in patients with mechanical prostheses, until new evidence becomes available.

Genotype-based Warfarin dosing has shown some promise during the initiation phase of Warfarin therapy [(326)]. These trials have, however, been limited to patients with European ethnic and socioeconomic backgrounds and provide no guidance on long-term anticoagulation management in our environment.

The recent results from the PROACT trial are encouraging in that INR levels following mechanical AVR with the On-X prosthesis can be safely maintained at lower levels (1.5 to 2.0), without increased risk of anticoagulation-related events [(327)]. This strategy, however, still requires the use of Warfarin with careful monitoring (including home-based monitoring), and is better suited for selected patients only. Furthermore, the results from this study only demonstrated a reduction in the rate of major bleeding events, but a higher number of thromboembolic events.

Transcatheter valve-in-valve (VIV) procedures are also of potential interest in this setting [(328)]. Results of peri-operative outcomes from global valve-in-valve registries are encouraging, but the paucity of information about the long-term durability of aortic VIV procedures warrants further investigations [(329)].

CONCLUSION

In low- to middle-income countries, rheumatic heart disease still accounts for the major burden of disease in patients needing heart valve interventions. None of the current heart valve prostheses offer a lifelong solution. Given that, [1] the life expectancy following an AVR (with either prosthesis), particularly in younger patients suffering from RHD, is substantially lower than the life expectancy of the general population; [2] Warfarin compliance and INR control is suboptimal in developing countries; [3] the incidence of major bleeding and thromboembolic complications is significantly higher in developing countries; and [4] a significant part of rheumatic patients present during their child-bearing years, a substantial number of young rheumatic patients living in low-to middle-income countries may be exposed to a lower life-time risk of experiencing a valve-related event by selecting a bioprosthetic heart valve from the outset. Despite the relative increased mortality risk associated with re-operations for degenerated bioprostheses, new technological developments that may increase the longevity of soft-leaflet prostheses [(22, 32)] as well as evolving trans-catheter solutions for low-income countries that may broaden the access of patients to heart valve replacements [(174)], may together favor a more liberal use of bioprosthetic valves in young patients suffering from rheumatic heart valve disease.

LIMITATIONS

This study is observational and data were collected retrospectively.

Conflict of Interest: None

Acknowledgements:

The authors herewith acknowledge the consultation and statistical support provided by Prof Benjamin Landon Myer from the Division of Epidemiology and Biostatistics in the School of Public Health and Family Medicine at the University of Cape Town, South Africa.

TABLES AND FIGURES

Table I: *Preoperative Demographic characteristics of 108 rheumatic patients who underwent an isolated first-time mechanical aortic valve replacement*

Baseline characteristics	N (%)
Age, mean (SD), y	43.1 (11.6)
Men	69 (63.8%)
Race/ethnicity	
Mixed race	62 (57.4%)
Black	41 (34.2%)
White	4 (3.7%)
Indian	3 (2.8%)
Asian	2 (1.9%)
Cardiovascular risk factors/comorbidities	
Hypertension	25 (23.1%)
Diabetes	7 (6.5%)
Dyslipidemia	7 (6.5%)
Smoker	14 (12.9%)
Atrial fibrillation	9 (8.3%)
Immunocompromised (HIV positive)	4 (3.7%)
New York Heart Association class	
I	7 (6.5%)
II	59 (54.6%)
III	38 (35.2%)
IV	4 (3.7%)
Left ventricular ejection fraction	
<35%	11 (10.2%)
35%-49%	30 (27.8%)
≥50%	67 (62.0%)
Aortic valve pathology	
Regurgitation	66 (61.1%)
Stenosis	9 (8.3%)
Mixed disease	33 (30.6%)
STS score (mortality), mean (SD)	0.7 (0.2)
Level of education	
Did not complete secondary school education	91 (84.3%)
Completed secondary school education	14 (12.9%)
Tertiary education	3 (2.8%)
Employment status	
Unemployed	77 (71.3%)
Employed (temporary or permanent)	28 (25.9%)
Social grant/retired	3 (2.8%)

SD, Standard deviation; *HIV*, human immunodeficiency virus; *STS*, Society of Thoracic Surgeons.

Table II: *Late Mortalities*

	Mechanical AVR prosthesis (n = 106 patients)
Total all-cause late mortalities	N = 18 (17.0%)
Valve related	n = 7 (38.9%)
Endocarditis	1
Thromboembolism	1
Bleeding event	1
Reoperation	2
Sudden unexplained	2
Other cardiac related	n = 9 (50.0%)
Congestive cardiac failure	9
Acute myocardial infarction	0
Arrhythmias	0
Noncardiac	n = 2 (11.1%)

AVR, Aortic valve replacement.

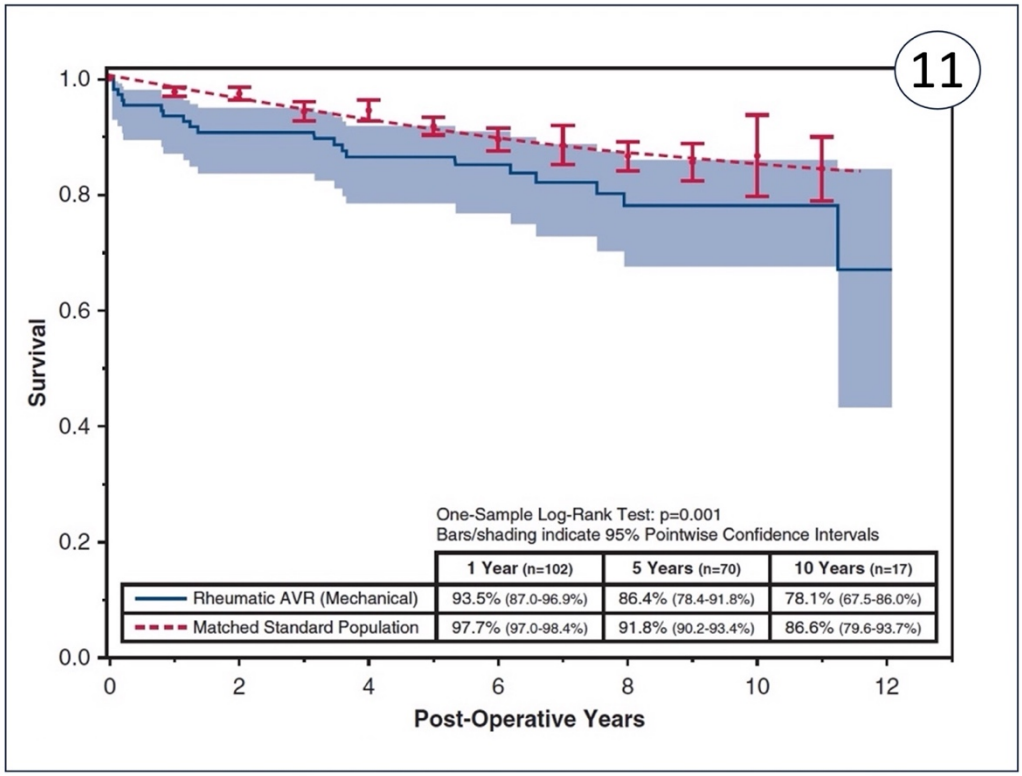


***Figure 11**: Survival in a rheumatic cohort of patients who underwent isolated mechanical AVR compared with sex- and age-matched population in the Western Cape, South Africa. AVR = Aortic Valve Replacement.*

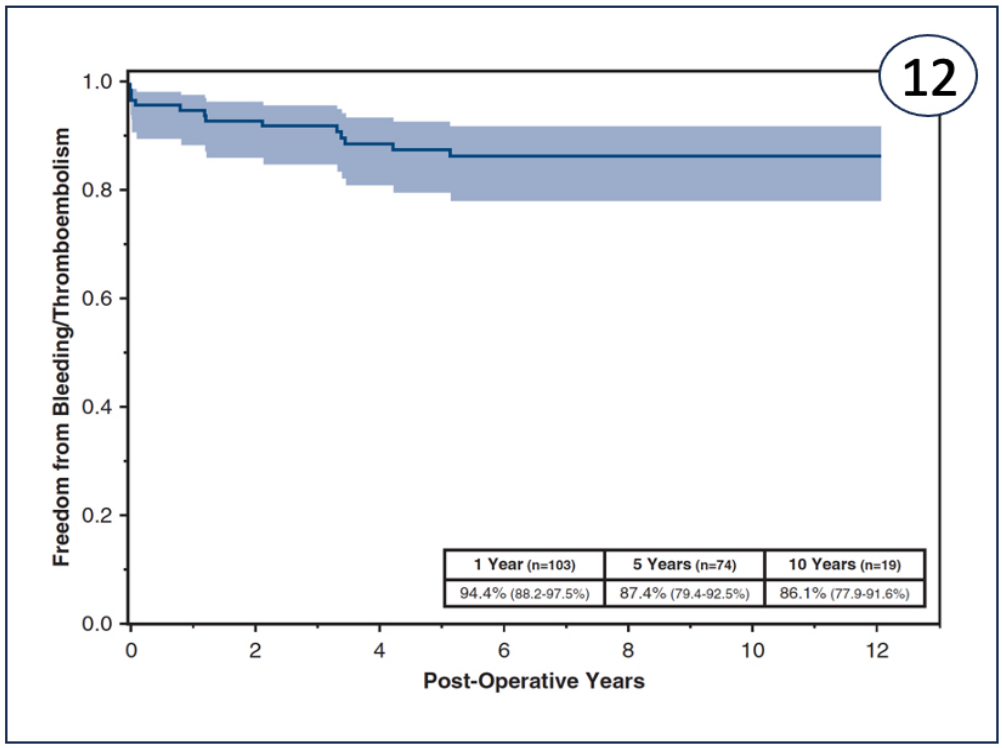


***Figure 12:** Freedom from major bleeding and thromboembolic events in a rheumatic cohort of patients who underwent isolated mechanical AVR.*

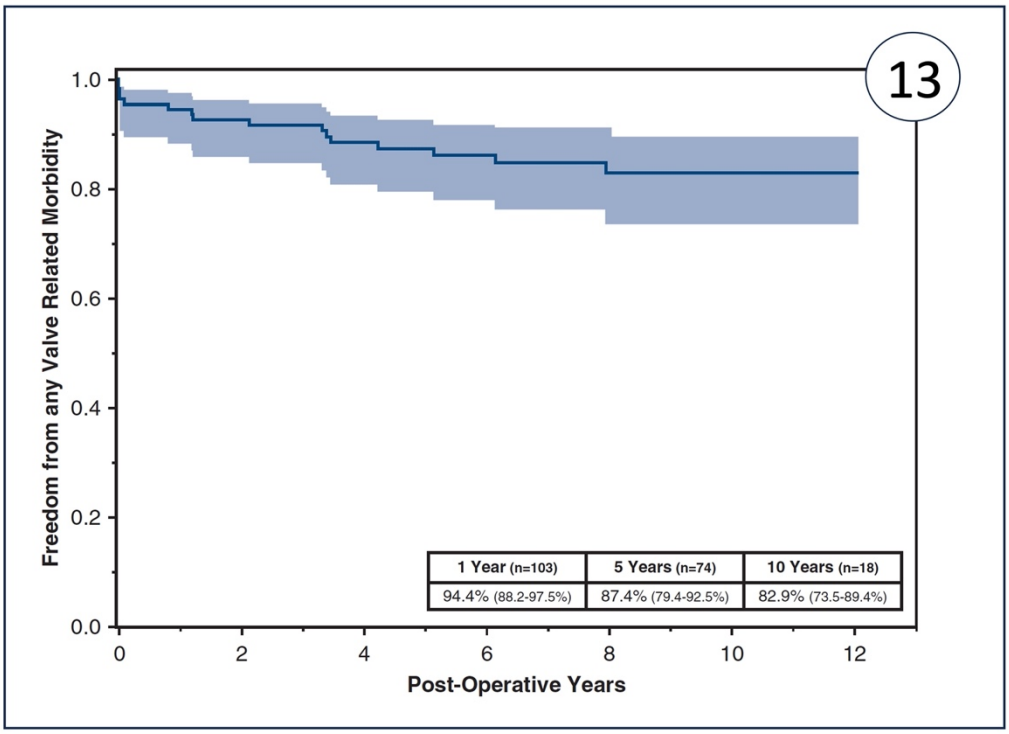


***Figure 13**: Freedom from any valve-related complication (including prosthetic valve dysfunction, bleeding and thromboembolic events, prosthetic valve endocarditis, and the need for reintervention) in a rheumatic cohort of patients who underwent isolated mechanical AVR.*

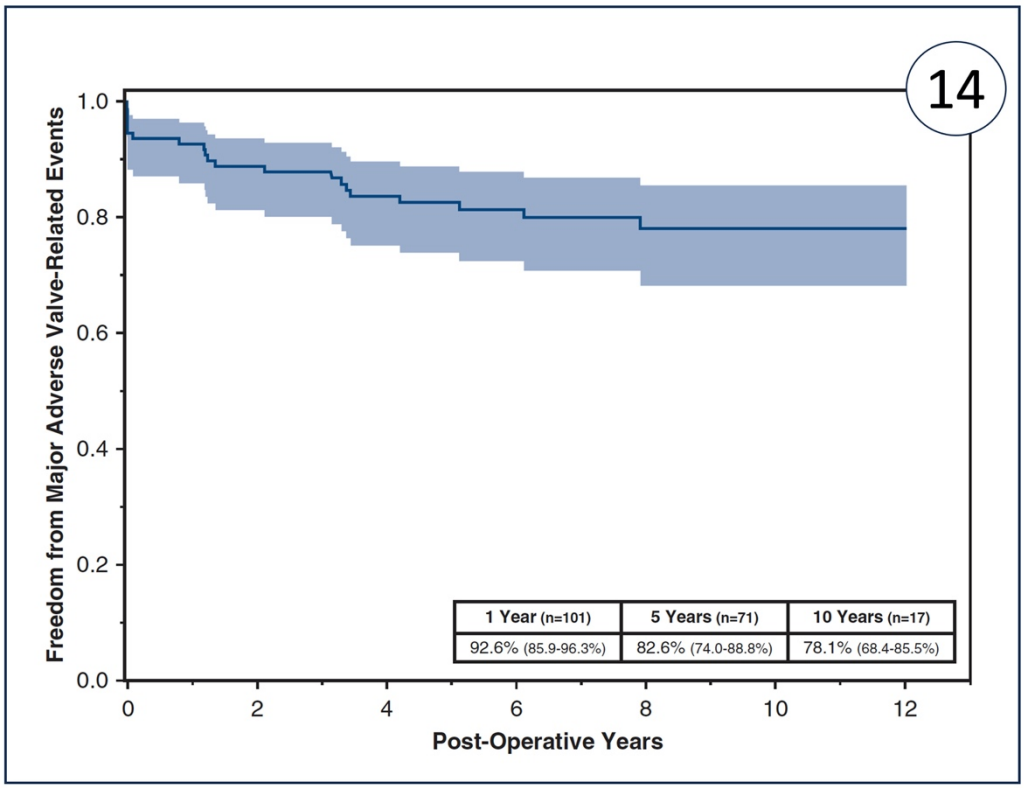


***Figure 14**: Freedom from major adverse valve-related events in a rheumatic cohort of patients who underwent isolated mechanical AVR.*

CHAPTER 5

INTRODUCTION OF THE TAVI SYSTEM DEVELOPED BY SAT/UNIVERSITY OF CAPE TOWN

Background and technical description of the tailor-made trans-catheter replacement heart valve developed by the University of Cape Town/SAT in response to the specific needs of LMICs. The SAT valve addresses both, the lack of open heart surgery in the majority of countries most affected by RHD and the need for long lasting leaflet materials. The latter is a crucial component of any 'tailor-made' solution for patients with RHD given their young age and the known rapid degeneration of bioprosthetic valves in such patients. The key underlying idea of this concept was to adopt transcatheter valve technologies which make open heart surgery increasingly superfluous in industrialised countries to the often basic facilities of low-income countries thereby resolving the dilemma of largely non-existent cardiac surgical health facilities.

1. THE UCT/SAT TRANSCATHETER HEART-VALVE TECHNOLOGIES

This Chapter introduces and describes the technologies related to the transcatheter heart valves and peripheral devices used for their insertion and deployment. The devices were developed and supplied by University of Cape Town based "Strait Access Technologies" (SAT) with continual input by myself. Although the technologies contain proprietary technical features that are outside the scope of this thesis, the following description is disclosed to facilitate the understanding of the devices and for further ease of reference to their use, function and features throughout this document. Basic operations related to the crimping, loading, deployment and retrieval are also described, while the reader is referred to the other chapters for further details pertaining to their use in the pre-clinical studies including publications [153, 174, 175, 330].

The Transcatheter Heart Valve system comprise the following main units, each of which is described in turn and in more detail on the subsequent paragraphs:

1. Transcatheter Heart Valves (one of 2 types)
2. A delivery device
3. A crimping device

1.A. TRANSCATHETER HEART VALVES

The two heart valve types, namely the Bioprosthetic (BPTHV) and Polymeric Transcatheter Heart Valves (PTHV) are made up of three main components that have the following features:

1.A.1. A cobalt chromium (Co-Cr) stent (nominal sizes 23, 26 or 29mm), with

- Scalloped continuous leaflet attachment zones that are:
    - Perforated for precise and secure placement of sutures used to attach the bioprosthetic leaflets (BPTHV; Fig 15 A1)
    - Unperforated for encapsulated and continuous attachment of polymeric leaflets (PTHV; Fig 15 B1)
- Anchoring arms that spontaneously protrude (Fig 15 A3, B3) upon post-crimp balloon expansion to resist retrograde pressures and antegrade forces
- Proximal flaring superstructures that additionally prevent antegrade dislodgement forces.

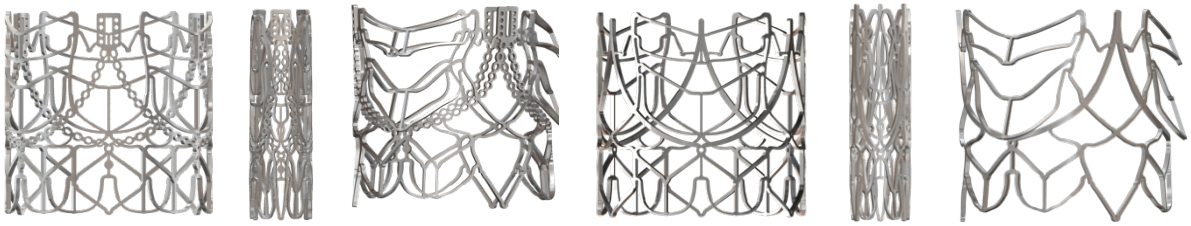
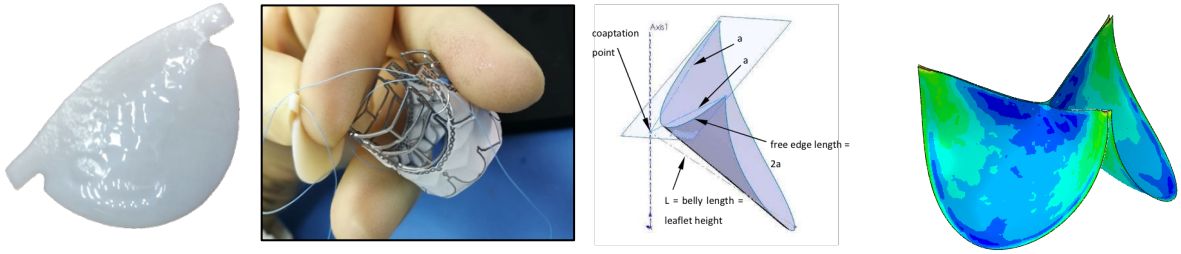


Figure 15*. Stents for bioprosthetic (A) and polymeric (B) valve in original manufactured (1), crimped (2) and expanded (3) configurations. Note the scalloped attachment zone (perforated for BPTHV) protrusion of the anchoring arms of the expanded versions (A3 and B3).*

1.A.2. Three leaflets that are securely attached to the scalloped members of the stents, comprising either:

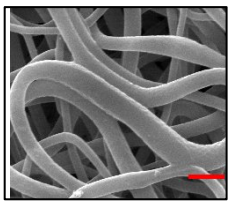
- Decellularised bovine pericardium that has been fixed using lysine-extended glutaraldehyde (GA) treatment and borohydride reduction and manually sutured to the stent scallops, or
- Biostable (Carbosil™) polyurethane cusps defined by Bezier and trigonometric functions, integrally formed onto the stents and thus securely and seamlessly attached to the scallops for maximum durability



A B C D

Figure 16. *Bioprosthetic (A) and polymeric (C) leaflets design and implementation (B, D), showing finite element analysis to minimise stresses in the leaflets*

1.A.3. Sealing Skirt that is designed to prevent paravalvular leakage, and that comprises an electrospun tube (SEM picture, right insert) made from the same polymer as the leaflets of the polymeric valve, that is shaped and bonded to the stent either before (BPTHV) or after (PTHV) attachment of the leaflets, as shown in Figure 17.



A B C

Figure 17. *Full BPTHV (A) and PTHV (B) assemblies (pre-2018 version) and both BPTHV and PTBHV in post 2018 design (C).*

1.B. DELIVERY DEVICE

The delivery device used to insert and expand the crimped valve contains the following main components that are required for the insertion and orthotopic delivery of the valves

- A helical expansion balloon that is designed to be non-occlusive to blood flow, as it is in the form of a tubular, non-compliant balloon helically attached to a frame that supports the windings and provides the stability and ability to reach the radial forces required to expand the valve
- Location trunks made from a similar tubular balloon material to the helical expansion balloon, but configured in such a way that it is extendable (by inflation separate to that of the main expansion balloon) to provide temporary rotational and axial stability during the expansion through location in the native cusps, and retractable by

depressurisation and simultaneous invagination in order to obviate snagging between the expanded prosthetic and native valves.

- A central tip that also acts, when retracted, as terminator for the delivery catheter
- An actuator handle for the mechanical actuation of the device functions (ejection and retraction of the valve/helical balloon assembly) and through which the pressurisation and depressurisation of the helical and trunk balloons are effected. The sequential mechanical actions of extending the helical balloon, extending the trunks, retracting the trunks, as retracting the helical balloon are controlled by the numbers (1 through 4) rotation of the front and rear parts of the delivery handle. (Fig 18A)

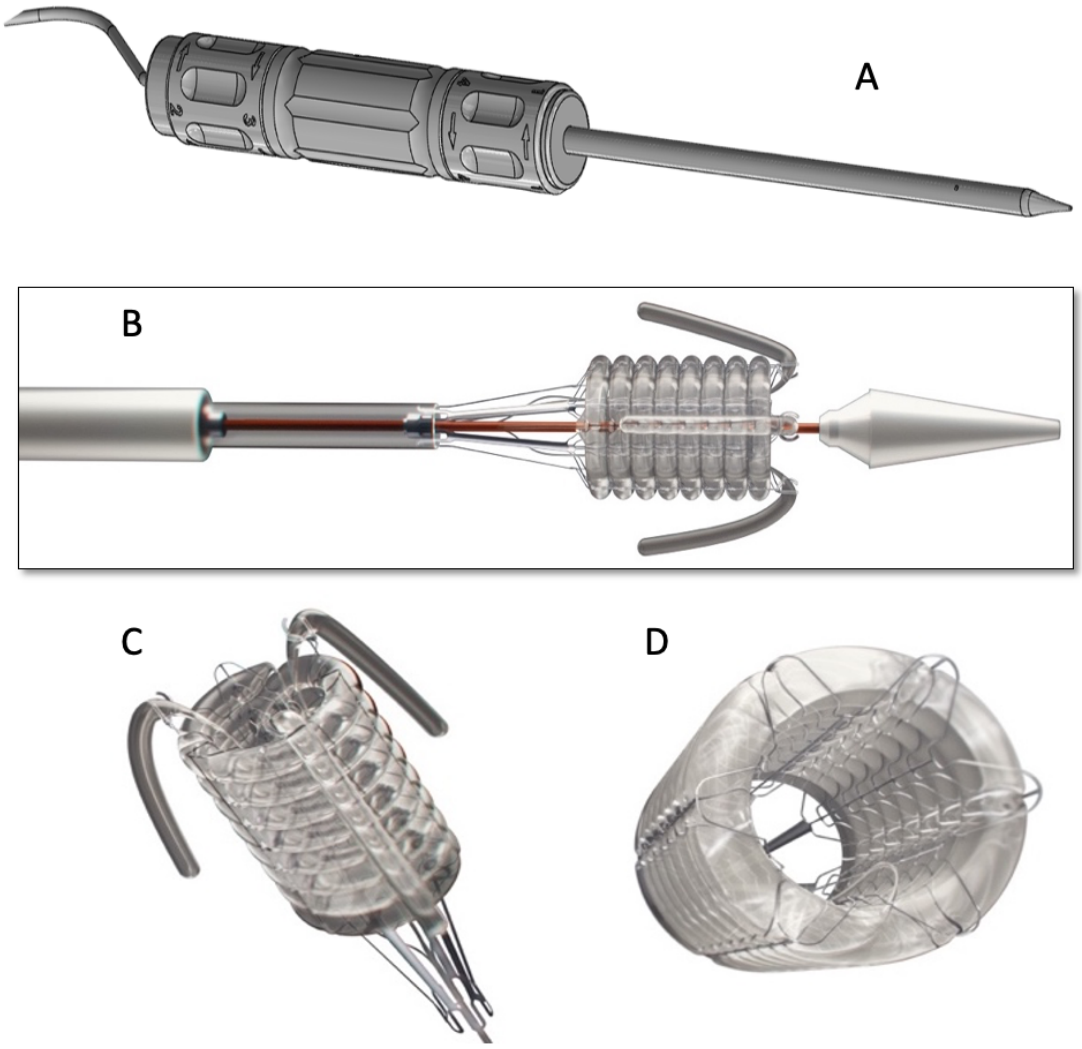
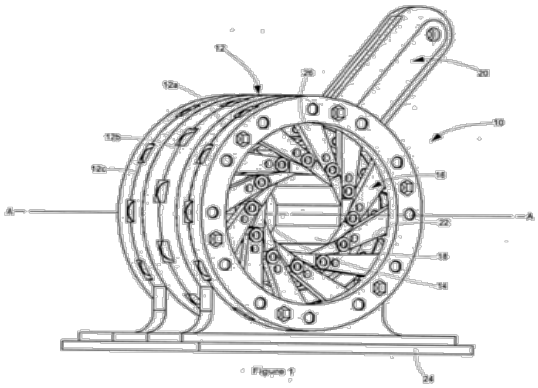


Figure 18. *rendering of A: complete device with inflation lines, activation handle, multilumen catheter assembly and tip (helical delivery balloon inside distal end of catheter). B. Details of distal end of device showing the delivery catheter with invaginating retrieval end, framed helical balloon, three location trunks and tip .C and D: Views of delivery balloon in which additional details of the frame and helical balloon, as well as the non-occlusivity of the device, is exemplified.*

- A catheter/retrieval assembly that connects the actuator handle with the expansion/location balloon assemblies, comprising a multilumen extrusion containing the required channels for a guidewire and inflation/deflation lines for the balloons. The

distal end of the catheter assembly contains a bespoke delivery/retrieval section that also works on the invagination principle. In this case the sheath invaginates in itself while loading the crimped valve/balloon assembly and when the delivery balloon is retrieved after valve deployment. This mechanism prevents relative motion and shear forces during loading, advancement and retrieval.



1.C. CRIMPING DEVICE

A bespoke crimping device, developed for this application, was supplied with the valves and delivery devices. The device works on the iris principle with proprietary mechanisms (Fig 19 shows some of the component details from which its basic action and function can be derived). The device is supplied together with sizing mandrels and stoppers to control and limit the extent of the pre and main crimping of the helical balloon and valve assemblies.

Figure 19*. Detailed drawing of the SAT device used for crimping transcatheter valves onto delivery balloons*

1.D. BASIC OPERATION

A concise description of the steps involved in the valve preparation and implant procedure is given as an overview to supplement the more detailed descriptions in the chapters dealing with the pre-clinical studies:

Preparation of the device

i) de-airing and priming the retrieval, helical balloon and location trunk balloons
ii) retracting the trunks
iii) pre-crimping the helical balloon assembly using the crimper and stopper
iv) pre-crimping the valve onto the balloon in stages to the final diameter using the bespoke crimper in conjunction with the supplied mandrel
v) Rinsing and de-airing the guidewire lumen
vi) Crimping the valve onto the helical balloon
vii) Retracting the valve/balloon into the retrieval balloon section of the delivery catheter

Implantation of the valve

i) Inserting a transfemoral pigtail catheter into the aortic cusp
ii) Preparing transapical access
iii) Inserting a guidewire through the delivery device assembly
iv) Inserting the device through the apex into the ascending aorta
v) Exposing the valve/balloon assembly by actuation of the handle
vi) Injecting contrast medium for orientation under fluoroscopy
vii) Aligning the delivery device with the native cusps
viii) Extending the location trunks by combination of handle activation and inflation
ix) Using tactile feedback to locate/anchor the trunks in the native cusps
x) Injecting contrast to verify positioning (axial and rotational)

xi) Retracting the pigtail catheter into the ascending aorta
xii) Inflating the helical balloon to expand the replacement valve
xiii) Retracting the location trunks by invagination through handle activation combined with pressure decrease
xiv) Deflating the helical balloon
xv) Re-sheathing the collapsed helical balloon into the invaginating retrieval end of the delivery device
xvi) Removing the delivery device and closing the purse-string suture.

***Figure 20**: Rendition of the delivery end of the assembly showing invaginating retriever (bottom left), Nitinol balloon frame containing inflated helical balloon, the expanded transcatheter valve, the three inflated location trunks, and the distal tip.*

Video animations showing the basic functions of the valve, helical balloon expansion, location trunks and retrieval systems can be found at: http://www.straitaccesstechnologies.com/tavi-system/ and http://www.straitaccesstechnologies.com/retrieval-sheath/

CHAPTER 6

DEVELOPMENT OF A LARGE ANIMAL MODEL TO EVALUATE THE FEASIBILITY OF TAVIs IN COMPLIANT AORTIC ROOTS

Over the past 20 years animal models have slowly evolved for conventional TAVIs. Without stent features that can anchor the valve most of the contemporary TAVIs rely on the calcium deposits of degenerative, stenotic aortic valves to prevent dislocation. In the absence of such mineralisation-deposits the radial expansion force and lack of anchorage features of the majority of contemporary TAVIs is insufficient to avoid embolization of the prosthesis. To emulate this clinical situation, animal models had slowly evolved over the past 20 years which provided a rigid bed for TAVI placement. To test trans-catheter valves that were designed for younger patients with compliant aortic roots, large animal models did not exist and their development was part of my thesis. In view of the reliability of the SAT system evolving in parallel with my establishment of this animal model, a key challenge was to distinguish between failure due to anatomical peculiarities and failure due to design-immanent shortcomings.

In this chapter I present and discuss the results and conclusions of the animal studies which I conducted together with my interactions with the animal and human research ethics committees at the University of Cape Town which provided continuous feedback to the engineering side (UCT's SAT) and were used for getting permission for the next steps in the regulatory process.

1. OVERVIEW OF ANIMALS TRIALS CONDUCTED

During the 8 years of my involvement in the development of the SAT TAVI-System, eight (8) pre-clinical in-vivo large animal trials were conducted. The majority of these (7/8 trials) were performed at the animal facilities in the 'Cape Heart Centre' at the University of Cape Town, South Africa; and the remaining one at the 'Center for Biomedical Research' at the University of Vienna, Austria.

A total number of 178 large animal experiments/implants were performed in the pig (n=89) and sheep (n=89) models, which included both acute and chronic implants often done in parallel. All of the animal trials were approved by the relevant research and ethics committees. At the University of Cape Town this included the Department of Surgery Research Committee (SDRC) and the Faculty of Health Sciences Animal Ethics Committee (FHS AEC). The relevant AEC approval letters are attached in ***appendix 3.***

The 8 projects with main study objectives are listed below. I maintained the role of Principal Investigator and Surgeon throughout these animal trials.

UNIVERSITY OF CAPE TOWN

	FHS AEC Ref No:	Animal species, strain and gender	Number of animals
1.	013/021	Pigs, Landrace, female	12
2.	014/015	Pigs, Landrace, female	18
3.	015/008	Sheep, Dohne Merino, female	24
4.	016/009	Sheep, Dohne Merino, female	18
5.	016/015	Sheep, Dohne Merino, female	47
6.	017/017	Pigs, Landrace, female	4
7.	018/011	Pigs, Landrace, female	40

UNIVERSITY OF VIENNA

8.	Project 362174	Pigs, Mixed strain (x3), female	15

Figure 21*: Animal Facility at the Chris Barnard Division of Cardiothoracic Surgery: main Operating Room*

2. OVERVIEW OF PROJECT OBJECTIVES

2.A. PROJECTS 1-4: INITIAL RESEARCH AND DEVELOPMENT PHASE

(SAT-TAVI delivery device and TAVI valve)

- The in-vivo acute large animal studies (AEC Ref No: 013/021 and AEC Ref No: 014/015) were designed to evaluate the concept of non-occlusiveness of the delivery device and correct anatomical positioning within the aortic root during its use/deployment.
- The in-vivo acute large animal studies (AEC Ref No: 015/008 and AEC Ref No: 016/009) evaluated the procedural performance of the TAVI deployment system in an acute setting to demonstrate successful implantation of the new TAVI prosthesis in the sheep model.

2.B. PROJECT 5: EVALUATION OF LONG-TERM PERFORMANCE OF THE SAT-TAVI VALVE

(as per ISO 5840 valve specific standard)

- The in-vivo chronic large animal study (AEC Ref No: 016/015) evaluated the long-term performance (hemodynamic performance, calcification, structural and non-structural deterioration) of the SAT pericardial TAVIs in the sheep model. This pre-clinical study confirmed the longevity of the decellularized and specially crosslinked bioprosthetic pericardium and the ability of the valve stent to firmly anchor in non-calcified, compliant aortic roots. As this study represents the pre-clinical verification of a trans-apically inserted system, it was published in a high-impact journal, '*EuroIntervention*' and presented as *Chapter Nine* of this thesis.

2.C. PROJECTS 6-8: ESTABLISHING CLINICAL SAFETY AND EVALUATING ANATOMY-SPECIFIC SIZING REQUIREMENTS (EXCLUSION CRITERIA)

- The in-vivo acute large animal study (AEC Ref No: 017/017) was designed as a 'proctor-based' surgical technique training platform to familiarize and initiate the training of fellow cardiothoracic surgeons with the procedure we developed.
- The in-vivo acute large animal study (AEC Ref No: 018/011) and Project 362174 served to confirm pre-clinical safety and efficacy and to verify the anatomical exclusion criteria of the final TAVI deployment system and valve in the pig model.

  At the end of this final large series (n=59) of acute pig implants, size guidelines for animal implants and anatomical exclusion criteria have been established. As these exclusion criteria are also a prerequisite for being able to plan clinical trials while the dimensions of the animal trials can assist in the deduction of TAVI sizes expected in patients, the results of these final implants are presented in this *Chapter (Six)* providing the framework data for clinical planning.

3. THE BALANCE BETWEEN ESTABLISHING CLINICAL SAFETY VERSUS PREDICTING PRE-CLINICAL ANIMAL MORTALITY

Throughout the development of this novel TAVI system, an iterative approach was required where engineering design and testing were undertaken in tandem. Although extensive continual feed-back could be obtained on the basis of bench-top and ex-vivo testing, for example using isolated heart models, feedback within a contracting and ejecting heart against the background of a highly reactive circulatory physiology and anatomy required acute tests in large animal models. While none of the established animal models fully reflects the human situation, the most widely used models – the pig and the sheep – deviate least from the human

anatomy and circulatory physiology. However, the remaining significant deviations accounted for a notoriously high pre-clinical animal mortality in established TAVI valves: 31% for the Cribier-Edwards valve [331]; 27% for the Boston Scientific Lotus Valve [332] and 20% for the Jena Valve [333].

SAT's heart valve concept for low- to middle-income countries combines a delivery system that is tactile and does not require sophisticated infrastructure with a catheter-based replacement heart valve and which does not dislodge from the compliant, non-calcified aortic roots of the largely quadragenarian patients in need. The interdependence of these two devices (delivery device and TAVI valve) necessarily created an overlap in device failures during development. Furthermore, such failures of early devices also overlapped with animal mortality caused by model-immanent circumstances [331-333]. The major complicating factor was that no established animal model existed. While the sheep model has been the gold standard for surgically implanted heart valves for decades [334] and a 2-stage animal model for TAVIs destined for the typically heavily calcified aortic stenosis patients of North America and Europe was only introduced in 2019, no other heart valve prosthesis has ever needed to be tested in an animal model that has to emulate the unique situation of the millions of patients with rheumatic heart disease, living almost exclusively under the circumstances of low- to middle-income countries. The core quest for such an animal model was a compliant, non-stiffened aortic root – a diametrically different requirement to those conventional TAVIs which get implanted typically for degenerative calcific aortic valve stenosis in elderly patients.

Failures during the first 80% of the research and development work towards the SAT-TAVI system between 2012 and 2017 were dominated by the often-unreliable performance of certain device components which were still undergoing optimization of design and production. From 2016/2017 onwards, the devices became reliable, allowing the chronic long-term testing (internationally defined as 4-5 months sheep implants) of the SAT TAVIs. As our publication in the '*EuroIntervention*' journal (*Chapter Nine* of this thesis) showed, occasional sub-optimal function of the deployment device still led to some valves being deployed slightly too low, but the long-term function and durability of these valves in an FDA-recommended animal model was nevertheless outstanding.

Once the stage of device reliability was reached, it became possible to identify model-related deaths and define anatomical exclusion criteria.

4. ESTABLISHING ANIMAL MODEL-SPECIFIC ANATOMICAL PREDICTORS OF MORTALITY (EXCLUSION CRITERIA)

With more than 1.5 million implants worldwide [335], TAVIs have changed the paradigm in the treatment of aortic valve stenosis. The publication of the 'Partner 3' Trial in March 2019 [336] closed the last indication-gap and made it the preferred treatment for all risk classes for aortic valve replacement.

The principle of a TAVI is that a catheter-delivered, expanding, stent-mounted heart valve prosthesis is deployed which is largely seated supra-annularly but yet reaches into the left ventricular outflow tract, while allowing unobstructed inflow of blood into the coronary arteries. Two potential dangers of TAVI deployment are coronary artery obstruction, with potentially life-threatening myocardial infarction, and compression of the subvalvular electrical conduction system. The latter can potentially cause arrest in cases of total interruption of the electrical signals in the absence of a slow autochthon baseline heart rate. Without pacemaker implantation, this condition is also potentially life-threatening. Two additional complications that can occur during TAVI deployment relate to incorrect sizing or a sizing mismatch between

the TAVI prosthesis and the native aortic root. These include annular rupture (which could occur in cases with significant oversizing) and embolization of the TAVI prosthesis (in cases with a certain degree of under sizing).

To avoid these potential dangers accurate measurements of the aortic root dimensions are paramount. In clinical practice, cardiac CT and 3D transesophageal echocardiography have been shown to be the most accurate and reliable imaging modalities for this use. Neither of these modalities were routinely available for pre- or intraoperative use during our animal trials, which confronted us with the problem of determining the best possible way to measure the aortic root dimensions in animals. As such we evaluated the use of the following imaging modalities:

- Fluoroscopy
- Transthoracic 2D echocardiography
- Transoesophageal 2D echocardiography
- Intra-operative 2D epicardial echocardiography

In determining the most reliable and most reproducible option we validated these against the use of intra-operative 3D TOE, which was available during all the implants (n=15) that was performed at the 'Center for Biomedical Research' at the University of Vienna. It turned out that *intra-operative 2D epicardial echocardiography* proved to be the most consistent and most reproducible imaging modality when determining the aortic root dimensions in the large animal models.

4.A. CORONARY ARTERY OBSTRUCTION:

On the basis of >1.5million clinical implants over almost 20 years [(335)], there is a large body of evidence underpinning the anatomical guidelines for safe TAVI implantation in patients with aortic stenosis. As it can be expected that the danger of coronary obstruction is lower in the absence of large mineral deposits in patients with non-calcific aortic regurgitation, existing guidelines should safely cover this patient group, too. The situation is distinctly different in pigs and sheep with their known hyper-compliant roots and a very different anatomy of the sinuses of Valsalva, the supra-valvular aortic pouches which primarily determine the available inflow space for blood into the coronary arteries and the height and position of the coronary ostia themselves. A series of 59 acute pig implants allowed us to determine the anatomical characteristics associated with a statistically highly significant likelihood of coronary obstruction and death in pigs, particularly in those of a lower weight range. This was confirmed by a pig study attempting to optimize the animal models for pre-clinical trials [(337)] (Figure 22). We have therefore subsequently selected a more representative weight group of 60-70kg pigs that comes closer to the human situation.

The one exclusion criterion that was associated with coronary obstruction in pigs was a sinus portion of the aortic root that was too narrow. The cut-off ratio of aortic annulus to sinus of Valsalva (SOV) diameter from which onwards coronary occlusion increased significantly was > 0.82. In humans, this ratio is 0.66 (338) and in patients with aortic regurgitation (AR) even as low as 0.61 [(339)] (Figure 23 below). A further significant parameter associated with coronary obstruction was the annulus to ST-Junction (STJ) ratio, relating to both diameter and height. Apart from low coronaries, pig mortality was associated with a diastolic annulus to STJ ratio of ≥ 1.1. In healthy humans it is 0.77 [(338)] - 0.86 [(339)] with extremes of 0.69 [(340)] and 0.66 [(339)] in patients with AR (Figure 23).

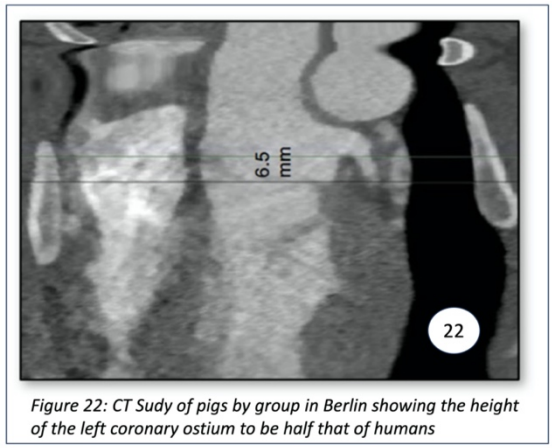


Figure 22: CT Sudy of pigs by group in Berlin showing the height of the left coronary ostium to be half that of humans

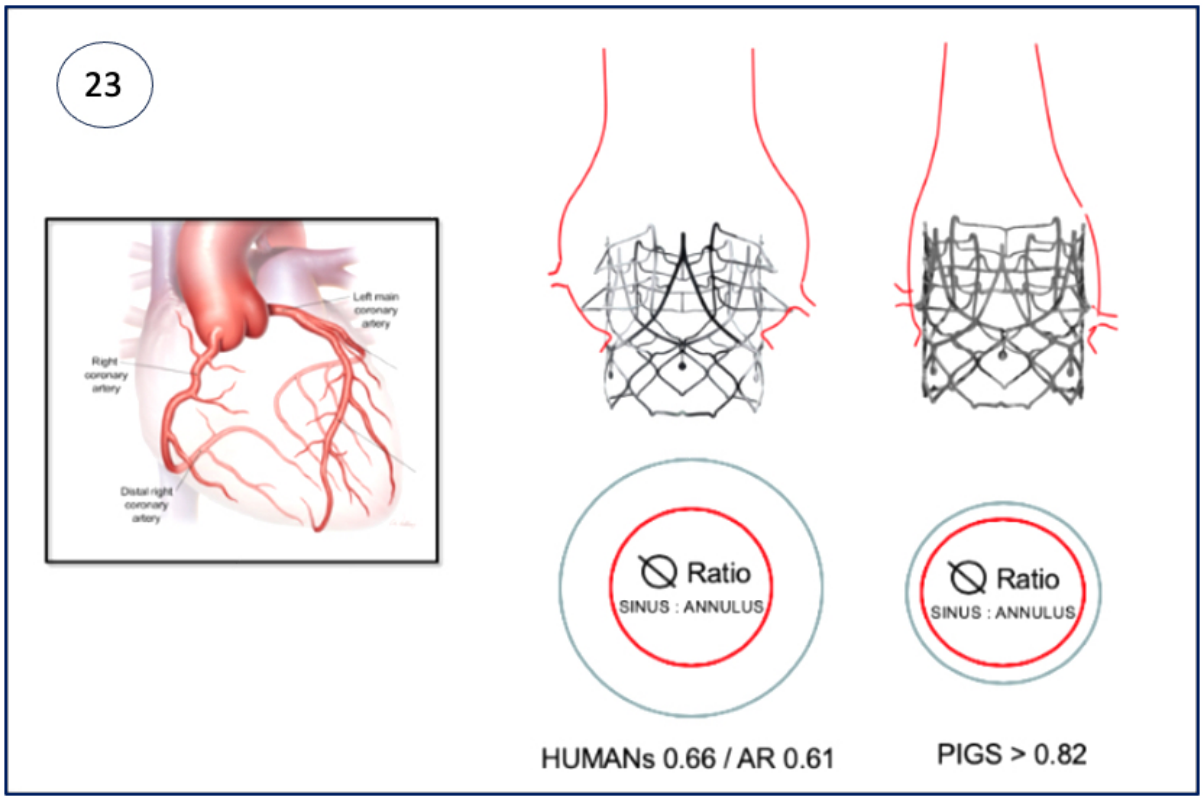


Figure 23: *Cut-off ratios of Aortic annulus to SOV diameters in humans and pigs that predicts coronary occlusion*

4.B. TOTAL HEART BLOCK

Although the difference in the rate for permanent pacemaker (PPM) implantations between balloon expandable and self-expanding TAVIs began to diminish in recent years [(341)], a relative superiority of balloon expandable TAVIs regarding conduction disturbances has continuously prevailed [(342, 343)] remaining as I write this in 2023 [(344)]. Given the unabated radial expansion force of the typically oversized self-expanding stents, it is intuitively logical that stents which are passively expanded by a balloon and would not exert continual radial expansion, pose less trauma to the adjacent conduction system. Amongst other considerations, this was one reason for us to choose a balloon expandable stent for the SAT-TAVI system. The absence of a single documented heart block in all chronic sheep and acute pig implants (n=59) and only one

unexplained late post-operative death (in a sheep on post-operative day 1) supports the assumption that self-limiting balloon expansion in compliant aortic roots together with a deliberately tailored stent profile may be protective towards the nearby conduction system. The known risk of conduction disorders and the need for a PPM through overexpansion of the left ventricular outflow tract (LVOT) by an oversized prosthesis, makes the optimal balance between anchorage in the absence of calcium and the need for a PPM an important target point at implantation [345, 346]. Furthermore, one of the most consistently reported predictors for the occurrence of new conduction disorders is depth of prosthesis implantation [341, 347]. The SAT-TAVI valve concept of supra-annular anchorage with a long, narrow waist accommodating the annular and immediate sub-annular region without excessive radial force has therefore been vindicated by the absence of post-implantation heart block.

4.C. SIZING MISMATCH – BALANCING THE RISK OF ANNULAR RUPTURE VERSUS EMBOLIZATION

Apart from the two potential dangers highlighted above, careful consideration towards size matching between a TAVI prosthesis and the native aortic root also needs to be applied to avoid the risk of annular rupture which could occur above a certain degree of over sizing, balanced against the risk of embolization which could occur below a certain amount of over sizing.

We have not observed any cases of aortic annular rupture during the acute pig implants whilst applying an average oversizing of 10.3 ± 7.9 % (range: -4.2% to 35.3%) to the annular diameter. To determine the 'most accurate' aortic annulus diameter we used intra-operative epicardial echocardiography to measure both the systolic and diastolic diameters and then used the average value of these as the 'best calculated' average aortic annulus diameter.

To the contrary we found that oversizing of ± 11.1% of the aortic annulus diameter (measured in diastole only) to the specified valve size was associated with the best protection against the risk of embolization. This is not an absolute cut-off value to be used as an exclusion criterium on its own, but should be interpreted in combination with the Annulus:SOV and the Annulus:STJ ratios as discussed above.

5. CONFIRMATION OF THE ANIMAL MODEL-SPECIFIC ANATOMICAL PREDICTORS OF MORTALITY

To see whether these criteria could be obtained independent of the local implant circumstances, a final safety and size verification study, which included 59 acute pig implants, was conducted in parallel in the world-class facilities of the "Center for Biomedical Research" at the University of Vienna and in the animal facilities in the University of Cape Town.

After completion of the first 18 of these final animal implants (Phase 1), an interim analysis was performed by Dr Paul Human (Pathobiology group leader, Cardiovascular Research Unit, University of Cape Town) to determine animal model-specific anatomical predictors of mortality (exclusion criteria) as highlighted in section 4 above. Phase 1 concluded with a mortality rate of 61% (6/18 related to embolization and 5/18 related to coronary occlusion). Retrospectively applied, all mortalities fell within the anatomical exclusion criteria. Phase 2, consisting of 41 consecutive pig implants, was performed with these known anatomical requirements in mind.

Although the framework conditions of the animal experiments only allow the assessment of anatomical dimensions on the operating table with the animal anaesthetised (and as such a post-factum rather than preventive response) larger animals with a lower incidence of exclusion criteria led to a significantly lower mortality rate. Excluding two deaths that were due to the surgical learning curve of new surgeons, the overall mortality during the final phase was 7.3% (n=3), far below that of the preclinical studies of currently approved TAVIs. Furthermore, all three these mortalities were predicted pre-operatively based on the anatomical exclusion criteria (*Table III below*).

Table III: Clinical outcomes of the final acute pig trials (AEC 017/017; AEC 018/011; Project 362174)

	Acute Pig trials AEC 017/017; AEC 018/011; Project 362174				
	Phase 1 Final Research and development		**Phase 2** **Verification of anatomical exclusion criteria**		
	n			**%**	
Number of Animals	18		**41**		2 mortalities were censored due to new surgeons placing the TAVIs incorrectly (as part of the learning curve).
Operative Mortality	11	61.1%	**3/41**	**7.3%**	(n=3): All three mortalities were predicted pre-operatively based on the anatomical exclusion criteria
Paravalvular Leaks (AR≥ 3+)	1	5.5%	**4/41**	**9.8%**	(n=2): as anatomical characteristics fell within exclusion criteria for coronary obstruction a smaller valve size was pre-emptively selected resulting in loose seat and some degree of proximal embolization with resultant AR (n=2): low implant height (valve placed in the intended position but on explant it was seated low). Most likely scenario: undersized for recipient
Migration of TAVIs	1	5.5%	**1/41**	**2.4%**	(n=1): TAVI migration due to significant septal hypertrophy resulting in partial distal embolization without coronary occlusion.

In the 'Phase 2' group using larger pigs, the ratio of annulus to sinus of Valsalva diameter was only in the borderline region of anatomical exclusion criteria (annulus to sinus ratio of 0.82 both for systolic and diastolic dimensions). The diastolic annulus to STJ ratio was just below exclusion dimensions (1.08 ± 0.13 diastolic and systolic 1.07 ± 0.12), and the average annulus oversizing (measured in diastole) was 10.6 ± 6.7%.

Applying these statistically evaluated anatomical exclusion criteria to the last 59 consecutive acute experiments, they would have predicted 100% of procedural deaths that was not related to a device failure or human (operator) error. The final analysis (by Dr Paul Human) allows us to arrive at the following anatomical predictors of mortality or failure (exclusion criteria) for the pig model.

6. EXCLUSION CRITERIA (PIG MODEL):

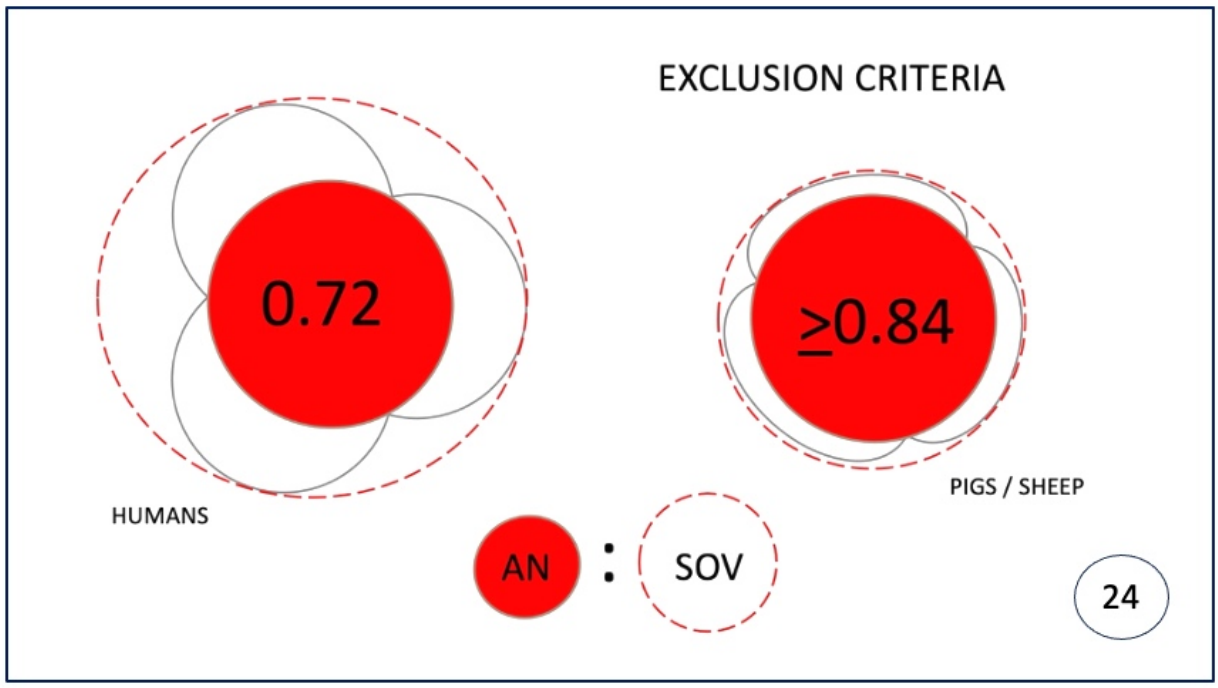


Figure 24: *Typically, the Sinus of Valsalvae turned out to be much narrower in Pigs and Sheep than in humans. As such, Annulus to Sinus ratios were larger than 0.84 compared to typical human ratios of 0.72 significantly narrowing coronary inflow at moderate degrees of oversizing.*

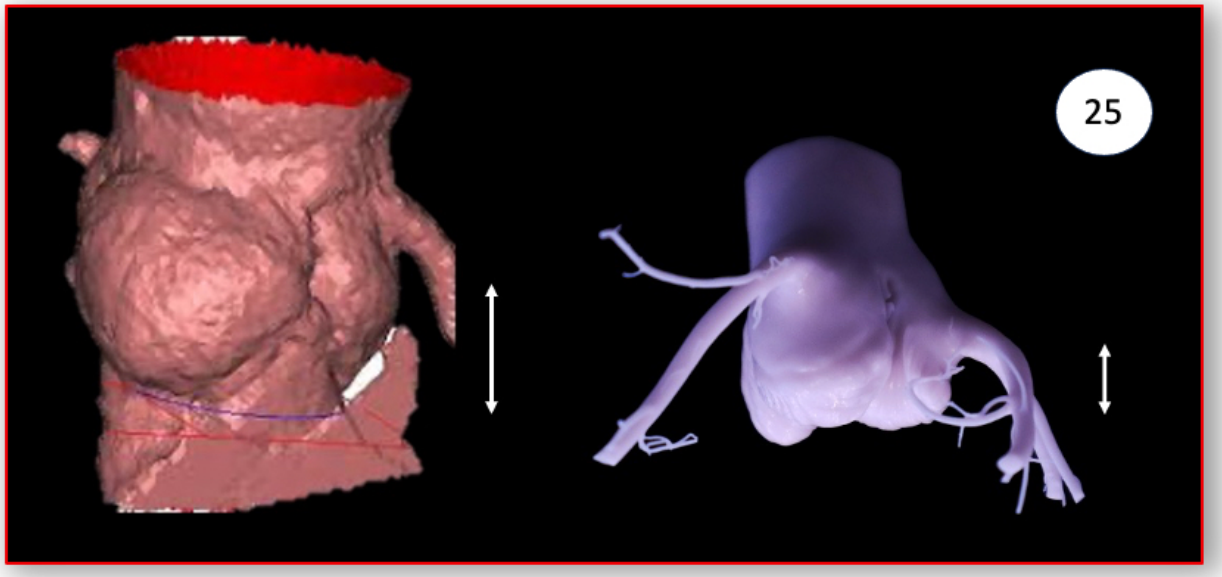


Figure 25: *3D reconstruction of human aortic root (left) versus solicon cast of a pig-root (comparable scale). Typically, coronary ostia of pigs are half as high above the nadir on leaflet insertion line and often rotated clockwise towards the commissure confirming pervious CT studies* [(337)].

6.A. PREDICTORS OF UNPLANNED MORTALITY

- Aortic Annulus Diameter:TAVI valve oversizing (%) [diastole, bottom of stent] ≤ 12.65%,
  AND
  Aortic Annulus Diameter:STJ Diameter (systole) [Echo] > 1.09
- Aortic Annulus Diameter:Sinus Diameter (diastole) [Echo] > 0.81

6.B. PREDICTORS OF CORONARY OBSTRUCTION

- Aortic Annulus Diameter:Sinus Diameter (systole) [Echo] > 0.83
- Coronary ostia height (above annulus) < 9mm

6.C. PREDICTORS OF EMBOLISATION

- Aortic Annulus Diameter:TAVI valve oversizing (%) [diastole] by specified valve size < 11.1%

(*Appendix 2* contains the statistical analysis of the retrospective data modelling that was performed to arrive at these exclusion criteria).

7. CONCLUDING REMARKS

- During the past decade of development of the SAT TAVI valve and deployment system, we successfully developed a large animal model for R&D purposes, acute verification as well as long-term TAVI valve performance testing.
- I came to the conclusion that the pig model is the most suitable large animal model for acute animal experiments and also has anatomical aortic root dimensions closer to that found in humans.
- As CT and 3D transoeophageal echocardiography are not always routinely available, the use of intra-operative 2D epicardial echocardiography could be considered as the next best alternative.
- Although we personally did not evaluate the use of the mini-pig model, it could potentially be considered as an alternative to the sheep model for long-term implants. The aortic root anatomy of sheep is even smaller and less forgiving than that of the pig model, which, because of its somatic growth, cannot be used for long-term implants.
- Having established certain animal-model specific predictors of mortality, we have concluded that exclusion criteria of an aortic annulus to STJ ratio of >1.1 and an annulus to SOV ratio of >0.82 will be part of the implant instructions for SAT TAVIs. In view of the different dimensions in humans (annulus to sinus ratio of 0.66 [(339)] and in patients with aortic regurgitation (AR) even as low as 0.62 [(340)]; and systolic annulus to STJ ratio of 0.77 [(339)] - 0.86 [(340)] with extremes of 0.69 [(341)] and 0.66 [(340)] in patients with AR), these exclusion criteria can be considered to be extremely stringent safety measures for clinical implants.

CHAPTER 7

ESTABLISHMENT OF THE SURGICAL TECHNIQUE WHEN USING THE UCT/SAT TRANSCATHETER SYSTEM.

Demonstration of the surgical technique developed for the implantation of the UCT-developed TAVI into a compliant, non-calcified root.

The pictures represent key moments of the implantation process highlighting the specific aspects of the tailor-made trans-catheter system. This surgical technique is being demonstrated in a 'how-to-do' publication in the internet-based educational tool of the European Journal of Cardio-Thoracic Surgery: 'Multimedia Manual of Cardiothoracic Surgery'

***Scherman J**, Van Breda B, Appa H, Van Heerden C, Ofoegbu C, Bezuidenhout D, Zilla P. Transcatheter Valve with Hollow-Balloon for Aortic valve Incompetence. Multimed Man Cardiothorac Surg. 2018, Feb 26.* doi: 10.1510/mmcts.2018.012.

1. THE CHALLENGE OF COMPLIANT ROOTS

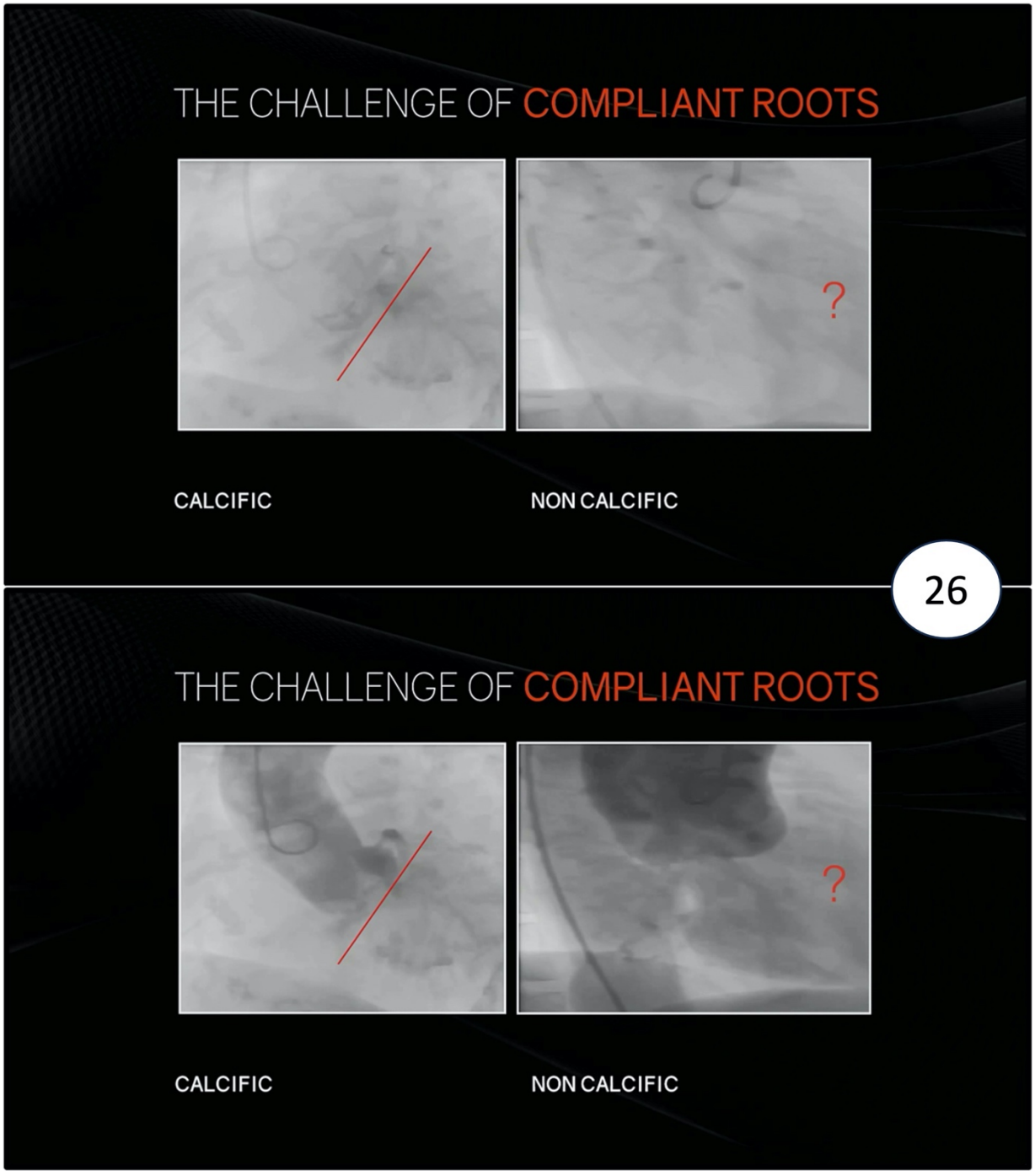


Figure 26: *The major differences between calcific degenerative and non-calcific aortic valve pathologies include the absence of a fluoroscopic footprint and the absence of calcium deposits. These presents challenges to position, place and anchor a TAVI device for non-calcific aortic valve insufficiency.*

2. PROCEDURAL SETUP

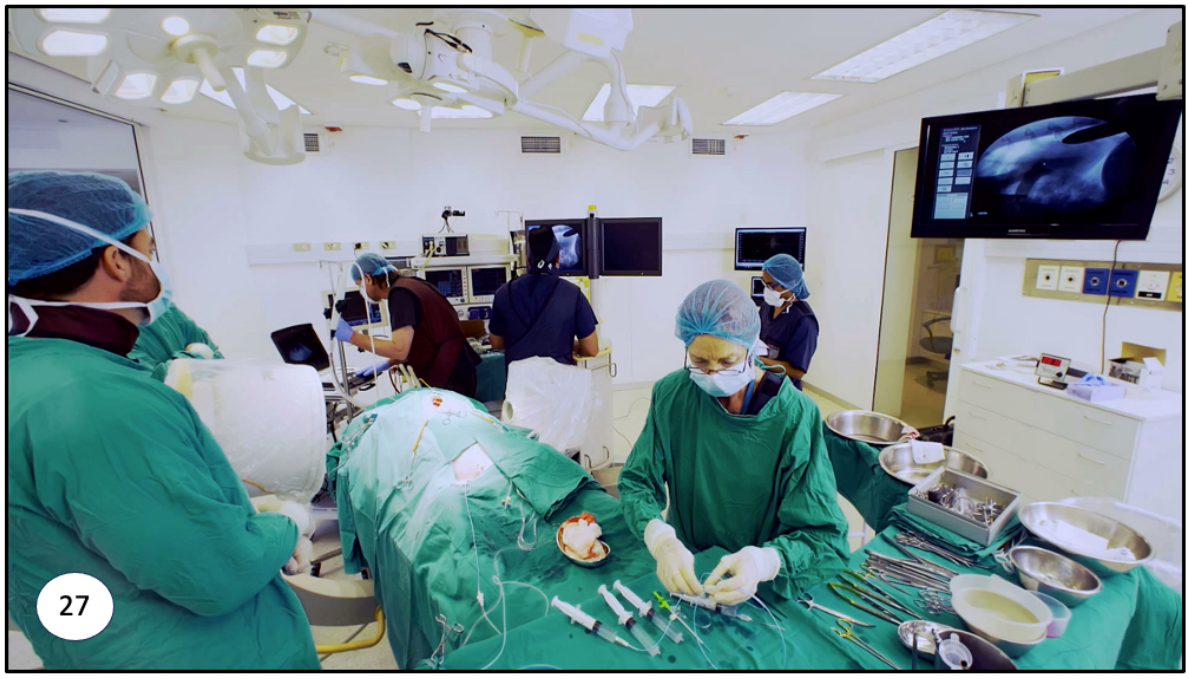


Figure 27: *Preparation and setup follow the standard for most transapical procedures, with the patient in a supine position and under general anaesthesia. Femoral arterial access is used to place diagnostic catheters and for blood pressure monitoring. In sheep, we routinely perform a subxiphoid incision to allow for easy access to the apex.*

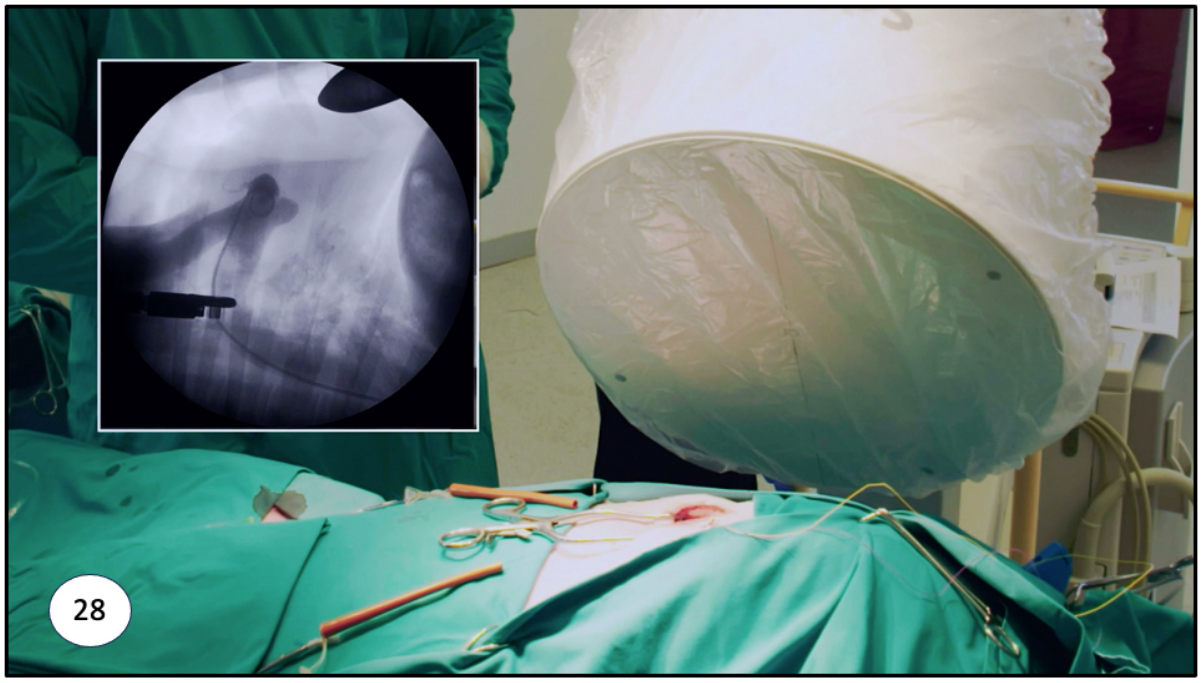


Figure 28: *The fluoroscopy is positioned in an almost lateral projection with some cranial or caudal tilt to align the aortic valve sinuses and also to have a long-axis view of the aortic root during implantation.*

2.A. APEX PUNCTURE

Figure 29: *Following the routine preparations, we proceed to puncture the apex and use a standard 6 Fr sheath and exchange catheters to position a working stiff wire through the apex into the descending aorta. Since we are dealing with non-calcific aortic valve disease, no pre-dilatation is required.*

2.B. DEVICE INSERTION

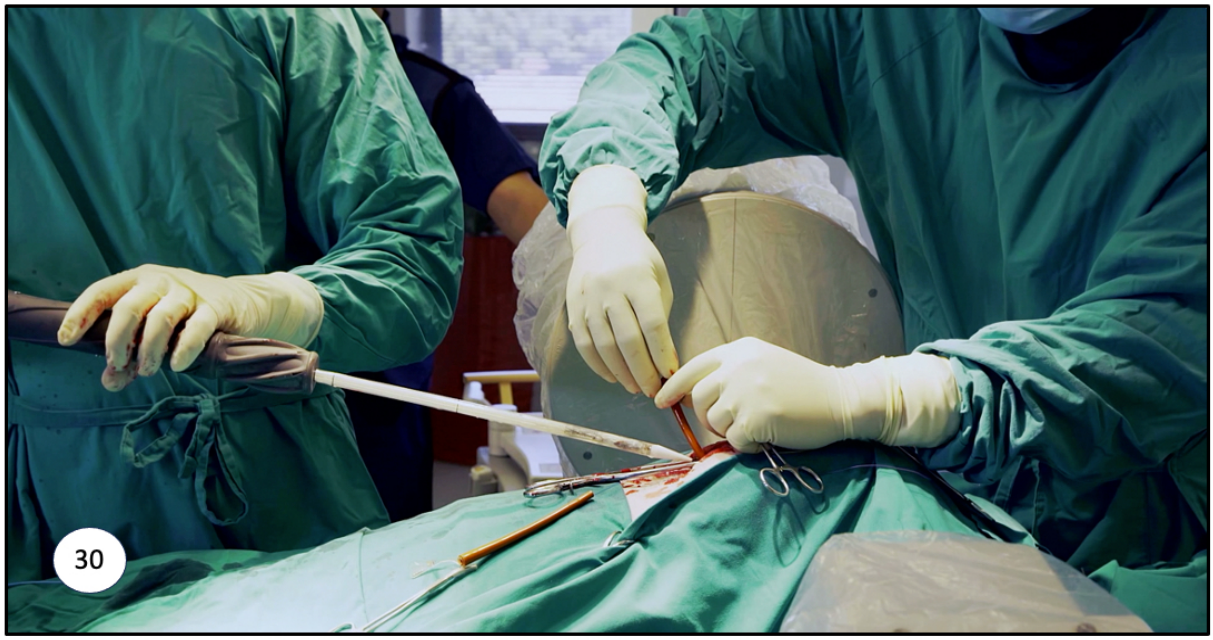


Figure 30: *Placement consists of 3 easy steps:*
1. Correct positioning, using the self-locating balloon trunks.
2. Valve implantation with the non-occlusive hollow balloon.
3. Retrieval of the system.

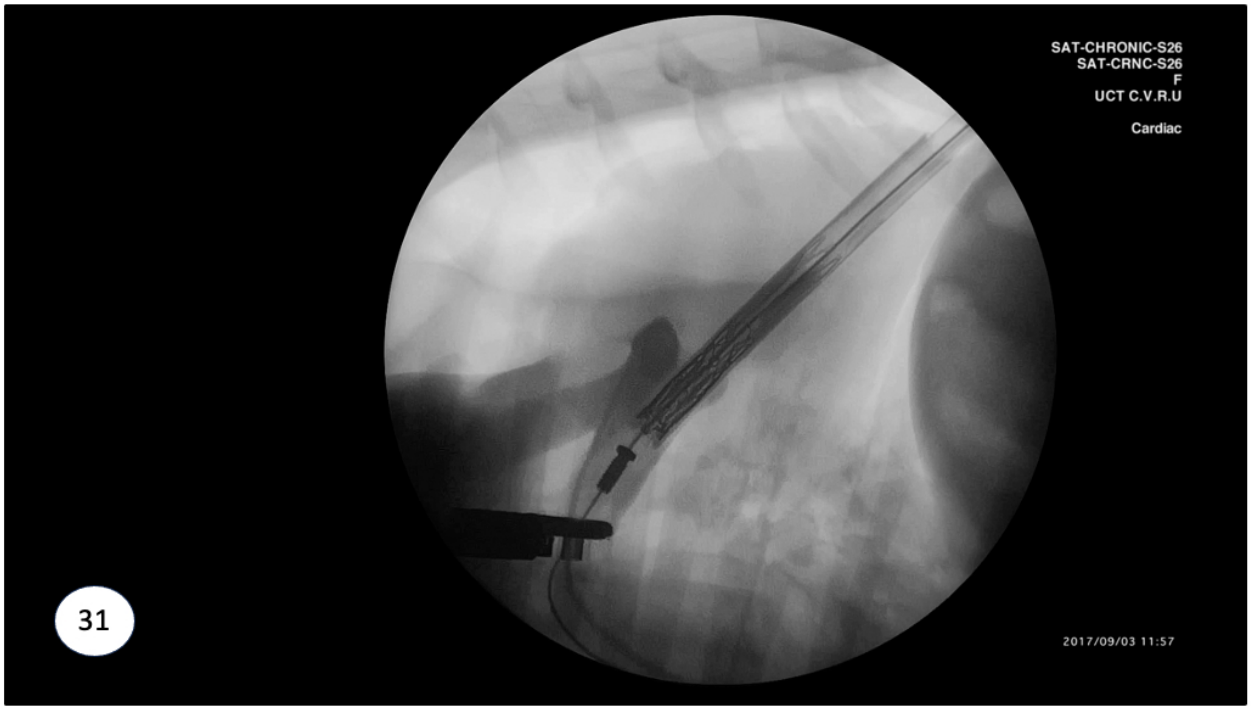


Figure 31: *We start off by advancing the TAVI system into the ascending aorta and, using a reference pigtail catheter, placing it into one of the aortic valve cusps. We then confirm the position of the device in the ascending aorta by doing an aortic root injection.*

2.C. POSITIONING USING SELF-LOCATING TRUNKS

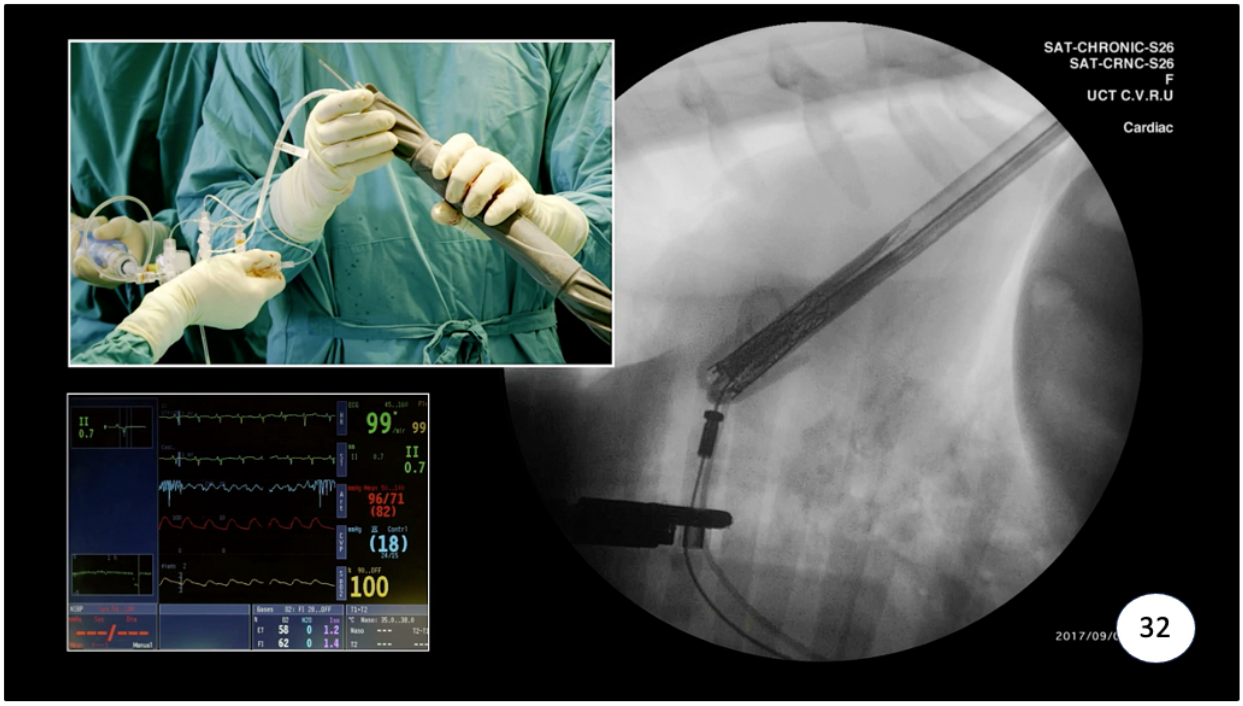
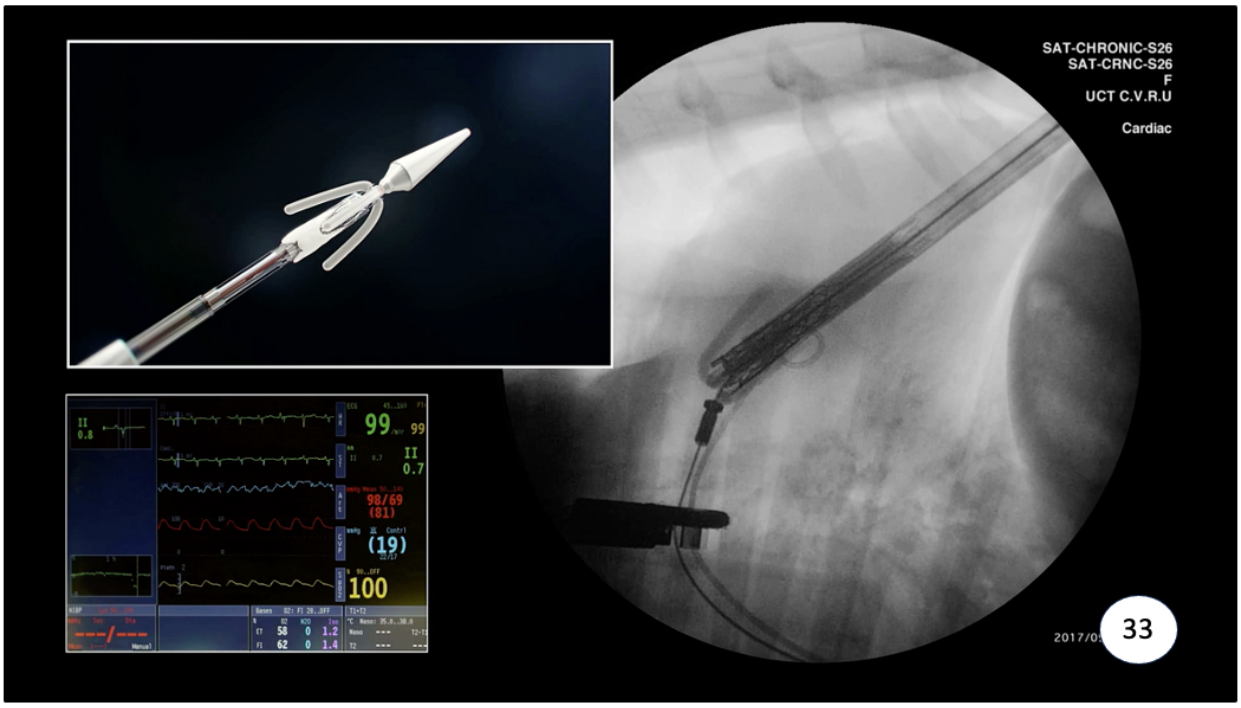


Figure 32 & 33: *The self-locating balloon trunks are now exposed, and this step is followed by inflation or - as we refer to it - the 'growing' of the balloon trunks. Once fully grown gentle traction is applied until tactile feedback confirms engagement of the balloon trunks in the aortic valve sinuses.*



2.D. CONFIRMATION OF POSITION

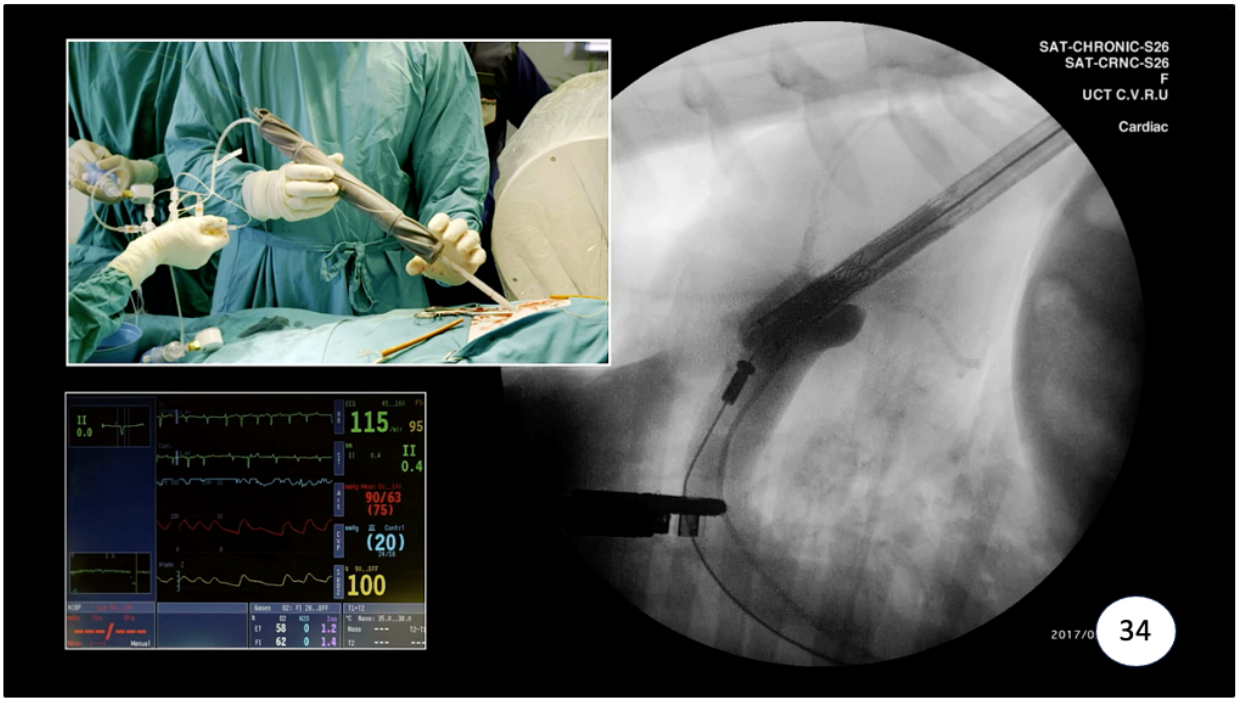


Figure 34: *Once the location is secured, the correct position is confirmed with another root injection. We now fully expose the helical balloon and the TAVI valve by completely unsheathing the TAVI system. Once done, a final root injection again confirms position, if necessary, and the pigtail catheter can now be removed. The correct position can be maintained by gentle traction on the device, which continuously provides tactile feedback.*

2.E. TAVI IMPLANTATION WITH THE NON-OCCLUSIVE HELICAL BALLOON

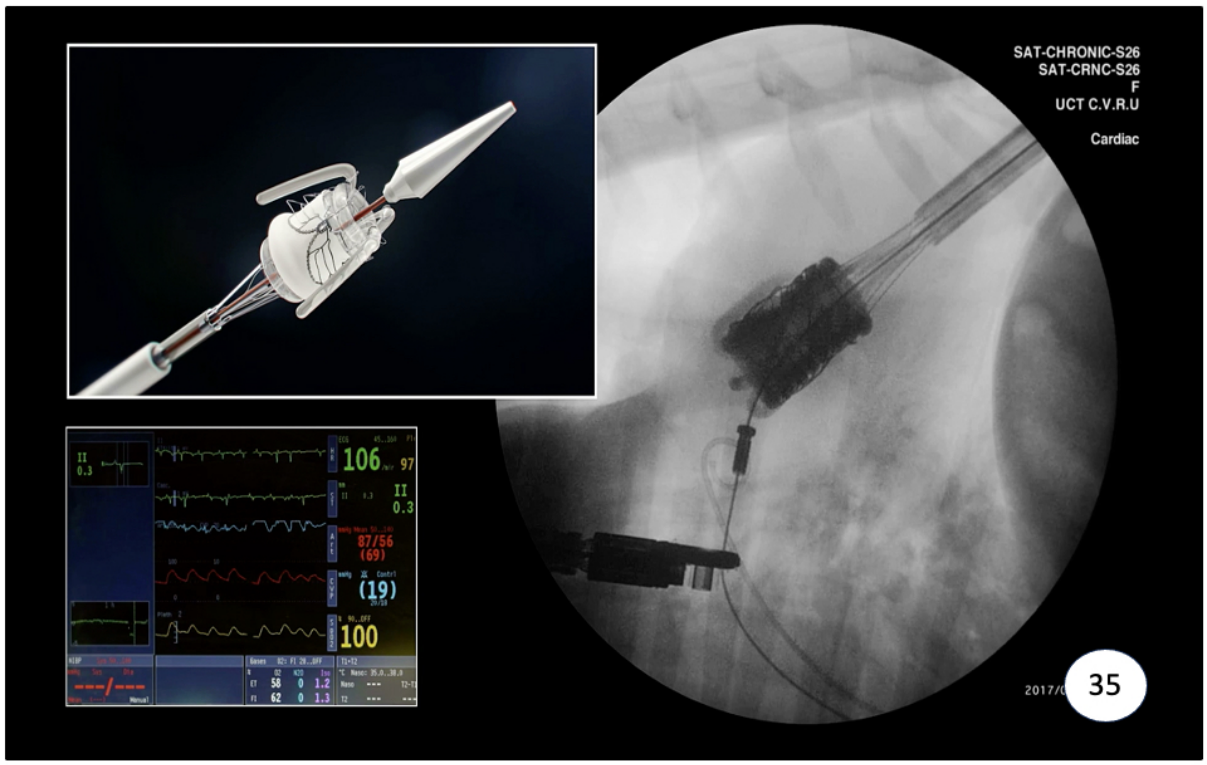


Figure 35: *The next step is to implant the new valve. Please note that we do not need rapid ventricular pacing, and also that cardiac output is maintained through expansion of the hollow balloon.*

2.F. RETRIEVAL OF THE SYSTEM

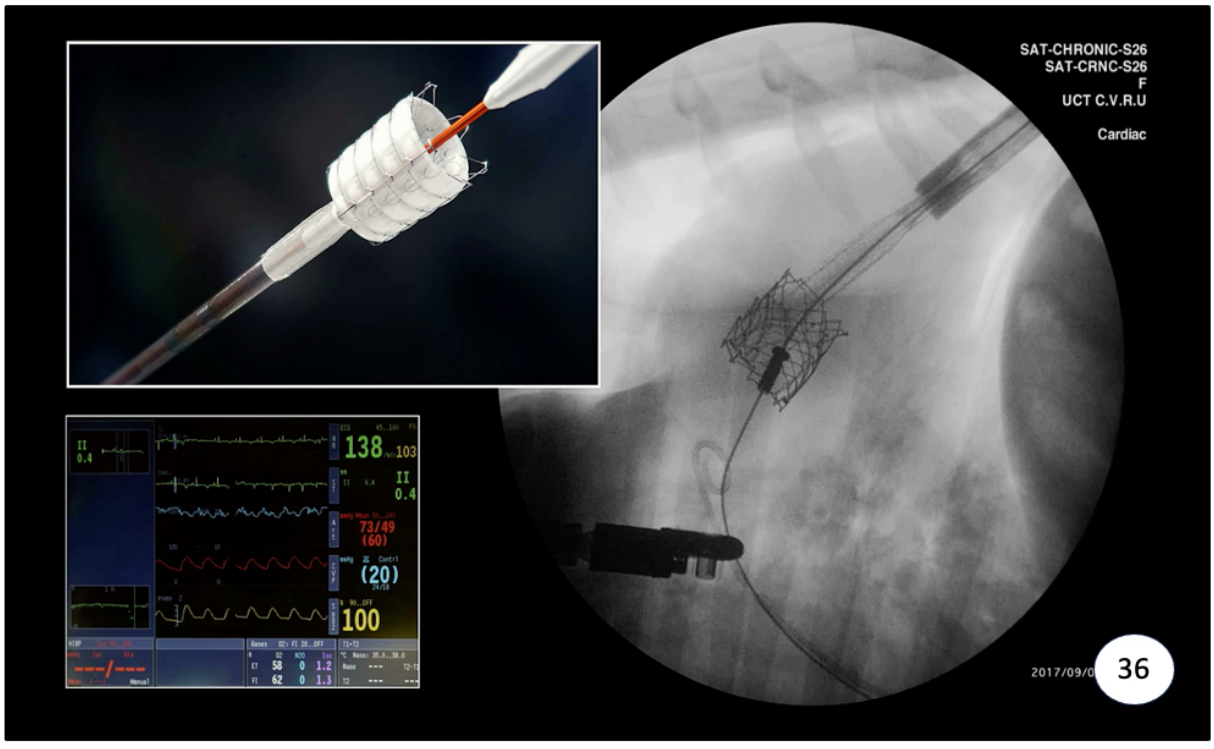
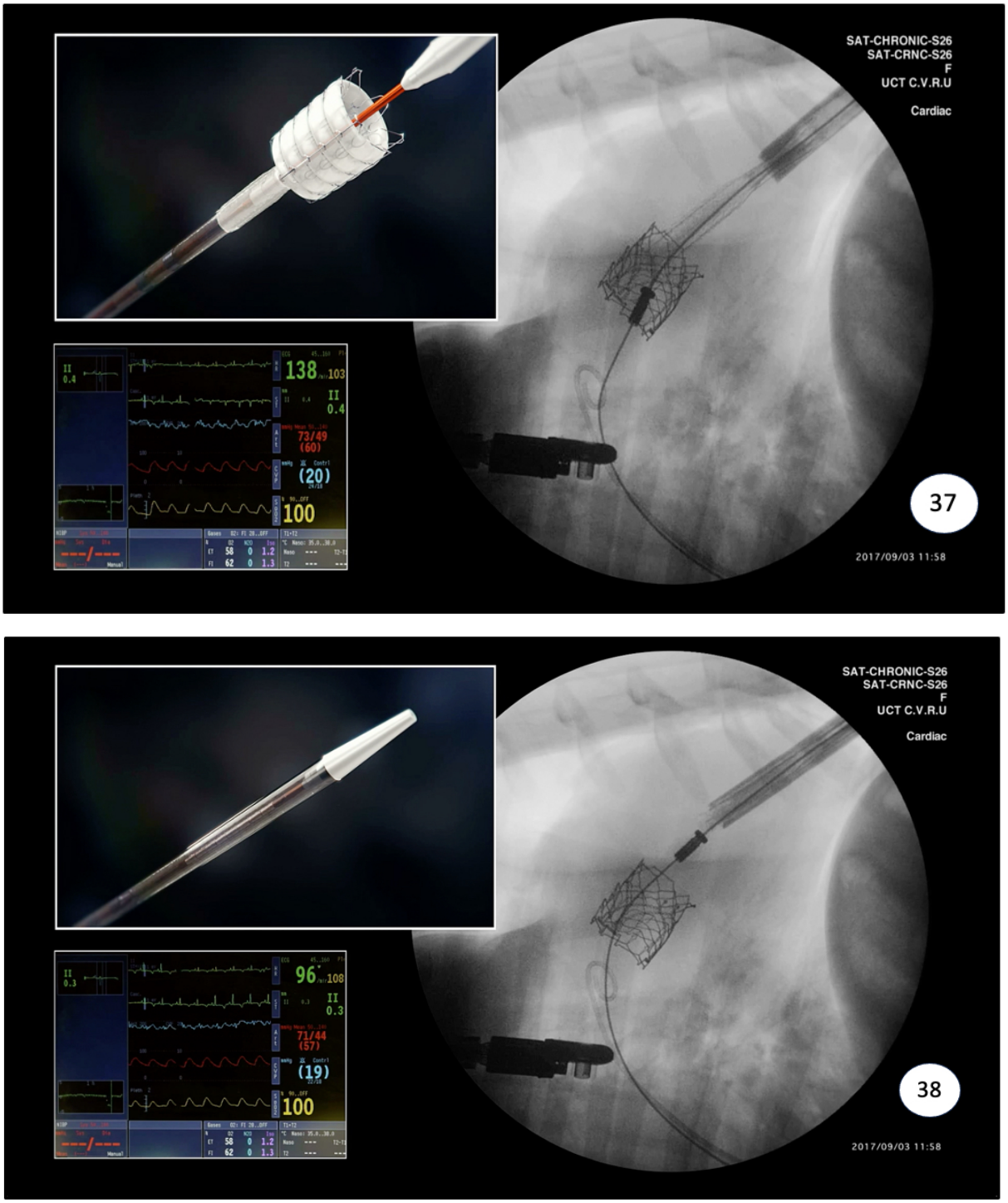
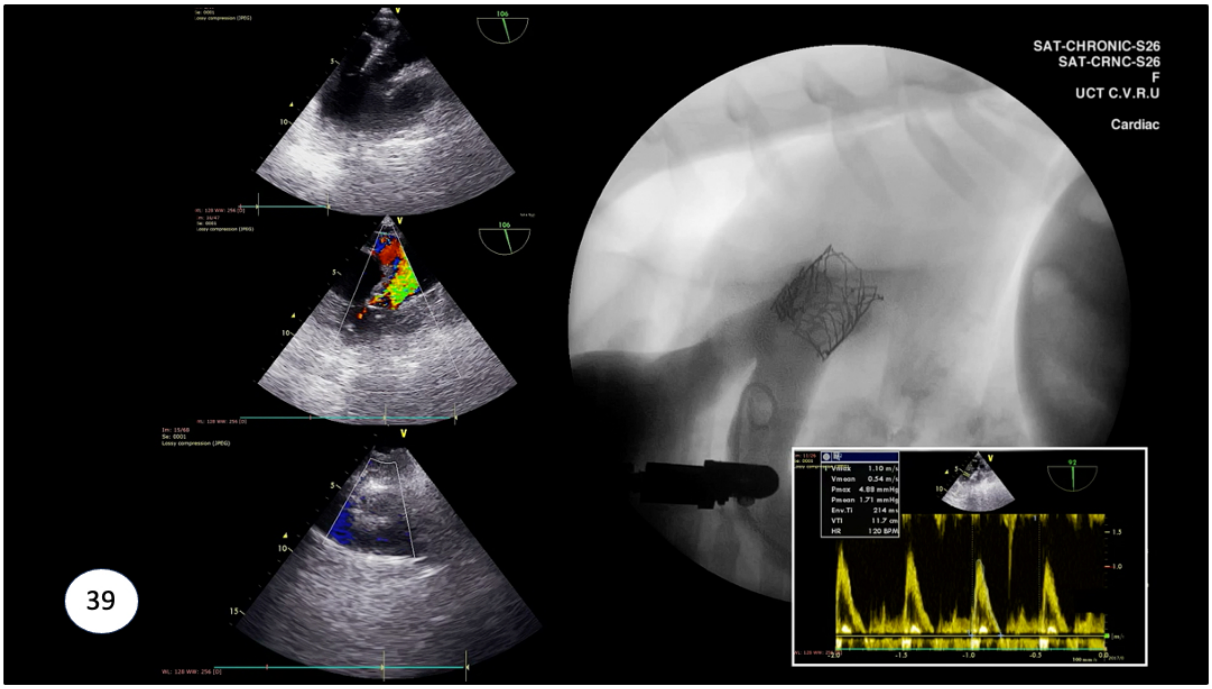


Figure 36-38: *The retrieval component consists of a pressurized rolling sheath that invaginates the entire hollow balloon before removal.*



2.G. FINAL EVALUATION

Figure 39 (next page): *Finally, we evaluate the function of the prosthesis. The aortic root injection shows optimal positioning and demonstrates that there is no paravalvular leak. This is also confirmed on echocardiography. As is typical with TAVI, there is virtually no gradient over the new prosthesis.*

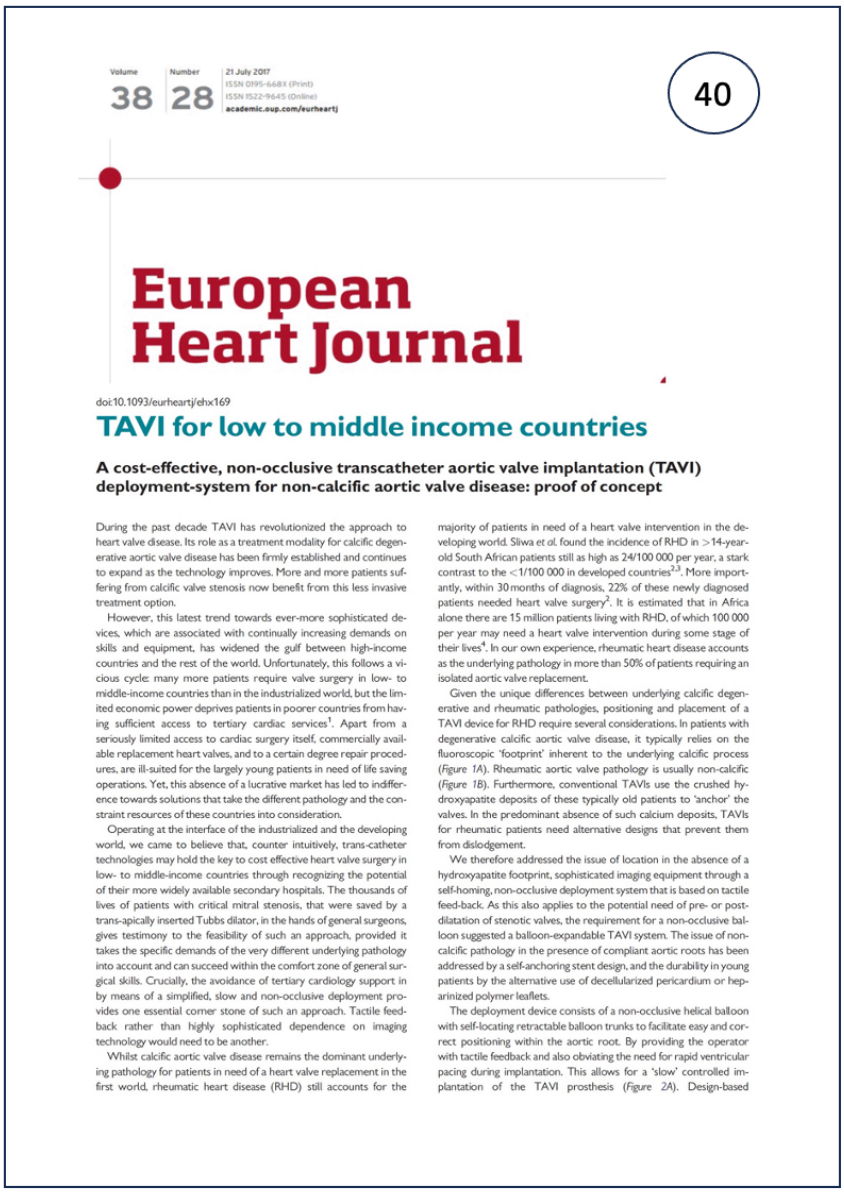

SAT-CHRONIC-S26
SAT-CRNC-S26
F
UCT C.V.R.U
Cardiac
39

CHAPTER 8

VERIFICATION OF POLYMERIC TAVI DEPLOYMENT IN AN ACUTE LARGE-ANIMAL

For the verification of the transcatheter system using a polymer valve version of the SAT TAVI system in acute implants I demonstrate the successful, completely non-occlusive, self-homing placement of this balloon expandable TAVI in pigs.

This acute verification was published in the top-ranked European Journal in the field with an impact factor of 36: 'European Heart Journal'.



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TAVI for low to middle income countries

A cost-effective, non-occlusive transcatheter aortic valve implantation (TAVI) deployment-system for non-calcific aortic valve disease: proof of concept

During the past decade TAVI has revolutionized the approach to heart valve disease. Its role as a treatment modality for calcific degenerative aortic valve disease has been firmly established and continues to expand as the technology improves. More and more patients suffering from calcific valve stenosis now benefit from this less invasive treatment option.

However, this latest trend towards ever-more sophisticated devices, which are associated with continually increasing demands on skills and equipment, has widened the gulf between high-income countries and the rest of the world. Unfortunately, this follows a vicious cycle: many more patients require valve surgery in low- to middle-income countries than in the industrialized world, but the limited economic power deprives patients in poorer countries from having sufficient access to tertiary cardiac services[1]. Apart from a seriously limited access to cardiac surgery itself, commercially available replacement heart valves, and to a certain degree repair procedures, are ill-suited for the largely young patients in need of life saving operations. Yet, this absence of a lucrative market has led to indifference towards solutions that take the different pathology and the constraint resources of these countries into consideration.

Operating at the interface of the industrialized and the developing world, we came to believe that, counter intuitively, trans-catheter technologies may hold the key to cost effective heart valve surgery in low- to middle-income countries through recognizing the potential of their more widely available secondary hospitals. The thousands of lives of patients with critical mitral stenosis, that were saved by a trans-apically inserted Tubbs dilator, in the hands of general surgeons, gives testimony to the feasibility of such an approach, provided it takes the specific demands of the very different underlying pathology into account and can succeed within the comfort zone of general surgical skills. Crucially, the avoidance of tertiary cardiology support in by means of a simplified, slow and non-occlusive deployment provides one essential corner stone of such an approach. Tactile feedback rather than highly sophisticated dependence on imaging technology would need to be another.

Whilst calcific aortic valve disease remains the dominant underlying pathology for patients in need of a heart valve replacement in the first world, rheumatic heart disease (RHD) still accounts for the majority of patients in need of a heart valve intervention in the developing world. Sliwa *et al.* found the incidence of RHD in >14-year-old South African patients still as high as 24/100 000 per year, a stark contrast to the <1/100 000 in developed countries[2,3]. More importantly, within 30 months of diagnosis, 22% of these newly diagnosed patients needed heart valve surgery[2]. It is estimated that in Africa alone there are 15 million patients living with RHD, of which 100 000 per year may need a heart valve intervention during some stage of their lives[4]. In our own experience, rheumatic heart disease accounts as the underlying pathology in more than 50% of patients requiring an isolated aortic valve replacement.

Given the unique differences between underlying calcific degenerative and rheumatic pathologies, positioning and placement of a TAVI device for RHD require several considerations. In patients with degenerative calcific aortic valve disease, it typically relies on the fluoroscopic 'footprint' inherent to the underlying calcific process (*Figure 1A*). Rheumatic aortic valve pathology is usually non-calcific (*Figure 1B*). Furthermore, conventional TAVIs use the crushed hydroxyapatite deposits of these typically old patients to 'anchor' the valves. In the predominant absence of such calcium deposits, TAVIs for rheumatic patients need alternative designs that prevent them from dislodgement.

We therefore addressed the issue of location in the absence of a hydroxyapatite footprint, sophisticated imaging equipment through a self-homing, non-occlusive deployment system that is based on tactile feed-back. As this also applies to the potential need of pre- or post-dilatation of stenotic valves, the requirement for a non-occlusive balloon suggested a balloon-expandable TAVI system. The issue of non-calcific pathology in the presence of compliant aortic roots has been addressed by a self-anchoring stent design, and the durability in young patients by the alternative use of decellularized pericardium or heparinized polymer leaflets.

The deployment device consists of a non-occlusive helical balloon with self-locating retractable balloon trunks to facilitate easy and correct positioning within the aortic root. By providing the operator with tactile feedback and also obviating the need for rapid ventricular pacing during implantation. This allows for a 'slow' controlled implantation of the TAVI prosthesis (*Figure 2A*). Design-based

Figure 40: ***<u>Scherman J</u>****, Bezuidenhout D, Ofoegbu C, Williams DF, Zilla P. TAVI for low to middle income countries. Eur Heart J. 2017; 38(16): 1182-1184.*

During the past decade TAVI has revolutionized the approach to heart valve disease. Its role as a treatment modality for calcific degenerative aortic valve disease has been firmly established and continues to expand as the technology improves. More and more patients suffering from calcific valve stenosis now benefit from this less invasive treatment option. However, this latest trend towards ever-more sophisticated devices, which are associated with continually increasing demands on skills and equipment, has widened the gulf between high-income countries and the rest of the world. Unfortunately, this follows a vicious cycle: many more patients require valve surgery in low- to middle-income countries than in the industrialized world, but the limited economic power deprives patients in poorer countries from having sufficient access to tertiary cardiac services [(348)]. Apart from a seriously limited access to cardiac surgery itself, commercially available replacement heart valves, and to a certain degree repair procedures, are ill-suited for the largely young patients in need of life saving operations. Yet, this absence of a lucrative market has led to indifference towards solutions that take the different pathology and the constraint resources of these countries into consideration.

Operating at the interface of the industrialized and the developing world, we came to believe that, counter intuitively, trans-catheter technologies may hold the key to cost effective heart valve surgery in low- to middle-income countries through recognizing the potential of their more widely available secondary hospitals. The thousands of lives of patients with critical mitral stenosis, that were saved by a trans-apically inserted Tubbs dilator, in the hands of general surgeons, gives testimony to the feasibility of such an approach, provided it takes the specific demands of the very different underlying pathology into account and can succeed within the comfort zone of general surgical skills. Crucially, the avoidance of tertiary cardiology support in by means of a simplified, slow and non-occlusive deployment provides one essential corner stone of such an approach. Tactile feedback rather than highly sophisticated dependence on imaging technology would need to be another.

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Furthermore, conventional TAVIs use the crushed hydroxyapatite deposits of these typically old patients to ‘anchor’ the valves. In the predominant absence of such calcium deposits, TAVIs for rheumatic patients need alternative designs that prevent them from dislodgement. We therefore addressed the issue of location in the absence of a hydroxyapatite footprint, sophisticated imaging equipment through a self-homing, non-occlusive deployment system that is based on tactile feed-back. As this also applies to the potential need of pre- or post-dilatation of stenotic valves, the requirement for a non-occlusive balloon suggested a balloon-expandable TAVI system. The issue of non-calcific pathology in the presence of

compliant aortic roots has been addressed by a self-anchoring stent design, and the durability in young patients by the alternative use of decellularized pericardium or heparinized polymer leaflets. The deployment device consists of a non-occlusive helical balloon with self-locating retractable balloon trunks to facilitate easy and correct p pacing during implantation. This allows for a 'slow' controlled implantation of the TAVI prosthesis (Figure 42A). Design-based anchorage arms that elevate through the expansion process secure the position of the prosthesis on the native aortic valve leaflets whilst a sealing skirt (positioned at annular level) eliminates any potential paravalvular regurgitation (Figure 42B).

The proof of this concept was successfully demonstrated in benchtop tests using an ex vivo heart model followed by pre-clinical acute animal studies. Both the pericardial and the polymeric version of the TAVI are nearing half a billion cycles in the fatigue tester. Final deployment tests of the polymeric TAVI prosthesis were performed in vivo using trans-apical access in the sheep model with successful location and implantation achieved in 7/9 animals (77.8%). The average deployment time (measured from balloon expansion to balloon collapse) was 54.6±11.5 seconds. Physiological pressures were maintained throughout the implantation of the non-occlusive balloon expandable TAVI prosthesis without the need for rapid ventricular pacing (Figure 43). Correspondingly, the mean gradients during the entire deployment time were 19.4±9.3mmHg, with peak gradients of 32.0±6.5mmHg. On transoesophageal echo, the mean annulus size of the compliant aortic roots was measured to be 20.3±2.1mm. Oversizing of 18.7±8.7% was applied in order to assure a firm, non-leaking TAVI seat.

With further optimizations of the deployment system and the stent design since the acute tests, and chronic implant studies having now commenced, we have successfully concluded the proof-of concept phase for a transcatheter system that could eventually offer hope for the millions of patients with rheumatic heart disease who have no access to cardiac surgery.

FIGURES

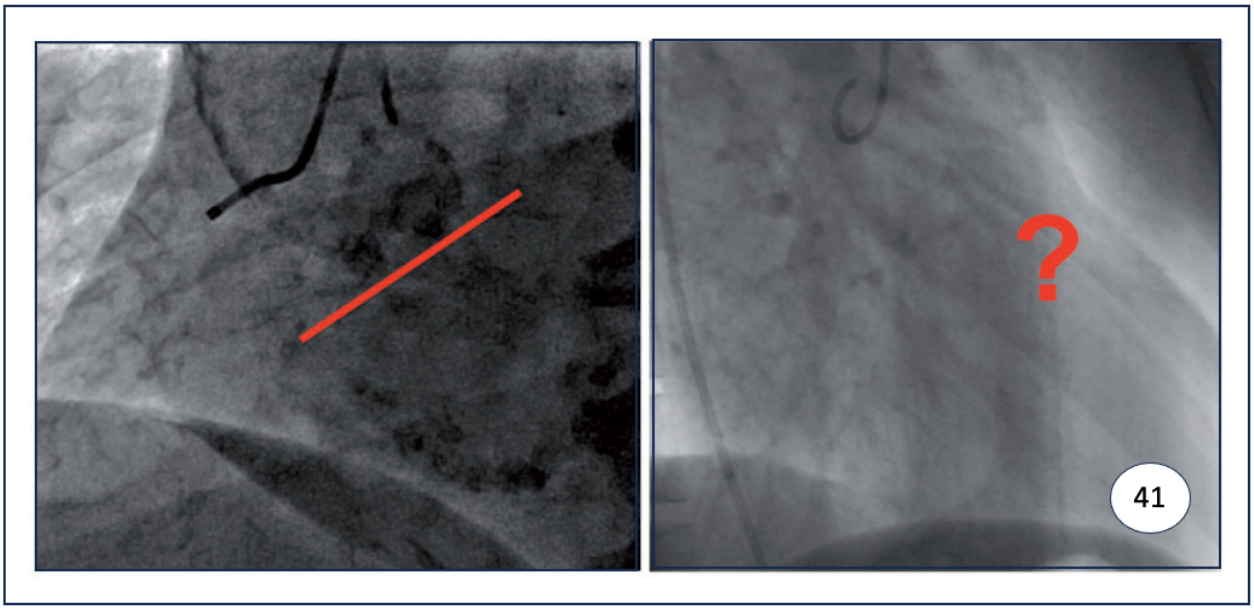


Figure 41: *(A) Calcific aortic valve disease. Placement of a transcatheter aortic valve implantation (TAVI) prosthesis typically relies on the fluoroscopic landmarks inherent to the underlying disease. (B) Non-calcific ('compliant') aortic valve disease. Absence of fluoroscopic landmarks requires alternative solutions for optimal positioning of a TAVI prosthesis.*

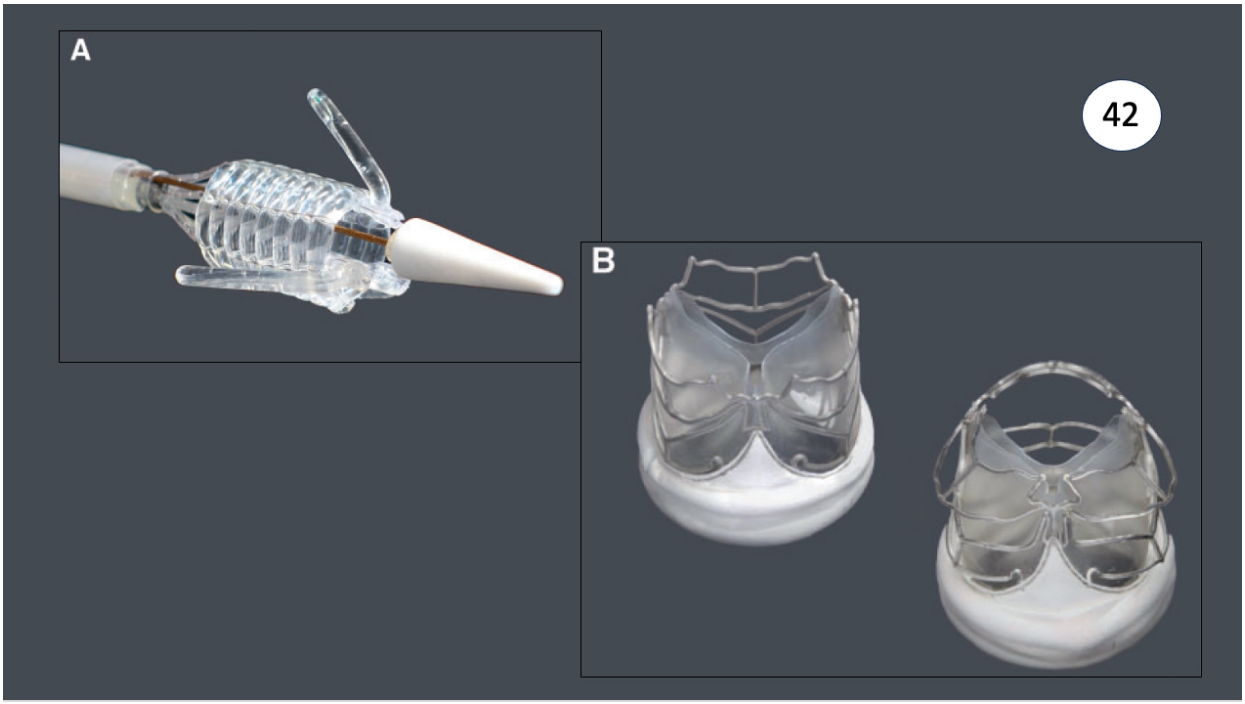


Figure 42: *(A) Non-occlusive device with helical deployment balloon and retractable location trunks. (B) Polymeric transcatheter aortic valve implantation prosthesis before crimping (left) and after crimping and expansion, showing elevated expansion arms (right).*

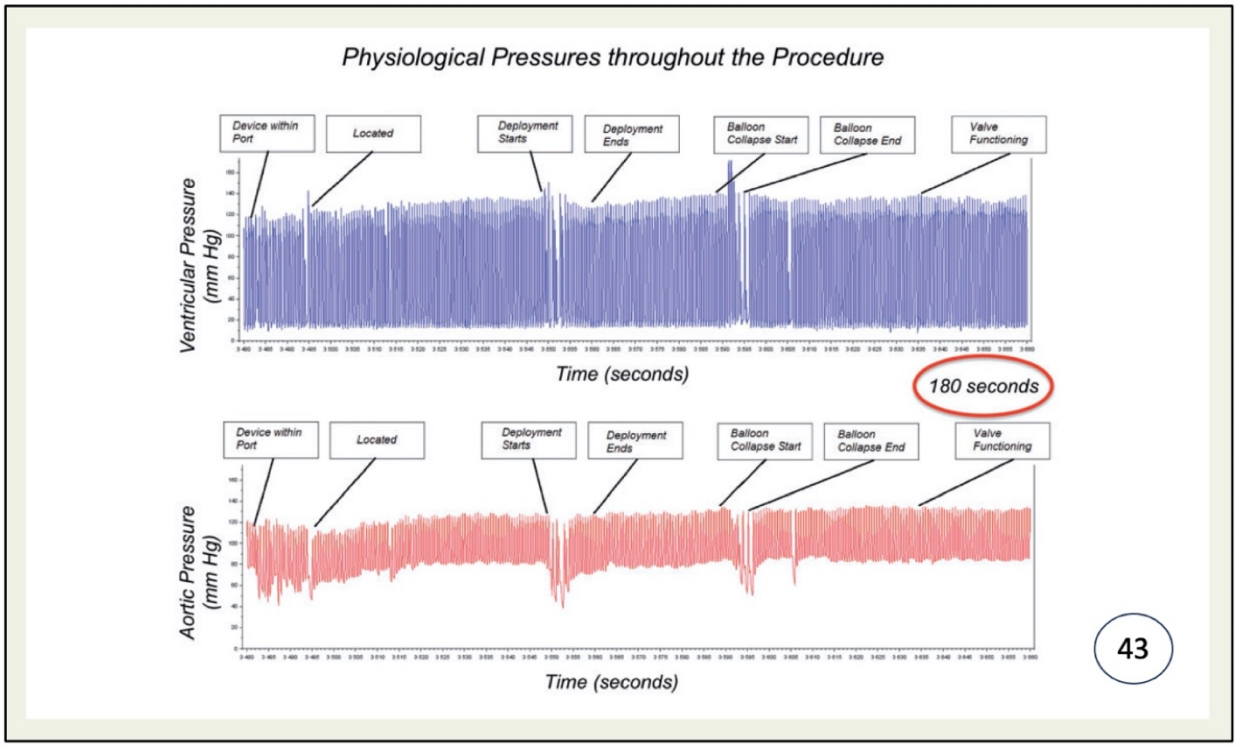
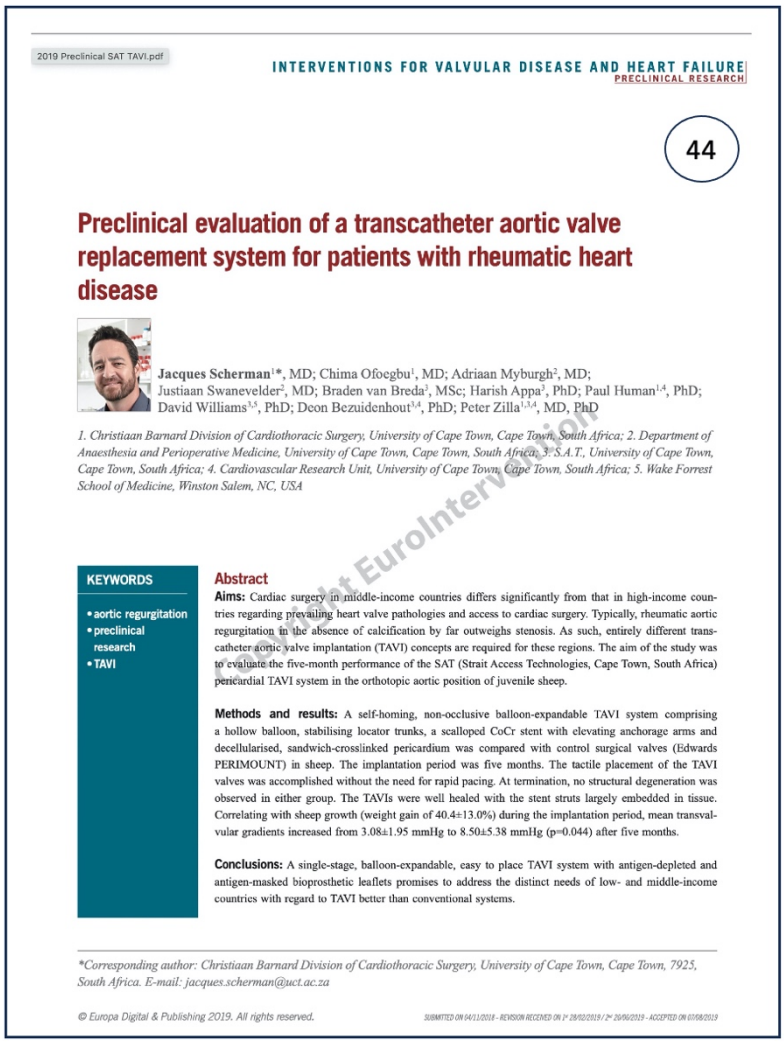


Figure 43: *Physiological aortic and ventricular pressures were maintained during the non-occlusive deployment of the novel self-locating balloon expandable polymeric transcatheter aortic valve implantation prosthesis.*

CHAPTER 9

PRE-CLINICAL IN-VIVO TESTING OF BIOPROSTHETIC TAVI DEPLOYMENT IN A CHRONIC SHEEP MODEL.

The chronic long-term performance of the SAT pericardial TAVIs in sheep was the last pre-clinical step towards clinical trials confirming the longevity of the decellularized and specially crosslinked bioprosthetic pericardium and the ability of the valve stent to firmly anchor in non-calcified, compliant aortic roots. It also demonstrated the complete tissue integration with advanced surface endothelialisation and as a consequence no traces of thrombotic appositions.



2019 Preclinical SAT TAVI.pdf

INTERVENTIONS FOR VALVULAR DISEASE AND HEART FAILURE
PRECLINICAL RESEARCH

44

Preclinical evaluation of a transcatheter aortic valve replacement system for patients with rheumatic heart disease

Jacques Scherman[1]*, MD; Chima Ofoegbu[1], MD; Adriaan Myburgh[2], MD; Justiaan Swanevelder[2], MD; Braden van Breda[2], MSc; Harish Appa[3], PhD; Paul Human[1,4], PhD; David Williams[3,5], PhD; Deon Bezuidenhout[1,4], PhD; Peter Zilla[1,3,4], MD, PhD

1. Christiaan Barnard Division of Cardiothoracic Surgery, University of Cape Town, Cape Town, South Africa; 2. Department of Anaesthesia and Perioperative Medicine, University of Cape Town, Cape Town, South Africa; 3. S.A.T., University of Cape Town, Cape Town, South Africa; 4. Cardiovascular Research Unit, University of Cape Town, Cape Town, South Africa; 5. Wake Forrest School of Medicine, Winston Salem, NC, USA

KEYWORDS

- aortic regurgitation
- preclinical research
- TAVI

Abstract

Aims: Cardiac surgery in middle-income countries differs significantly from that in high-income countries regarding prevailing heart valve pathologies and access to cardiac surgery. Typically, rheumatic aortic regurgitation in the absence of calcification by far outweighs stenosis. As such, entirely different transcatheter aortic valve implantation (TAVI) concepts are required for these regions. The aim of the study was to evaluate the five-month performance of the SAT (Strait Access Technologies, Cape Town, South Africa) pericardial TAVI system in the orthotopic aortic position of juvenile sheep.

Methods and results: A self-homing, non-occlusive balloon-expandable TAVI system comprising a hollow balloon, stabilising locator trunks, a scalloped CoCr stent with elevating anchorage arms and decellularised, sandwich-crosslinked pericardium was compared with control surgical valves (Edwards PERIMOUNT) in sheep. The implantation period was five months. The tactile placement of the TAVI valves was accomplished without the need for rapid pacing. At termination, no structural degeneration was observed in either group. The TAVIs were well healed with the stent struts largely embedded in tissue. Correlating with sheep growth (weight gain of 40.4±13.0%) during the implantation period, mean transvalvular gradients increased from 3.08±1.95 mmHg to 8.50±5.38 mmHg (p=0.044) after five months.

Conclusions: A single-stage, balloon-expandable, easy to place TAVI system with antigen-depleted and antigen-masked bioprosthetic leaflets promises to address the distinct needs of low- and middle-income countries with regard to TAVI better than conventional systems.

**Corresponding author: Christiaan Barnard Division of Cardiothoracic Surgery, University of Cape Town, Cape Town, 7925, South Africa. E-mail: jacques.scherman@uct.ac.za*

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PRECLINICAL EVALUATION OF A TRANSCATHETER AORTIC VALVE REPLACEMENT SYSTEM FOR PATIENTS WITH RHEUMATIC HEART DISEASE.

Jacques Scherman[1], Chima Ofoegbu[1], Adriaan Myburgh[2], Justiaan Swanevelder[2]; Braden van Breda[3], Harish Appa[3], Paul Human[1,4]; David Williams[3,5], Deon Bezuidenhout[3,4], Peter Zilla[1,3,4]

1 Christiaan Barnard Division of Cardiothoracic Surgery, University of Cape Town, South Africa
2 Department of Anaesthesia and Perioperative Medicine, University of Cape Town, South Africa
3 S.A.T., University of Cape Town, South Africa
4 Cardiovascular Research Unit, University of Cape Town, South Africa
5 Wake Forrest School of Medicine, Winston Salem, USA

ABSTRACT

Aims: Cardiac surgery in middle-income countries differs significantly from that in high-income countries regarding prevailing heart valve pathologies and access to cardiac surgery. Typically, rheumatic aortic regurgitation in the absence of calcification by far outweighs stenosis. As such entirely different trans-catheter aortic valve (TAVI) concepts are required for these regions.

Methods and Results: A self-homing, non-occlusive balloon-expandable TAVI system comprising a hollow-balloon, stabilizing locator-trunks, a scalloped CoCr-stent with elevating anchorage-arms and decellularized, sandwich-crosslinked pericardium was compared with control surgical valves (Edwards Perimount) in sheep. The implantation period was five months. The tactile placement of the TAVI valves was accomplished without the need for rapid pacing. At termination, no structural degeneration was observed in either groups. TAVIs were well-healed with the stent-struts largely embedded in tissue. Correlating with sheep-growth during the implantation period, transvalvular gradients increased mildly from 3.1±1.9 mean/8.0±5.1mmHg peak to 8.5±5.4/20.9±9.4mmHg (NS) after 5 months.

Conclusion: A single-stage, balloon-expandable, easy-to-place TAVI system with antigen-depleted and antigen-masked bioprosthetic leaflets promises to address the distinct needs of low and middle-income countries in regard to TAVI better than conventional systems.

Classifications: TAVI, Aortic regurgitation, Pre-clinical research

ABBREVIATIONS

TAVI:	transcatheter aortic valve insertion
SAT:	Strait Access Technologies
AS:	aortic stenosis
AR:	aortic regurgitation
HICs:	high-income countries
MICs:	middle-income countries
RHD:	rheumatic heart disease
AVR:	aortic valve replacement
BRICS:	Brazil, Russia, India, China, South Africa
sAVR:	surgical aortic valve replacement
TTE:	transthoracic echocardiography
PVL:	paravalvular leak
EOA:	effective orifice area

INTRODUCTION

Trans-catheter aortic valves (TAVI) were conceived for calcific aortic stenosis (AS) prevalent in the aging population of North-America and Europe [200, 349]. Even in the few patients with predominant aortic regurgitation (AR) [349] the underlying pathology in these regions is largely degenerative in nature [349], often showing some degree of calcification. Contemporary TAVI valves could therefore rely on the crushed mineral deposits for anchorage, obviating the need for stent features that could independently secure the TAVIs in non-calcified, compliant roots. Therefore, with a few exceptions [350, 351], stent designs continued to be based on smooth diamond-shaped elements. Naturally, when applied to non-calcific aortic regurgitation (AR) they had to be excessively oversized to avoid valve embolization [352], making it a sub-optimal treatment choice. Yet, with four to five times more patients of high-income countries (HICs) suffering from calcific AS than AR [200, 349], this limitation of conventional transcatheter valves has still to become a clinical urgency there.

In contrast, in middle-income countries (MICs), four times more patients are affected by non-calcific AR than calcific AS [353] due to the prevalence of rheumatic heart disease (RHD) [2, 5, 183]. It is estimated that 56% of all patients requiring single aortic valve replacement (AVR) in these countries would need it for rheumatic AR [2]. As this percentage represents a mean value between a rapidly Westernizing urban population and a rural majority [2], a large proportion of patients requiring an AVR outside the reach of metropolitan centres needs it for RHD. These patients are usually young. While even the non-rheumatic AR patients of HICs are on average 11-12 years younger than AS patients [349], rheumatic AR patients in MICs are in their mid-forties when they come to surgery [5, 183]. It is this large group of patients that need a lateral solution outside the algorithms of HICs. First, only a fraction of these patients have access to cardiac surgery, due to limited capacity [2]. The majority of Chinese heart centres, for instance, operate less than 100 cases per year [2]. Even at big urban centres, costs, availability and patient-suitability limit the access to conventional trans-catheter valve replacements. In 2016 only 160 TAVI procedures were performed in India and 900 in China [2] (pro-rata corresponding German numbers would have been approximately a quarter of a million [198]. Secondly, the high failure rate of mechanical prostheses due to poor anticoagulation compliance [183] and the early degeneration of bioprosthetic heart valves due to the young age of the patients adds urgency to the need for alternative long-lasting soft-leaflet valves [22].

With an estimated annual need for 360,000 single AVRs in the BRICS countries alone, where only 118,000 are currently provided together with the relative paucity and low capacity of cardiac surgical centers [2] and the young age of patients, an easy-to-place, long-lasting TAVI that is tailor-made for the population-specific pathology and addresses leaflet longevity would have the potential to expand capacity and improve the performance of valve prostheses in these regions.

In the current study, a TAVI system that has been developed to address the key challenges of MICs was evaluated in a chronic sheep model. These challenges include valve deployment in the absence of sophisticated imaging technology, the insertion into the hyperdynamic hearts of AR patients in the absence of anchoring leaflet mineralization, and the use of a bioprosthetic material that significantly mitigates accelerated leaflet degeneration anticipated in younger patients.

METHODS

The aim of the study was to evaluate the 5-months performance of the SAT (Strait Access Technologies, Cape Town, South Africa) pericardial TAVI system [354] in the orthotopic aortic position of juvenile sheep. Implantation success in the compliant non-reinforced roots, healing, hemodynamic performance, calcification and valve integrity (structural and non-structural) were assessed.

TAVIS AND CONTROLS

The self-locating, non-occlusive transapical deployment device comprises a unidirectionally flow-permissive hollow-balloon with retractable location and stabilization trunks and an invaginating retrieval sheath [174] (Figure 45). The SAT-TAVI stent is based on a scallop design with expansion-linked arm protrusion for supra-annular anchorage (Figure 46). At the defined balloon filling-pressure of 18 Bar, 23mm stents (n=10) deployed to an annular diameter of 22.2±0.3mm, with a distal diameter of 23.5±0.3mm and a proximal diameter of 24.6±0.3mm. The top arms elevated to a diameter of 25.4±0.5mm and the bottom supra-annular arms to 27.0±0.4mm. Sub-scallop leakage is prevented by an electro-spun elastomer skirt welded to the stent. The decellularized [355], sandwich-crosslinked [356] [17] bovine pericardial leaflets are continuously attached to the scallops. As controls, Edwards 'Perimount' valves (size 19)(Edwards Life Sciences; St. Ana CA) were implanted.

SURGICAL PROCEDURES/TAVI DEPLOYMENT AND POST-OPERATIVE FOLLOW-UP

The study was approved by the Faculty of Health Sciences Animal Ethics Committee, University of Cape Town (AEC 016/015). To compensate for the oversizing inherent to TAVI, larger animals were used for the surgical control group (53.8±2.8kg/12 months of age) than the TAVI group (37.8±2.4kg/10-months old). Preoperatively, animals were screened with transthoracic echocardiography (General Electric, Vivid I BT09 Norway) to pre-assess aortic dimensions. Group 1 (n=5) underwent a transapical insertion of a SAT pericardial TAVI valve (size 23mm) in the orthotopic position (330) and Group 2 (n=5) underwent a surgical-AVR (sAVR). In brief, the SAT-TAVI deployment system is trans-apically inserted and advanced into the ascending aorta under fluoroscopic and echo control allowing the confirmation of root dimensions (Table IV,V). Following the deployment and engagement of the downward-pointing balloon trunks into the nadirs of the leaflets and confirmation of rotational alignment and position on fluoroscopy, the tactile feedback allows the operator to continually apply a gentle pull to stabilise the moving valve plane while guarantying the correct position for the TAVI placement. Rapid inflation of the hollow deployment balloon allows full expansion of the TAVI valve stent and the six supra-annular anchoring arms while the temporary back-flow valve in the hollow balloon maintains normal diastolic pressures for coronary perfusion. After deflation of the stabilising balloon trunks and the deployment balloon, both are engulfed by a pressurized rolling-sheath for atraumatic retrieval.
Low-dose antic-platelet therapy (Aspirin 50mg daily) was commenced on day-1; clinical evaluations were performed daily. After animals were returned to pasture, the anti-platelet regimen was continued until termination. At 1- and 3-months post-operatively, transthoracic echocardiograms (TTE) were performed.

EXPLANT PROTOCOL

Termination (Sodium Pentobarbitone 200mg/kg iv and K-Chloride 3g) was performed 5-months (152±3 days) post-operatively, after prosthesis function was evaluated by echocardiography and fluoroscopy. Valves were explanted for macrophotography and histological assessment (Hematoxylin/Eosin, Brown/Brenn, Von-Kossa stains). Calcium

content was determined by lyophilization and ashing, dissolution in hydrochloric acid, with measurement by inductively coupled plasma-atomic emission spectroscopy (ICP-AES), the results expressed in μg/mg of dry weight.

STATISTICAL ANALYSIS

Inferential statistical analysis was performed using the JMP statistical software package (version 13.0.0; Cary; NC; USA). Distribution of continuous numerical data was evaluated using the Shapiro-Wilk test. Categorical variables were presented as frequencies (%) and continuous variables were reported as means±standard deviation. Parametric continuous data was analyzed using the Student's t-test and Non-Parametric data using the Wilcoxon test.

RESULTS

All ten consecutive sheep underwent successful AVR. Except for one animal in the control group that died of valve infection on day 120, all reached the 5-month observation endpoint. Two transcatheter valves that had been placed too low during deployment due to an entrapped control line of a locator arm had their resulting mild- to moderate paravalvular leak (PVL) continually detectable at month 1 and 3 and at termination.

At implantation, surgical control valves had been largely size-matched with the native annulus of the sheep while TAVIs were diameter-oversized by 16.4±5.8% and under-deployed by 5.4±2.3% diameter (range:2.7-9.0%). The tactile placement of all TAVI valves was accomplished within 9.6±2.2 minutes after transapical entry without the need for rapid pacing. Systolic pressures only mildly dropped by 17±2% during transapical entry (from 103±13mmHg to 85 ±12mmHg) and 26±11% during actual deployment (from 100±20 mmHg to 72±9mmHg). Correspondingly, diastolic pressures were maintained at means of 65.4±9.1mm Hg during the inflation of the deployment balloon, confirming the echo finding of an effective temporary back-flow valve inside the hollow-balloon.

In the TAVI group, which experienced a weight gain of 40.4±13.0%, after five months, mean transvalvular gradients increased from 3.08±1.95mmHg to 8.50±5.38mmHg (p=0.044; Student's t-test) and maximum transvalvular gradients from 8.04±5.13mmHg to 20.90±9.36mmHg (p=0.035). In the older control group, which experienced only a 14.3±5.3% weight increase, after five months, mean transvalvular gradients decreased from 14.58±2.64mmHg to 10.53±2.47mmHg (p=0.066) and maximum transvalvular gradients from 35.23±5.39mmHg to 19.55±7.13mmHg (p=0.014).

Apart from the animal implants, separate pulse duplicator tests (ISO 5840-5L/min) were also performed on 10 SAT TAVI and 2 surgical control valves which showed effective orifice areas (EOA) of 1.95±0.07cm^2 and 1.46±0.25cm^2; a transvalvular closure leakage of 0.83±0.90% and 1.56±1.02% and a total closing plus post-closure regurgitation volume of 4.38±1.65% and 1.79±0.08%, respectively.

MACROSCOPIC APPEARANCE

No structural degeneration was observed in any explanted valve (Fig.47a-j). All leaflets were free of blood clots. On the aortic side, stent struts of TAVI were largely embedded in tissue and white glistening neointimas covered most of the leaflets (Fig.47a-d). All coronary ostia were widely patent. Native leaflets had largely shrunk, resulting in a singular sinus space between the TAVI leaflets and the aortic wall. Control valves showed distinct, white tissue overgrowth onto the cloth-covered stent-posts but otherwise did not differ significantly from

the TAVI group. On the ventricular side, both groups showed a significant pannus-shelve formation consisting of a whitish, aperture-like, sharp-edged tissue and wart-like, flat microthrombi in the dead-space underneath the commissures and on the leaflets (Fig.48).

HISTOLOGY

Upon explant, leaflets were 41% thinner in the control group (438±52μm) than in the TAVI group (737±77μm). Both groups showed tapering pannus wedges at the base of the leaflets (Fig.49). On the aortic side, they continued as neo-intima of varying thickness covering most of the leaflet surface. This was more pronounced in the TAVI group where the neointima reached the cusp edge, forming a round cap (Fig.49a). On the ventricular side, neo-intimal coverage was sparce. The macroscopically visible small microthrombi consisted of pure platelet aggregates (Fig.49 a,b). The electro-spun skirt of the TAVI group showed complete transmural vascular ingrowth in the areas of tissue contact at the commissures and the annulus (Fig.49 c-e), while in areas without tissue contact, cell infiltration was patchy and lacking blood vessels.

CALCIUM ANALYSIS

Histologically, no traces of calcification were observed in either group. ICP-AES analysis confirmed similarly low calcium values for TAVI versus control groups in individual leaflets (8.4±19.6 versus 17.0±36.8μg/mg; p=0.437) and when combined (8.4±16.0 versus 17.0±27.2μg/mg; p=0.782 (Wilcoxon test).

DISCUSSION

Apart from cost-effectiveness, TAVIs need to address very different requirements in middle- and high-income countries. The specific requirements in MICs include independence from sophisticated imaging equipment, the ability to locate and anchor the valve in the absence of calcification, the acknowledgement of resource limitations that necessitate single-staged procedures and are near-prohibitive for potential downstream interventions such as PPMs, the appreciation of the predominance of rheumatic aortic regurgitation with its associated fundamentally different hemodynamics, and the need for long-lasting leaflet materials for use in younger patients.

We have previously shown [(174)] that these specific requirements are addressed by a purpose-designed transapical balloon-expandable TAVI system. The current chronic study confirmed the ability of the delivery system to deploy a balloon-expandable TAVI without the need for rapid pacing and with ejection maintained throughout cardiac systole. It also showed that tactile placement allows accurate positioning. The entrapment of the control line of the balloon-trunks that led to too-low a deployment in 2 sheep has since been addressed.

As the positioning trunks consist of smooth yet bend-resistant 4mm balloons, they do not have the traumatising potential of metal arms which may cause dissections [(357)]. The trunk retrieval through invagination at the end of the procedure guarantees a friction-free withdrawal preventing dislodgement of the deployed valve. An extremely tight aortic root model such as the sheep also demonstrated the ability of the balloon trunks to maintain sufficient inflow spaces to the coronary ostia when the helical deployment balloon was fully inflated. Despite tightly stretching the sino-tubular junction, the fully inflated balloons did not cause any signs of ischaemia. Confirming ex-vivo tests, this additional safeguard of coronary perfusion warrants sustained maximal balloon inflation at the conclusion of the deployment, thereby potentially minimising paravalvular leaks and ellipticity. The hollow balloon itself providing a luminal cross-sectional area of 1.8cm^2 for a 23mm valve and an effective backflow

valve that maintains sufficient diastolic pressures for coronary perfusion was hemodynamically almost 'invisible'.

The supra-annular stent arms resting on the ventricular side of the leaflet nadirs proved to be firm and effective anchors in the compliant non-calcified sheep roots. Once deployed, none of the valves migrated, dislodged or embolised. More than in pigs or calves, the over-elastic anulus of sheep had previously been shown to lead to device migration and paravalvular leaks unless stiffening reinforcements were pre-implanted [(358)]. Our elevating stent arms added an essential feature to balloon expandable TAVIs that has, until now, only been achievable with self-expanding valves. Purely on the basis of expansion-deformation of the cobalt-chromium stent, the radius of the fully deployed arms exceeded the annular stent diameter by 25%.

The scalloped attachment struts for the leaflets were designed to deploy to their perfect pre-crimping shape. This was confirmed on implantation fluoroscopy. We had previously shown that this scallop-design also allows the continuous attachment of durable polymeric leaflets [(174)]. Particularly for the latter, optimization of leaflet strain through avoidance of excessive oversizing made a balloon expandable concept additionally preferable. The de-facto under-deployment of valves in the present sheep study was at a modest 5%, preserving near-perfect leaflet geometry.

Although current guidelines for TAVI in middle-income countries mirror those of high-income countries, the slow but continual global trend towards younger patients has a different long-term connotation in countries like Brazil, South Africa, India or even China [(2)] compared to Europe or the USA. In MICs surgical valve replacements are far from representing a 'gold standard', as the mechanical prostheses prescribed for the largely young, rheumatic patient populations perform suboptimally under the prevailing circumstances [(183)]. Yet, adherence to the guidelines of high-income countries has so far prevented decisive head-to-head studies between modern tissue valves and mechanical valves. However, should such studies eventually show an overall benefit of soft-leaflet valves in the affected populations, a major hurdle towards using simple transcatheter therapies to augment the insufficient capacity of open heart surgery in these countries would have been overcome [(2)]. The implementation of scientific advances in bioprosthetic tissue preservation, therefore, has a higher priority for middle- than for high-income countries with their predominance of older patients combining limited life expectancy with slower bioprosthetic tissue degeneration. In this regard, the recent two-pronged approach towards eliminating remnant immunogenicity [(19)] holds great promise. One arm of this approach comprises the removal of cells as they represent the bulk of antigen carriers [(359)]. Various decellularization approaches have successfully found their way into clinical implementation since [(360)]. Concomitantly, a higher efficacy of antigen masking through improved sandwich-crosslinking was also shown to significantly mitigate calcification [(356)]. By combining both approaches, pericardial calcification could be abolished (from 127μg/mg to 3μg/mg $p<0.001$) in the commonly accepted rat model (unpublished data).

For size reasons, the current study used 10-12 months old sheep. As the sheep ceases to be a calcification model once older than 4 months, the present study was not expected to provide validation of the tissue preservation process with regards to mineralisation. Yet, the pristine histomorphology of all explants, and the complete absence of inflammatory cells at both the surface and inside the decellularized pericardium, suggested an absence of a significant immune response of the TAVI pericardium. With the choice of Perimount surgical valves as controls, a latest generation tissue valve was selected. Other than the thinner pericardium used in these control valves, the two groups barely differed in their explant macro-

morphology, neither in their aperture-like sub-valvular tissue shelf nor in the platelet microthrombi on the ventricular side. Neointimal outgrowth was more pronounced on the TAVIs covering the entire aortic side of the leaflets. This may have had its reason in the healing ability of the electrospun skirt that facilitated complete transmural vascularization in areas of direct tissue contact with the aorta or myocardium. We believe that the unprecedented transmural endothelialisation through the skirt may also hold a key to future tissue regenerating TAVI concepts, as transmural ingrowth was recently shown to be the only significant source of prosthetic surface endothelialisation [(361)] other than transanastomotic pannus outgrowth [(362)].

CONCLUSION

The present study showed a promising 5 months performance of the SAT pericardial TAVI valve in sheep, validating the key characteristics underlying a transcatheter system that was specifically designed to address current and future requirements in middle- and potentially even low-income countries. By providing a self-homing and stabilising balloon expandable TAVI system that obviates fast-pacing, several prevailing paradigms were disproved:

- Self-homing locator arms do not need to be part of self-expanding stents but can be balloon-based and be part of the dilatation balloon. By retraction through invagination, they were proven to resist pinching even under the extremely tight conditions of the sheep model.
- Protruding stent structures required for the anchorage of TAVI valves in compliant non-calcified annuli do not need to rely on the shape-memory feature of self-expanding stents or two-component designs. By plastic deformation of a cobalt-chromium stent during balloon inflation, firm anchorage was achieved in the hyperelastic sheep model without excessive oversizing.
- Rapid pacing does not need to be an integral part of balloon expandable TAVIs. By utilizing a widely open helical balloon, the TAVI deployment was possible at the required radial forces, with continuing unimpeded ejection.
- The presence of a ‘shielding’ cloth-skirt does not preclude tissue ingrowth from the surrounding tissue. The electrospun skirt allowed full transmural vessel ingrowth and may have facilitated the complete neointimal coverage of the adjacent leaflets.
- The integration of scallops into cobalt-chromium stents, and the direct attachment of the leaflets to these scallops, does not result in an uneven post-crimping shape and detrimental stress concentrations. The structural integrity of the leaflets after 5 months in the sheep confirmed fatigue test data of >800 million cycles.

The successful realisation of a stent design that allows direct attachment of leaflets to scallops allowed us to also pursue a twin version with polymeric leaflets. After proof of concept and acute animal implants (174), a chronic sheep study has commenced with the SAT polymeric TAVI.

IMPACT ON DAILY PRACTICE

The present study validated in the chronic sheep model a transcatheter system that was specifically designed for the largely young patients in need of aortic valve replacement for rheumatic heart disease with predominant aortic regurgitation. Having overcome the disadvantages of conventional balloon-expandable TAVIs, a single-stage balloon-based procedure can be offered that takes both the specific pathology and the resource-constrained circumstances of low- to middle-income countries into account.

TABLES

Table IV: Baseline dimensions of sheep aortic root in TAVI Group

Table IV

Aortic root dimensions prior to TAVI	
Aortic annulus diameter, mm	18.1±1.1
Sinus diameter, mm	22.6±1.9
Sinotubular junction (STJ) diameter, mm	17.1±1.5
Sinus height, mm	13.7±1.1
Coronary ostia height, mm	9.7±1.6

Table V: Individual dimensions of Sheep receiving a TAVI valve and the degree of oversizing versus under-deployment of the valves.

Table V

Sheep	TAVI diameter at annulus (mm)	Native annulus diameter (mm)	% Oversized	Fully deployed TAVI valve diameter at annulus	% Underdeployed
1	20.9	18.1	15.7%	22.2	5.9%
2	20.2	16.8	20.0%	21.8	7.3%
3	21.2	17.1	24.2%	22.4	5.3%
4	21.1	19.2	9.9%	22.3	5.4%
5	21.6	19.2	12.3%	22.4	3.6%
	21.0±0.5	18.1±1.1	16.4±5.8%	22.2±0.2	5.5±1.3%

FIGURES

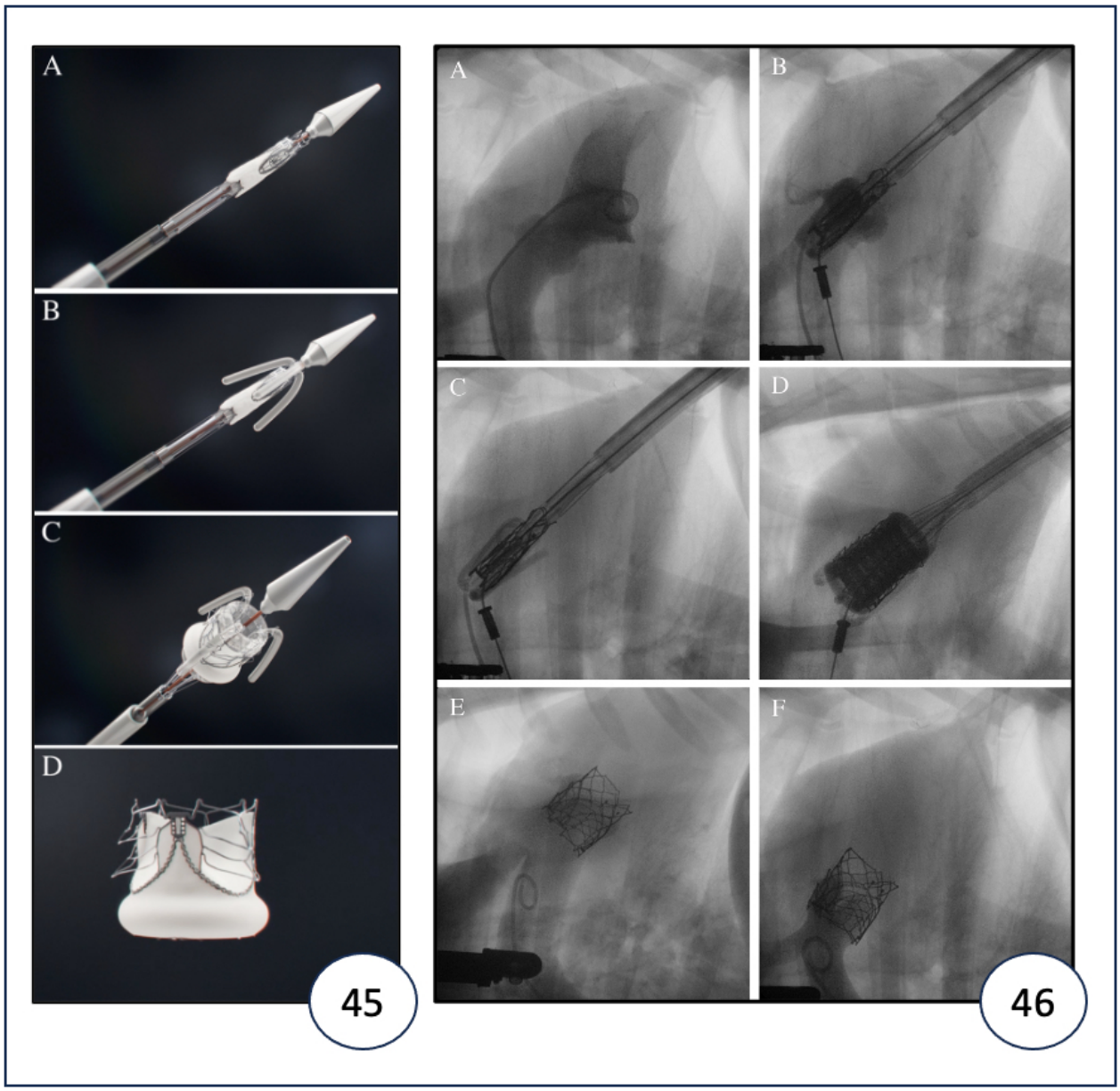


Figure 45: *Crimped SAT TAVI System pushed out of the deployment sheath (a); with the locator and stabilizer trunks deployed (b) followed by the full expansion of the scalloped, self-anchoring stent (c). The Cobalt-Cromium stent is designed to lift-up 6 arms through plastic deformation (d). All arms are seated supra-annularly creating sinus-like outward bulges of the leaflets that firmly anchor the stent in the absence of leaflet calcification.*

Figure 46: *Fluoroscopy-guided transapical insertion of the SAT-TAVI system followed by visualization of the aortic root through a contrast medium injection (Fig.46 A,B). The self-locating balloon trunks are now inflated (Fig.46C) followed by gentle traction on the system providing tactile feedback for the trunks engaging in the native aortic valve cusps thereby ensuring optimal positioning and root-stabilisation. The valve is deployed by inflating the hollow balloon (Fig.46D), without rapid pacing. Following deployment, coronary perfusion and absence of regurgitation is angiographically confirmed (Fig.46E-F).*

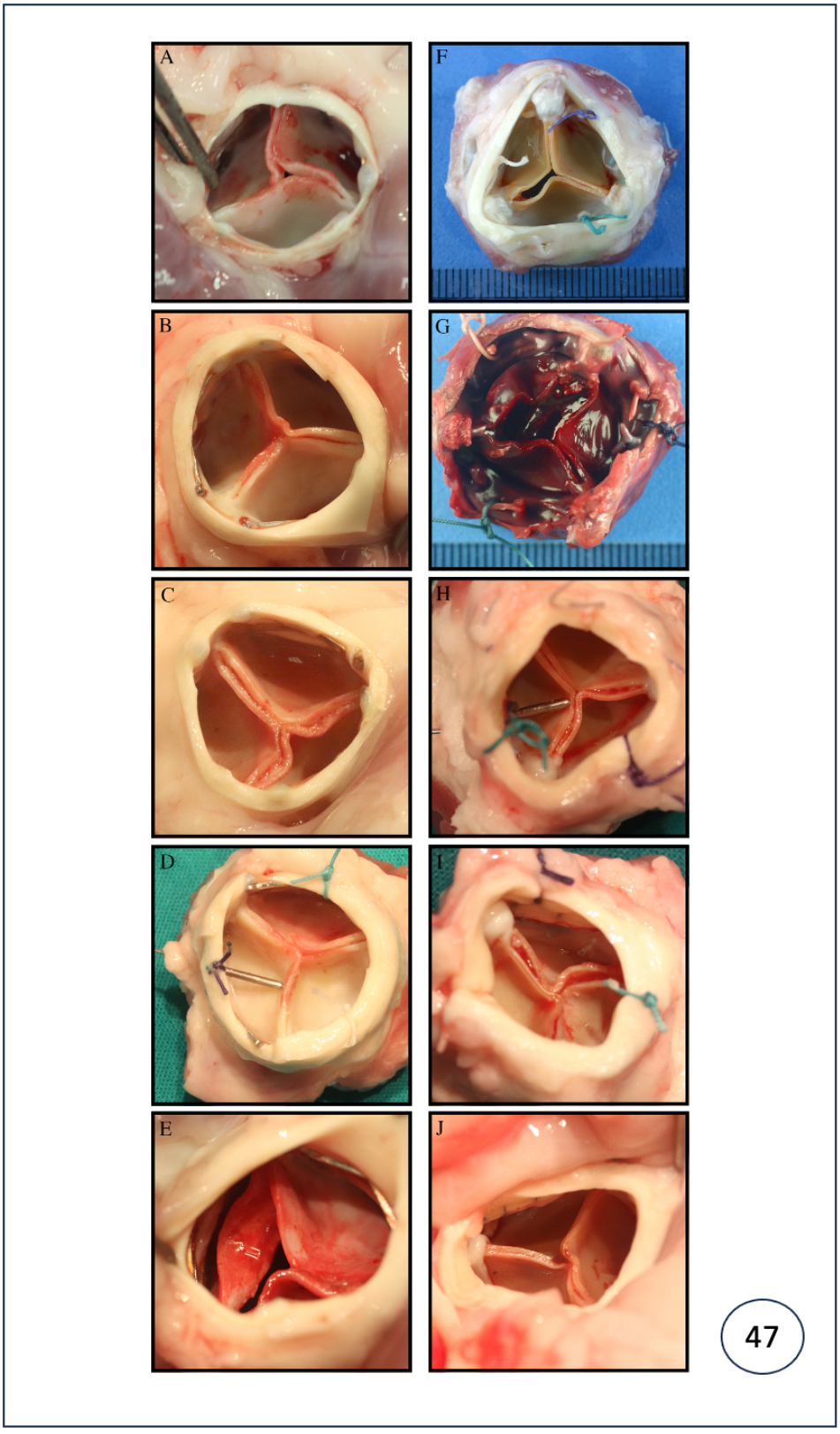


Figure 47: *Explant macro-photographs of SAT's pericardial TAVI (left/a-e) and Edwards Perimount control valves (right/f-j) after 5 months in orthotopic position in sheep. Only one sheep died prematurely on day 120 (g) with the vegetations of the prosthetic endocarditis visible between the commissures (post mortem picture). The whitish neo-intimal outgrowth is visible on the aortic side of the leaflets in both groups but more complete in the TAVI group where it reached the cusp edges in 4/5 valves (a-d). The TAVI stents are well embedded in tissue with only the distal commissural tips being visible. The 4 long-term control valves show distinct pannus outgrowth onto the fabric-covered stent-posts.*

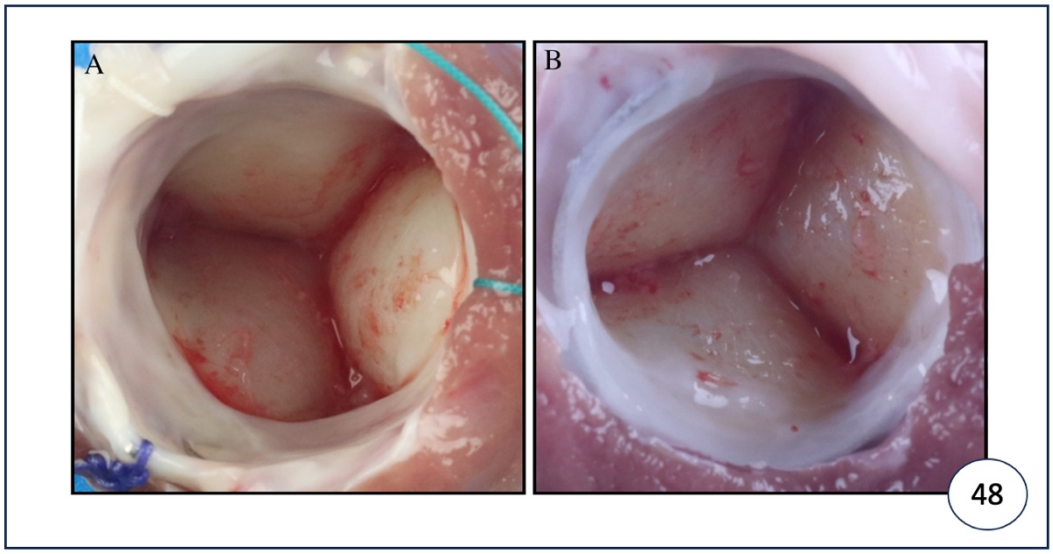


Figure 48: *View of a TAVI (a) and a control valve (b) from the ventricular side. In both groups, typical infra-valvular pannus shelves formed and neo-intimal outgrowth was scarce.*

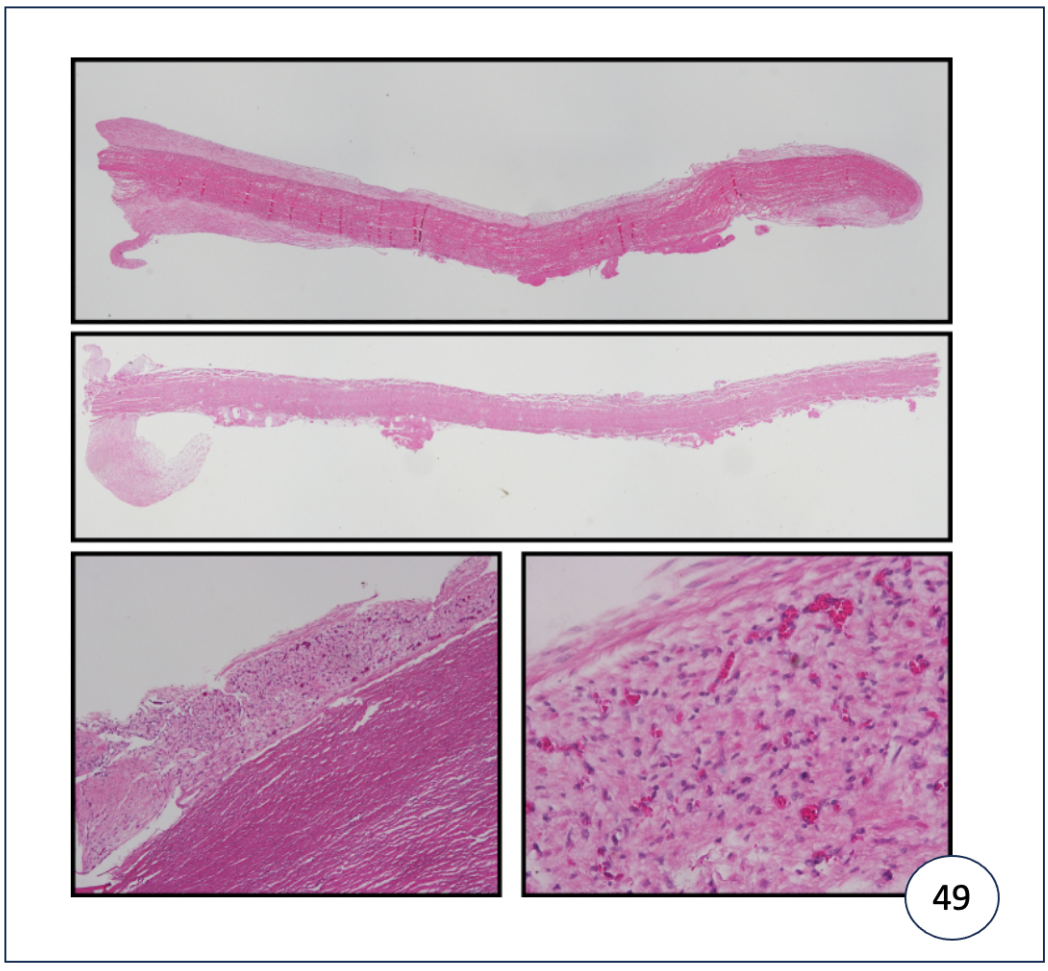


Figure 49: *Longitudinal cross sections of leaflets. The decellularized, sandwich-fixed pericardium of the TAVI (a) is thicker than the Perimount leaflet (b) with clearly visible neo-intimal outgrowth onto the aortic surface. The infra-valvular pannus-shelves are visible on both groups. The TAVI skirt shows complete transmural tissue ingrowth in proximity to the aorta (c) with numerous blood vessels throughout (d).*

CHAPTER 10

STATISTICAL BASIS FOR 'INFORMED BEST ESTIMATE' OF EXPECTED TAVI SIZES

All TAVI patients in industrialised countries undergo Computer Tomography prior to implantation to determine the precise anatomical dimensions. In calcific aortic stenosis this baseline has allowed both optimal patient-sizing and the actual TAVI sizes themselves to evolve without uncovered gaps between two sizes.

In the absence of sophisticated CT imaging technologies in regions where RHD is prevalent, the available dimensional data rely on echocardiography with its lower accuracy regarding annular diameters.

As a teaching hospital in a middle-income country we operate at the interface of the developed and developing world. As such, urban patients with degenerative, calcific aortic stenosis who receive a TAVI undergo pre-implantation CTs whereas patients with rheumatic aortic regurgitation undergoing surgical aortic valve replacement are being operated on the basis of echocardiography.

In order to obtain a first indication as to the ability of proposed TAVI sizes to cover the entire size spectrum within a range of oversizing stipulations and to anticipate which sizes are most needed for patients with rheumatic AR, a statistical extrapolation of existing data was undertaken using both the clinical patient data from patients with aortic stenosis as well as surgically implanted valve sizes in AS and AR patients. This chapter summarises the difficult journey towards the size-estimates of TAVIs for rheumatic AR.

1. BACKGROUND CONSIDERATIONS

Over the past 20 years a well-tested and detailed pre-insertion protocol has been established to determine the TAVI size for individual patients with calcific aortic stenosis (AS). Globally, with > 1.5mio TAVIs implanted, there is a profound body of evidence regarding sizing. In spite of the often rigid aortic roots of patients with AS, TAVI sizes are in average bigger than corresponding surgical prostheses. This seems counterintuitive as surgically implanted valves are mostly being tightly fitted with very limited compliance reserve of the annulus for being further stretched to accommodate a bigger valve size.

In contrast to AS, no experience exists with the implantation of TAVIs into the normal, compliant roots of patients with rheumatic aortic regurgitation. Moreover, the sizes of SAT valves are different from contemporary TAVIs. As the initial success of clinical trials with this novel valve will rely on optimal sizing the accuracy of size predictions will be crucial.

Potential TAVI patients with degenerative aortic stenosis routinely have pre-operative CT-scans. As such, the relationship between aortic root dimensions as assessed by CT and the actually implanted TAVI sizes is known for each patient. In contrast, no regular CTs are available from patients with rheumatic aortic regurgitation where echo suffices. Since comparable dynamic echo data are also not available for both patient groups, any extrapolation of the known aortic dimensions of patients with degenerative AS to those of patients with rheumatic AR would at least need one common denominator of sizing. The only common denominator known for both pathologies at our institution is the size distribution of surgically implanted heart valve prostheses. Therefore, we had one measurement available that allowed the direct dimensional comparison between rheumatic AR and degenerative AS (sizes of surgically implanted valves) and three indirect size correlations within AS (surgical valve sizes, CT dimensions and actual TAVI sizes) which were mirror-used for size predictions of SAT TAVIs in patients with rheumatic AR.

A further unknown in rheumatic AR is the extent of root compliance one can expect in these largely young patients. As higher root compliance may result in more pronounced oversizing of TAVIs, its accurate prediction holds a key to meaningful modelling. Again, in the absence of comparable dynamic imaging data, the degree of oversizing in successfully implanted TAVIs was chosen as an indirect reflection of annular compliance. To narrow the range, three scenarios were chosen: oversizing observed at the implantation of conventional balloon-expandable TAVIs in patients with calcific AS; the arbitrarily chosen exaggerated oversizing in patients with pure degenerative AR undergoing successful implantation of conventional TAVIs and oversizing seen in successfully implanted SAT TAVIs in healthy pigs (see chapter 6).

Underlying this approach was the desire to base the calculations on patients typically seen in a middle-income country where both urban patients with degenerative AS and rural patients with rheumatic AR coexist. Furthermore, institutional experience suggests that aortic roots are in average smaller in African patients and as such predictions should be based on local baselines.

In order to tie these data meaningfully together, deduct linear regression curves that can be tilted towards assumed degrees of annular compliance and predict a ranking of expected TAVI sizes extensive statistical analyses and modelling were applied on the basis of own, institutional patient data.

2. METHODOLOGICAL OVERVIEW

The problem of the lack of clinical data for providing guidance regarding the appropriate sizing of TAVI valves in rheumatic patients was therefore addressed by analysis and extrapolation based on the following staged approach:

1. Firstly, a dataset of aortic valve replacements performed at Groote Schuur Hospital in patients 75 years of age or older and presenting with aortic stenosis who either underwent conventional open-heart surgical replacement of the valve or, alternatively, underwent trans-catheter replacements with the Edwards Sapien XT valve.
2. Secondly, a dataset containing Computed Tomography-based measurements of perimeter-defined aortic annuli representing the pre-operative root assessment of the same TAVI patients examined under Phase 1 and the analysis of that relationship.
3. Thirdly, theoretical assignment of Strait Access Technology (SAT) TAVI valves sizes to the patients with aortic stenosis and assessment of over-/under-sizing.
4. Fourthly, a dataset of patients without aortic stenosis but presenting with rheumatic aortic regurgitation and undergoing surgical replacement of the aortic valve without associated computed tomography data and the extrapolation of the relationship identified in Phase 1 (using computed tomography data from the TAVI patients) between surgical implants and annulus dimensions to permit the hypothetical assessment of the distribution of aortic annuli in rheumatic patients.
5. Fifthly, evaluation of the extent of over-/under-sizing of the SAT TAVI valves against the hypothetical annulus sizes for a rheumatic population of patients with AR and the application of published oversizing estimates.
6. Finally, a research dataset of TAVI replacements of the aortic valve in healthy pigs which included two-dimensional echo-based measurements of the annulus.

Analysis within **Phases 1 and 2** in the case of aortic stenosis patients, and the optimization of SAT TAVI valve sizes based on that analysis in **Phase 3**, hypothetically provided very conservative estimates of the oversizing potential of SAT TAVI valves for rheumatic patients with AR, given the underlying limited compliance obtained from aortic stenosis.

Phase 4 permitted an estimate of the required minimal degree of over-sizing in rheumatic patients whereas incorporation of published exaggerated oversizing estimates in rheumatic patients under **Phase 5** provided as the other end of the spectrum the upper end of over-sizing. It also permitted a comparison with the theoretical distribution of SAT TAVI valve sizes described under Phase 3.

Analysis of the set of healthy pig data in Phase 6 alternatively provided a practical estimate of the extent of over-sizing possible with SAT valves in a healthy root scenario.

PHASE 1:
COMPARATIVE ANALYSIS BETWEEN SURGICALLY IMPLANTED AND EDWARDS SAPIEN XT TAVI IN AORTIC STENOSIS PATIENTS

***Figure 50** (**next page**): Analysis of the distribution of surgical versus TAVI valve sizes*

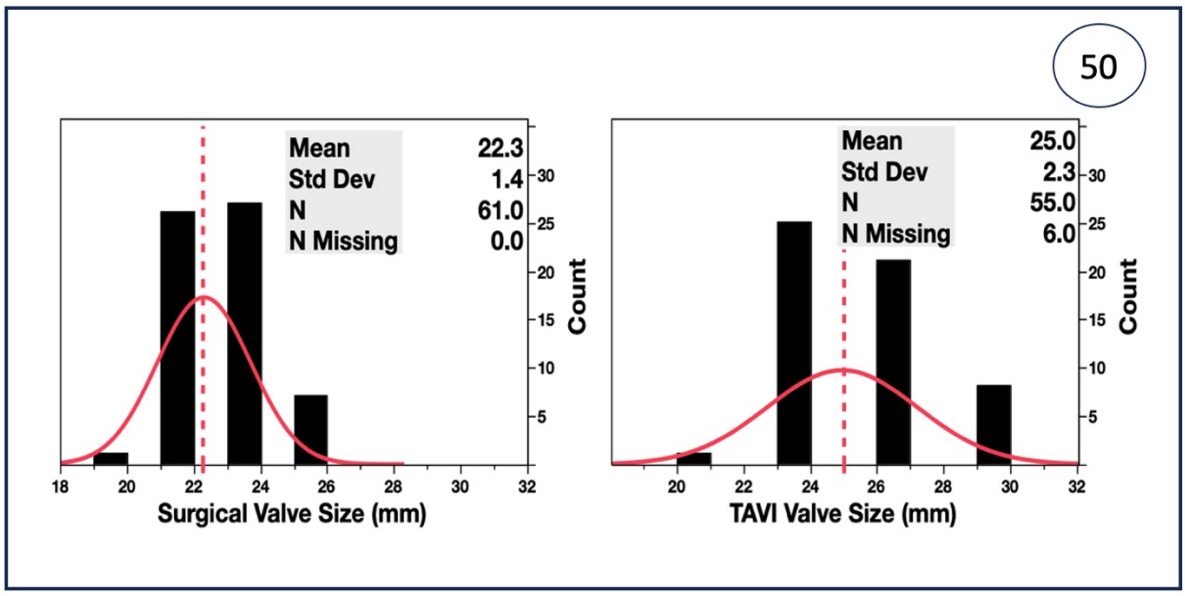
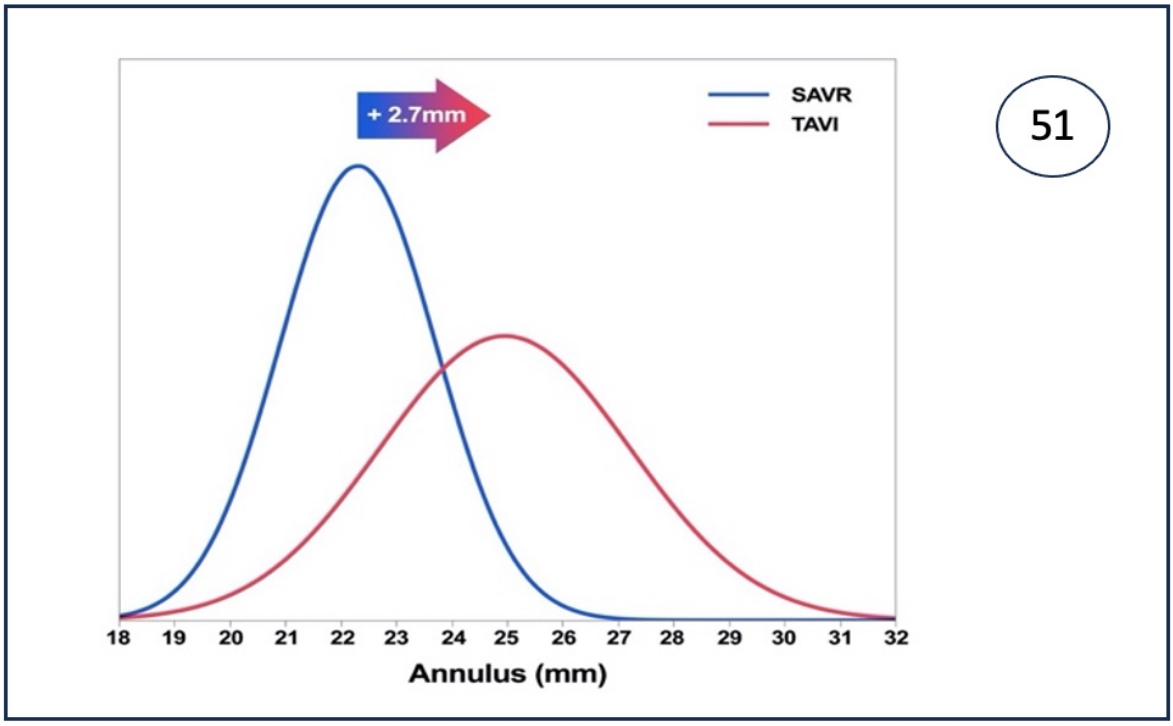


Figure 51 (below): *Calculation of the difference in valve size means (25.0mm - 22.3mm = 2.7mm) between the two subgroups of patients provides a simple estimate of the larger TAVI valve size relative to the annulus-equivalent surgical valve size.*



However, due to the distinct difference in kurtosis of the two distribution curves, a more accurate assessment is provided through a process of quantile matching where valve sizes are matched according to which quantile they represent in each of the two distributions, allowing accurate conversion across the full range of valve sizes.

Considerations regarding matching of Distribution Curves

There are two almost identical approaches for matching otherwise unrelated variables, that is, where a variable common to both is unavailable, for the purpose of investigating their direct relationship, for example when assessing the relationship between annuli measured for patients undergoing TAVI valve replacement in aortic stenosis patients and valve prostheses

implanted surgically for the same pathology but where annular data are unavailable. This is especially necessary when the level of kurtosis for the two variables are distinct or there is an obvious difference in symmetry (that is left or right shifted) between the two variables, thereby preventing simple bivariate analysis.

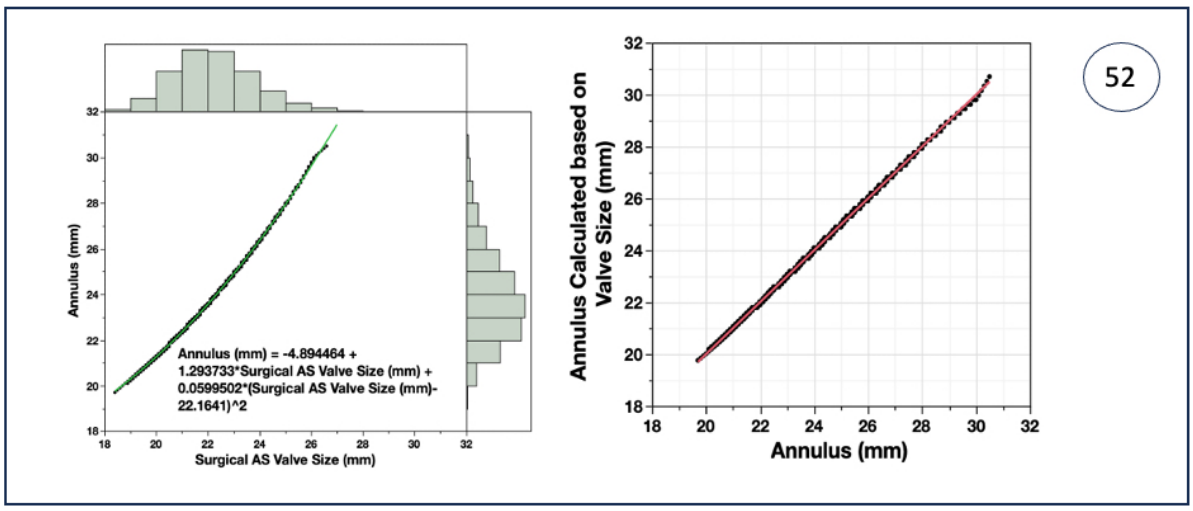


Figure 52: *Without performing pre-regression matching, other than simply row-by-row matching following sorting, it may appear that a fit appears possible, as can indeed be seen from applying the regression formula to the surgical AS valve size data to arrive at a calculated annulus which perfectly matches the original annulus data. However, in reality, the success is dependent on an identical number (N) of data points for each set, which is almost the case here.*

If the set sizes are very different, insufficient matching will result and the regression formula will not hold across the full range of values. Therefore, quantile and density matching described below have instead been applied in the analyses contained within this document.

Quantile Matching

This method calculates the quantiles for each of the two distribution curves and subsequently reports the respective values corresponding with identical quantile values thereby providing matched X-Y data pairs.

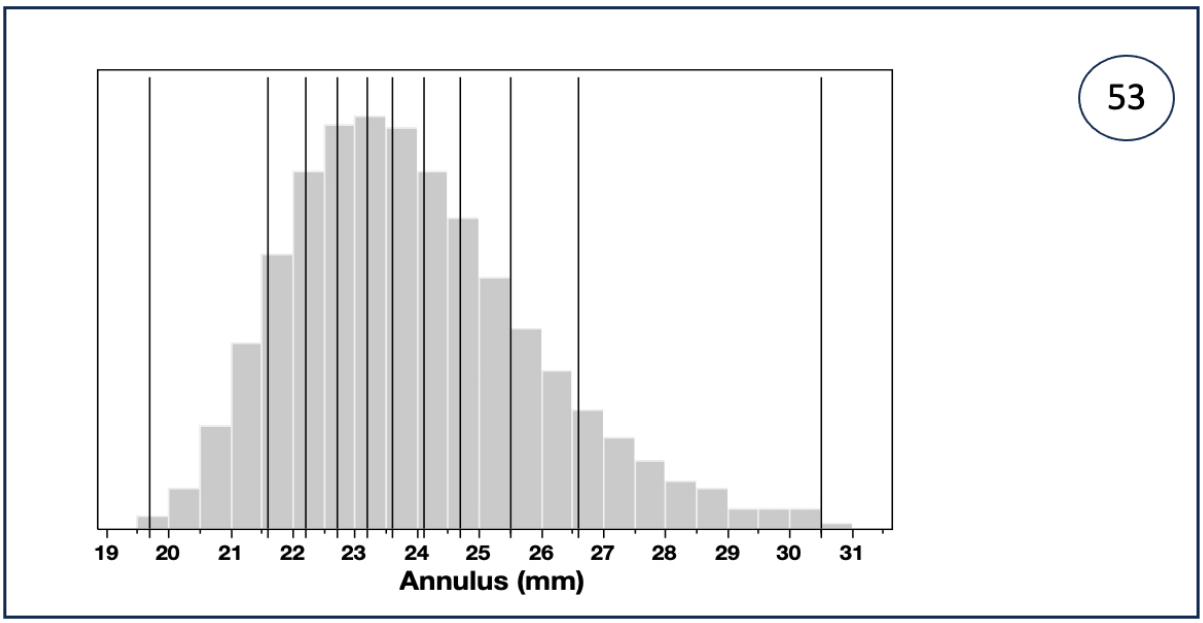


***Figure 53* (previous page):** *Here 10% quantile increments are applied but can be seen to be focused more around the mean than being evenly distributed resulting in fewer matching points in the shoulder areas of the distribution curves. This is dependent on the level of granulation set for the quantiles but the shoulders will always remain slightly underrepresented.*

Density Matching

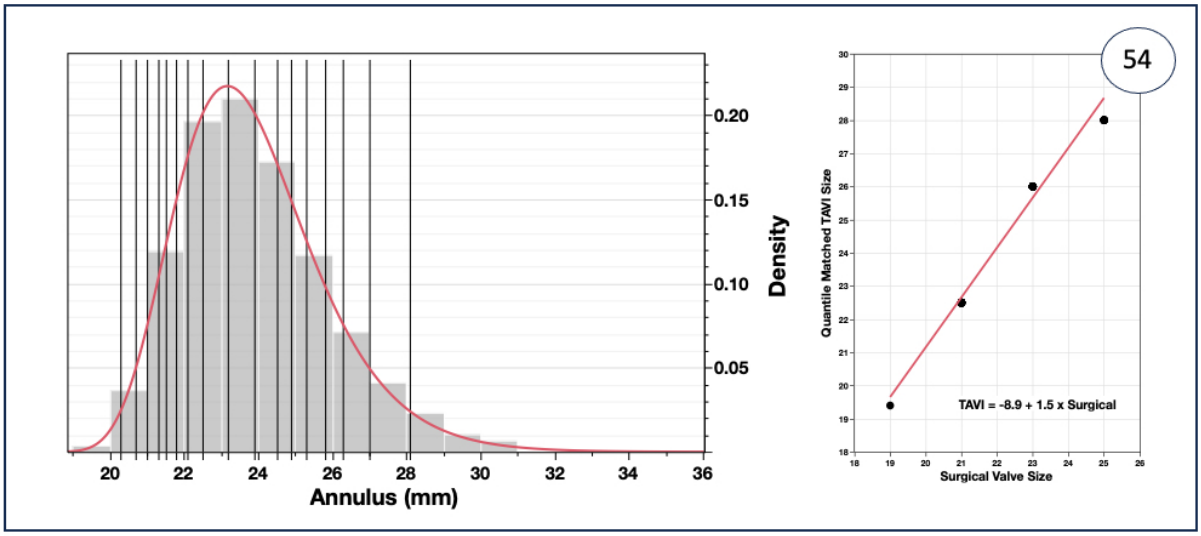


Figure 54: *This method relies on matching values of equal density of the fitted distribution curves for the two variables, that is matching y-axis values between the two to arrive at matched X-axis pairs. Typically, the shoulders are better represented than in the case of quantile matching and, since they represent the extremes of the relationship, may offer improved regression analysis than could be expected with quantile matching.*

Quantile matching was applied to determine the relationship between surgical and TAVI valve sizes in aortic stenosis patients.
The resulting linear regression provides a more accurate estimation of this 'upsizing' and with the following resulting relationship:

TAVI size (mm) = (Surgical valve size x 1.5) - 8.5
In **smaller annuli**, this **upsizing is approximately 3%** whereas in **larger annuli**, this can be **as high as 15%.**

PHASE 2:
ANALYSIS OF TAVI VALVE SIZING BASED ON CT ASSESSMENTS OF VALVE ANNULI IN AORTIC STENOSIS PATIENTS

Analysis of the degree of oversizing for each of the three Edwards valve sizes was calculated. A fair amount of overlap of the annulus size ranges between the three valve sizes was observed.

Sapien XT Valve Size	Maximum Over-sizing	Annulus Range	Minimum Over-sizing	Mean Over-sizing
Small	23	20.2 - 24.8mm	-7.3%	3.3%	13.9%
Medium	26	23.2 - 26.4mm	-1.5%	6.2%	12.1%
Large	29	25.5 - 29.0mm	0%	6.2%	13.7%

Since annuli were specifically determined for each patient prior to TAVI valve deployment and since evaluation of the distribution curves for the perimeter-derived annuli and the deployed TAVI Edwards Sapien XT valve sizes showed equivalent kurtosis, no quantile matching was required.

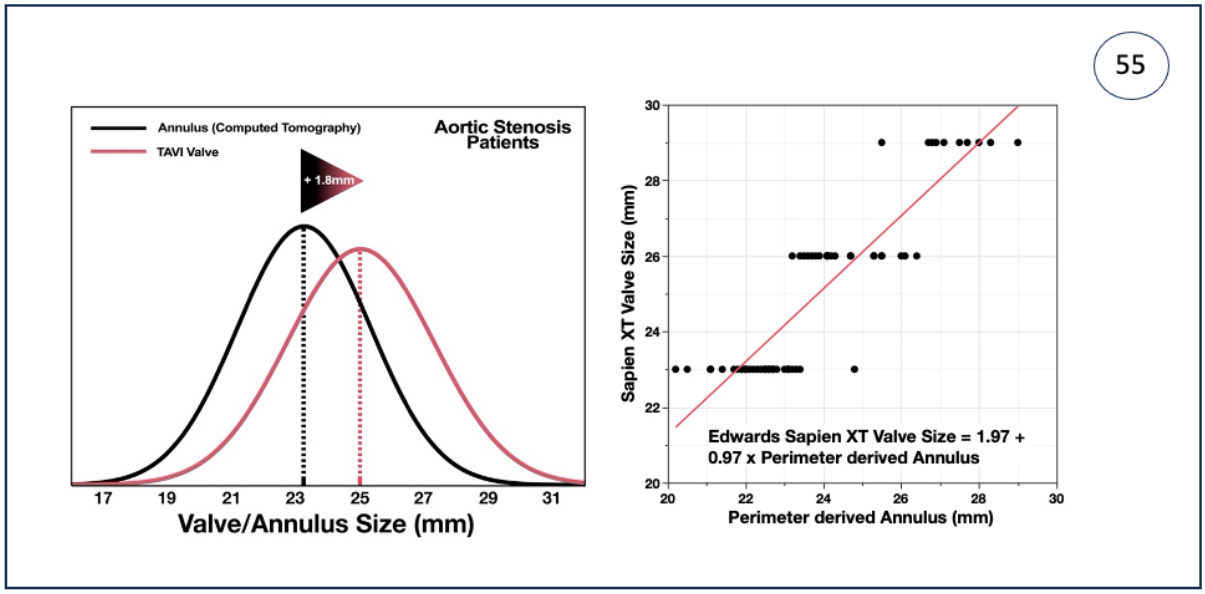


***Figure 55**: **(left)** The difference in the mean valve/ annulus sizes was shown to be 1.8mm **(right)**. A more accurate relationship was provided through linear regression between the CT-based perimeter-derived annulus sizes and Edwards Sapien XT valve sizes.*

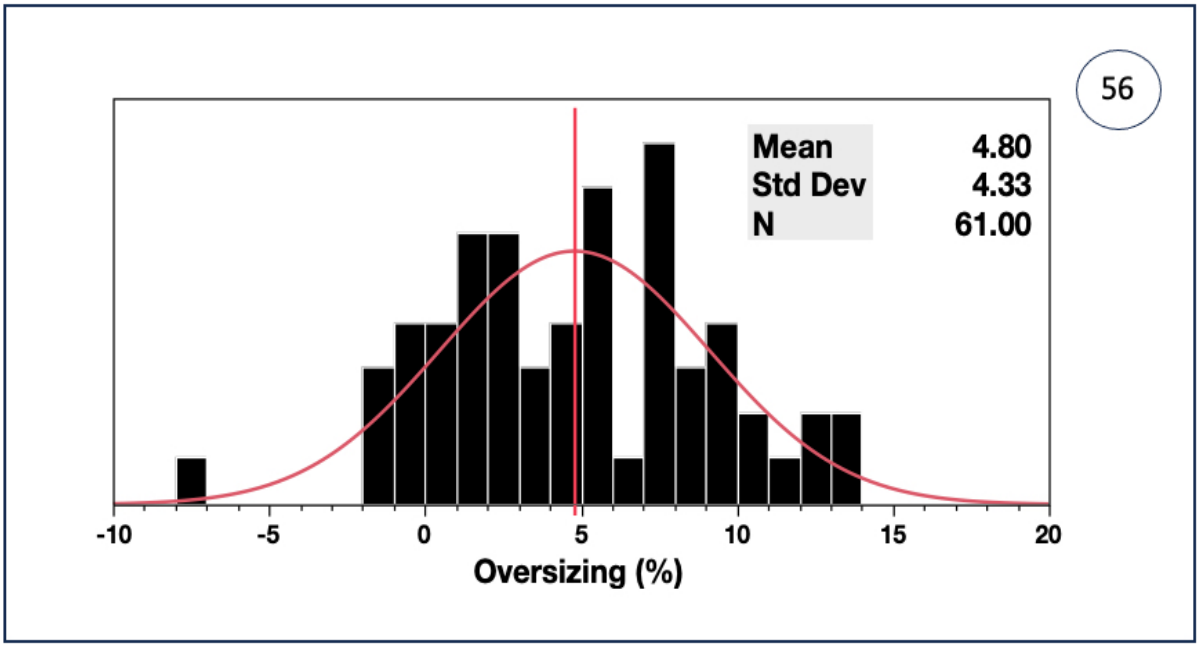


***Figure 56:** Assessment of the degree of oversizing of the deployed TAVI valves in this cohort of aortic stenosis patients based on perimeter-derived annulus diameter is shown below (Groote Schuur Hospital Cohort):*

Evaluation of different upper tolerance intervals of oversizing was performed to afford a defined statistically based upper limit for oversizing, and thereby minimum annulus limit, for each valve size. A 75% tolerance interval (with 95% confidence) of oversizing was found to provide the best outcome with regard to both over- and even, as the analysis demonstrated, coincidentally acceptable under-sizing despite a lower tolerance interval not being sought.

These upper tolerances (indicated by green vertical lines) were determined to be 7.9%, 10.7% and 11.8% for 23mm (small), 26mm (medium) and 29mm (large) Edwards Sapien XT valve sizes respectively.

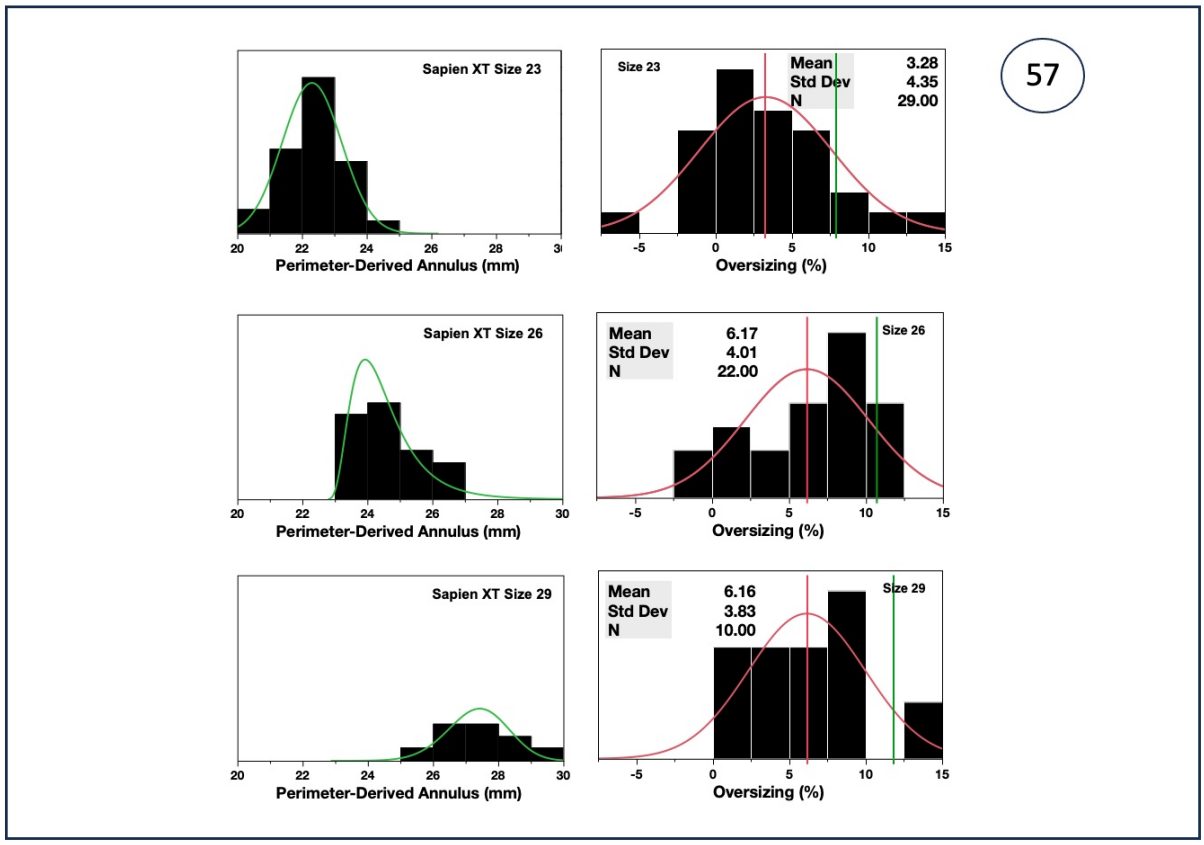


Figure 57: (left) *The fitted continuous distribution is Johnson SI.* ***(right)*** *The fitted continuous distribution is Normal. Also shown is 75% (95% Confidence) Upper Tolerance Interval (green vertical line)*

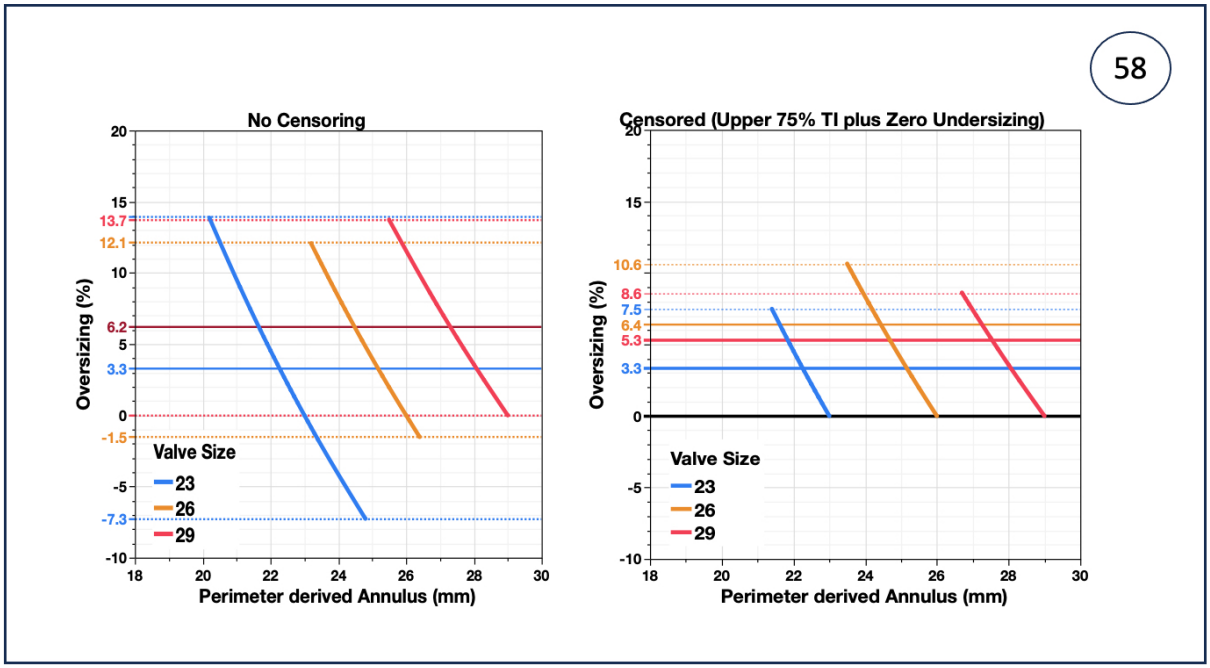


Figure 58: *The over- or under-sizing extent is shown against the associated perimeter-derived annulus sizes for the three Sapien XT valve sizes implanted ("No Censoring") and following censoring of cases where over-sizing exceeded these 75% upper tolerance limits or where under-sizing occurred ("Censored").*

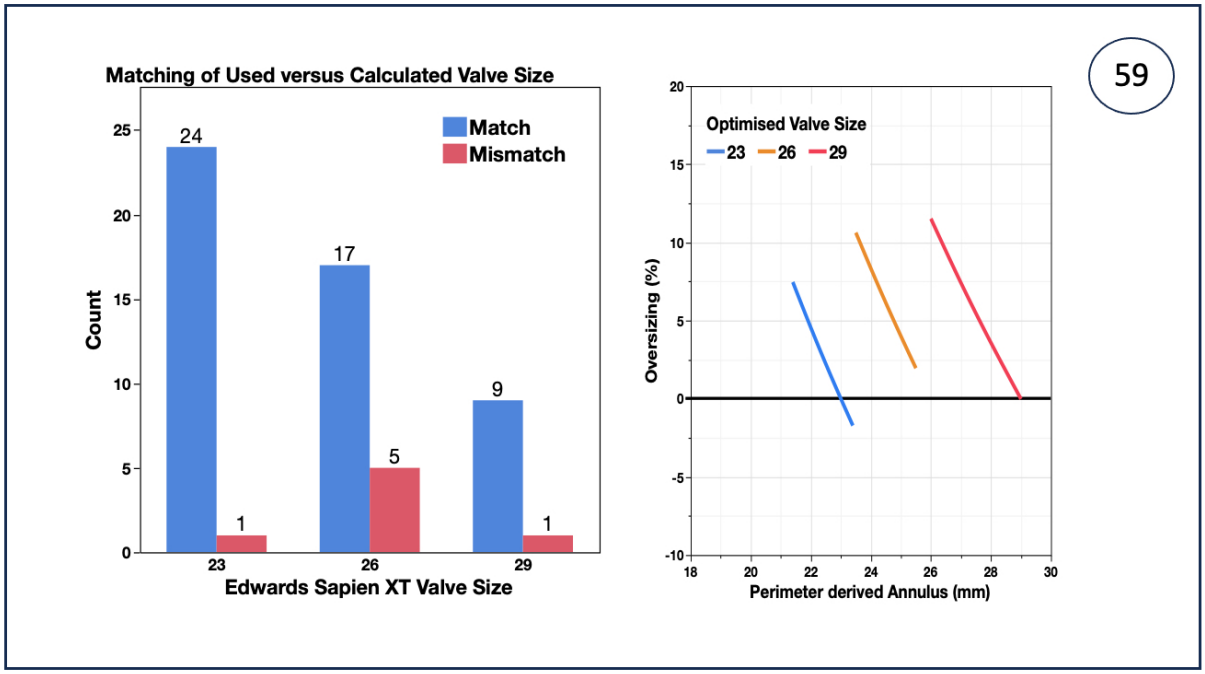


Figure 59: *Based on these theoretical considerations for valve size assignments, seven out of 57 valves (12.3%) were declared to be 'mismatched' based purely on sizing considerations alone (left). It is recognized that the extent and distribution of mineralization will likely have affected the choice of valve size. Optimizing, that is hypothetically reassigning, 'mismatched' Sapien XT valve sizes based on this 75% Upper Tolerance Interval, but not applying the zero under-sizing rule or a lower tolerance, achieved the outcome on the right: Following theoretical reassignment of the seven 'mismatched' valves, over-sizing was automatically limited to the selected over-sizing limits set by the upper 75% tolerance interval and only the small valve size was under-sized, maximally by less than 2%.*

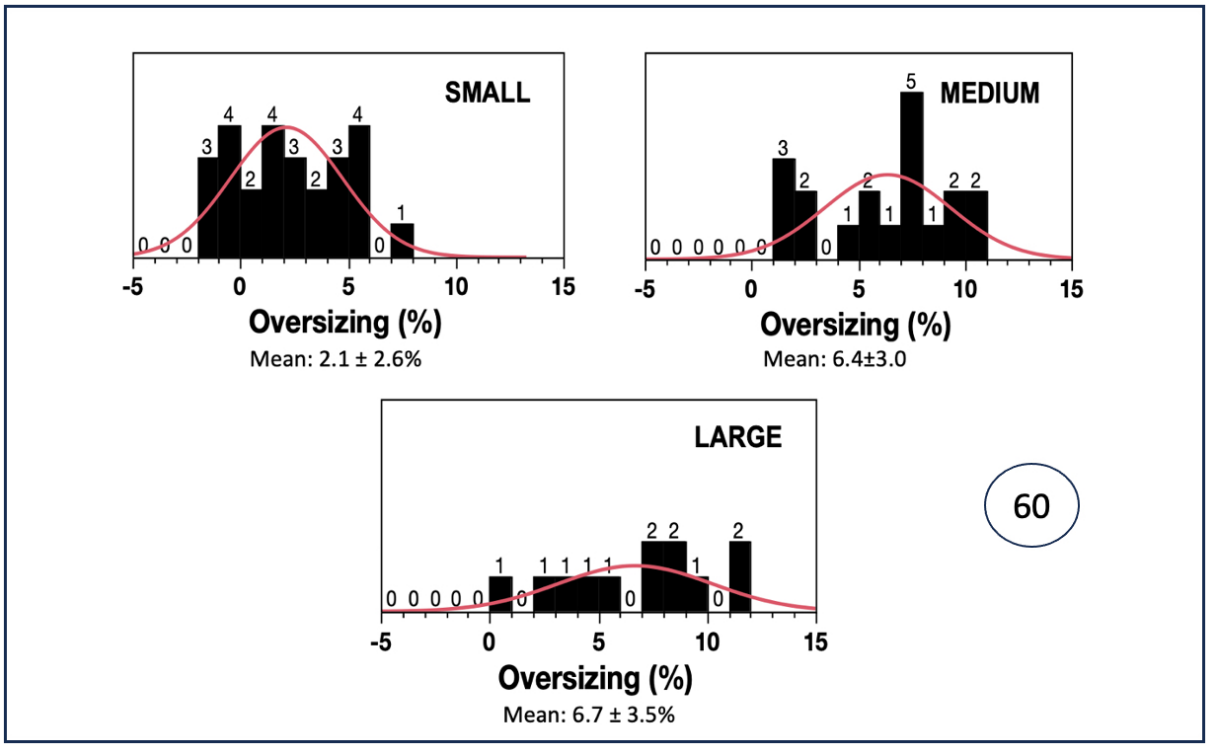


Figure 60: *Distribution of oversizing for each valve size following reassignment with counts being shown above each bar.*

In summary, a 75% upper tolerance limit for oversizing means that the most extreme quarter of oversized valves was censored. By doing this, **size gaps for which no TAVI existed opened up** between the 26mm and the 29mm TAVIs.

PHASE 3: EXTRAPOLATION OF STRAIT ACCESS TECHNOLOGY (SAT) VALVE SIZES TO ANNULI OF PATIENTS WITH CALCIFIC, DEGENERATIVE AORTIC STENOSIS

To determine the useable ranges for the SAT TAVI valve set, the maximum annulus for each valve was initially understood to correspond to the respective intended valve sizes to avoid under-sizing.

This approach was later modified to permit increasing extents of under-sizing with diminishing valves, and therefore annulus sizes to accommodate the exaggerated constriction caused by mineralization in the smaller annuli in the aortic stenosis scenario.

Actual valve sizes measured at the nadir-waist as the narrowest point were given as follows:

SAT Valve	Size	Intended Size
Small	23	21.7mm
Medium	26	24.3mm
Large	29	27.5mm

To determine the minimum annulus for corresponding SAT valve sizes, the same maximal oversizing limits based on the 75% Upper Tolerance Intervals used for the Sapien XT Valves were again applied, that is 7.9%, 10.7% and 11.8% respectively.
This corresponds to annulus sizes 20mm, 21.7mm and 24.3mm for the small, medium and large SAT valve sizes respectively.

The fraction of the three SAT valve sizes was calculated by estimating the probability from the normalized curve Z-Scores for the perimeter-derived annulus data and is as follows:

SAT Valve	Range	Fraction
Small	20.0 - 21.7mm	13.8%
Medium	21.7 - 24.3mm	43.3%
Large	24.3 – 27.5mm	38.8%
Total		**95.9%**

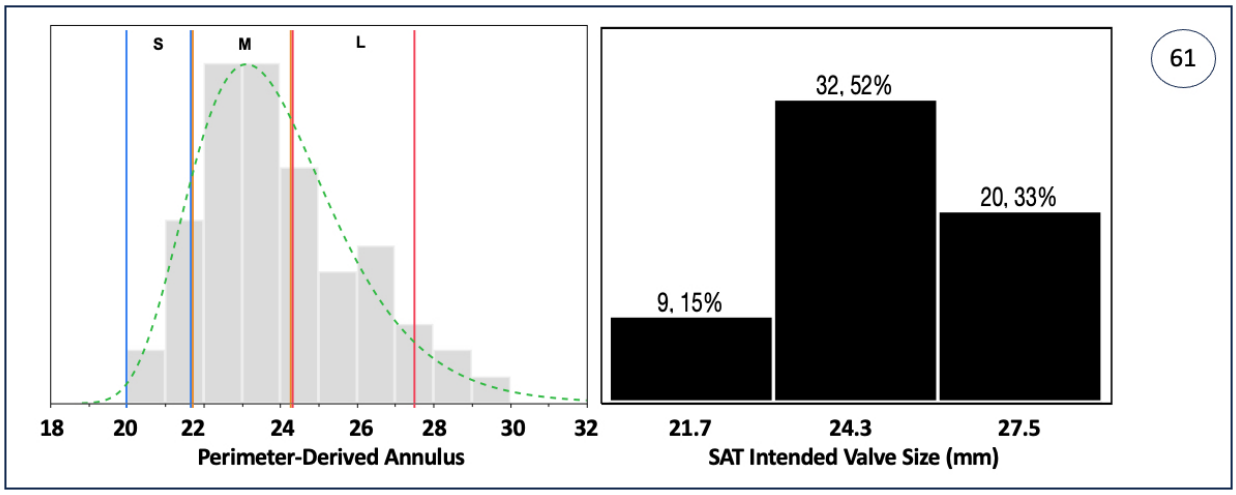


Figure 61: (Left) *These three ranges perfectly align with each other while accommodating the rules of no under-sizing and not exceeding the 75% Upper Tolerance Interval for our perimeter-derived annulus size based on the Edwards Sapien XT valve experience.* ***(Right)*** *Alternatively,*

SAT valves were assigned based solely on application of the upper 75% tolerance intervals determined from the Edwards Sapien XT data but ***not the zero under-sizing rule****.*

Only 9 (15% of cases) small valves (size 21.7mm) were automatically assigned, whereas 32 (52% of cases) medium size (24.3mm) valves and 20 (33% of cases) large size valves were assigned.

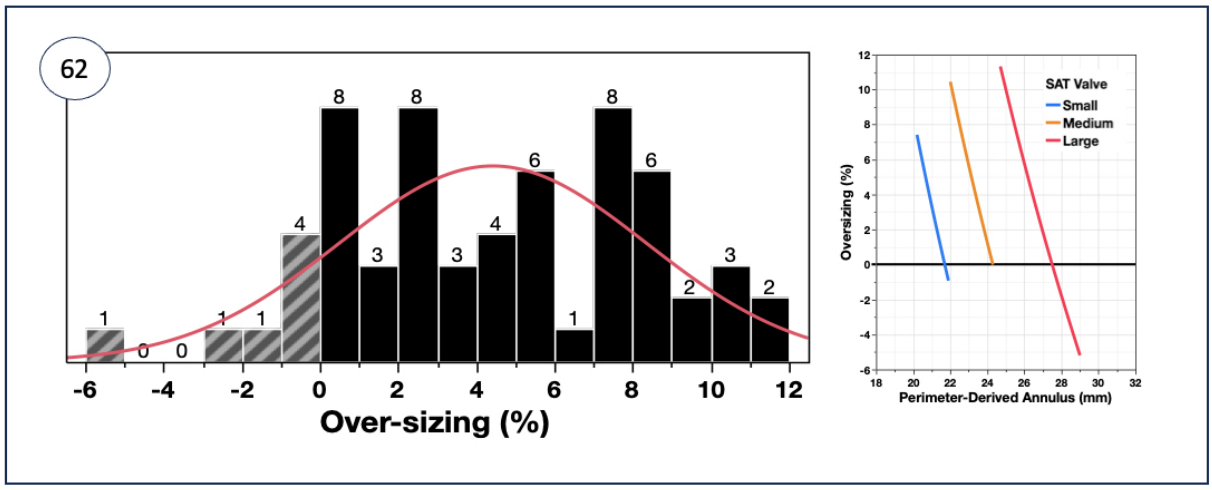


Figure 62: ***(Left)*** *The oversizing extent was calculated, giving the following distribution: Only 7 valves were under-sized (mean: 1.8 ± 1.7%; median: 0.9%; maximum: 5.2% under-sized).* ***(Right)*** *Medium and Large SAT valve sizes therefore accommodated 85% of cases from the CT aortic stenosis TAVI patient cohort with maximally 5.2% under-sizing (mean of 2.6±1.9%; median 2.3% under-sizing in 4 cases) and a maximum of 11.3% over-sizing (mean: 5.5±3.4%; median: 5.3% over-sizing).*

Based on the aortic stenosis CT TAVI Data Set, the perimeter-derived annulus ranges were as follows:

Valve	**Intended Valve Size to Annulus Range**		**Refined to:**
Small	21.7mm.	20.2 – 21.9mm	20.2 – 21.9mm
Medium	24.3mm	22.0 – 24.3mm	22.0 – 24.6mm
Large	27.5mm	24.7 – 29.0mm	24.7 – 28.0mm

This slight adjustment is to avoid a small gap between the annulus range for medium and large valves and to limit under-sizing to 2% in the large valve subgroup.

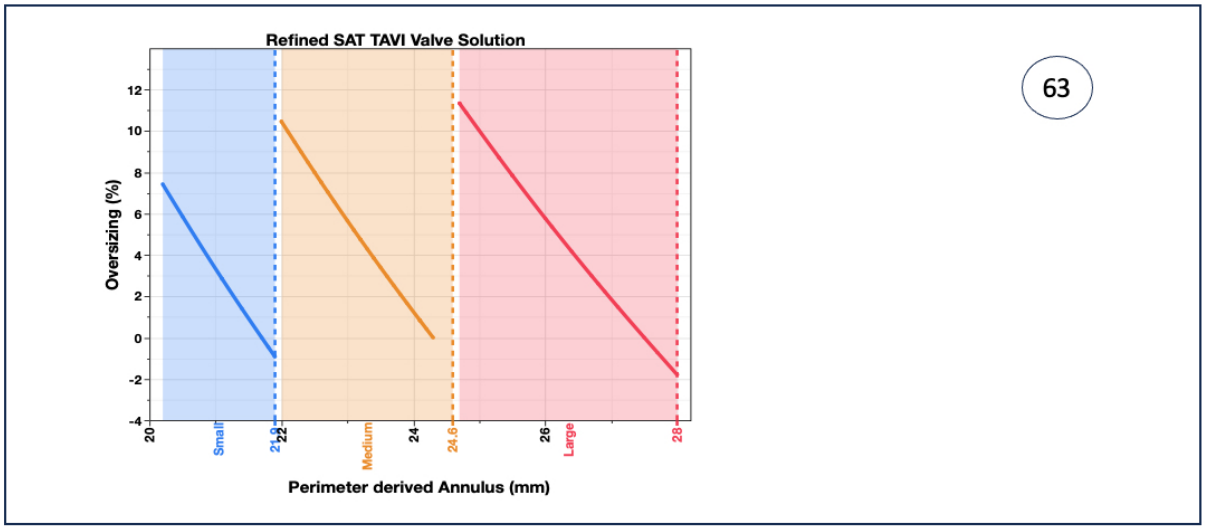


Figure 63: *The extent of over-sizing of this refined solution is well within that experienced with Edwards Sapien XT TAVI valve implantation in Aortic Stenosis patients (CT Data Set) and with minimal under-sizing.*

Simulated Aortic Stenosis Data Set

Due to the sampling error naturally associated with a limited set of patient data, fine adjustment of oversizing limits is dependent on the continuous distribution of annulus sizes available for analysis. To overcome this limitation, a simulated data set was produced based on the distribution curve best representative of the patient cohort.

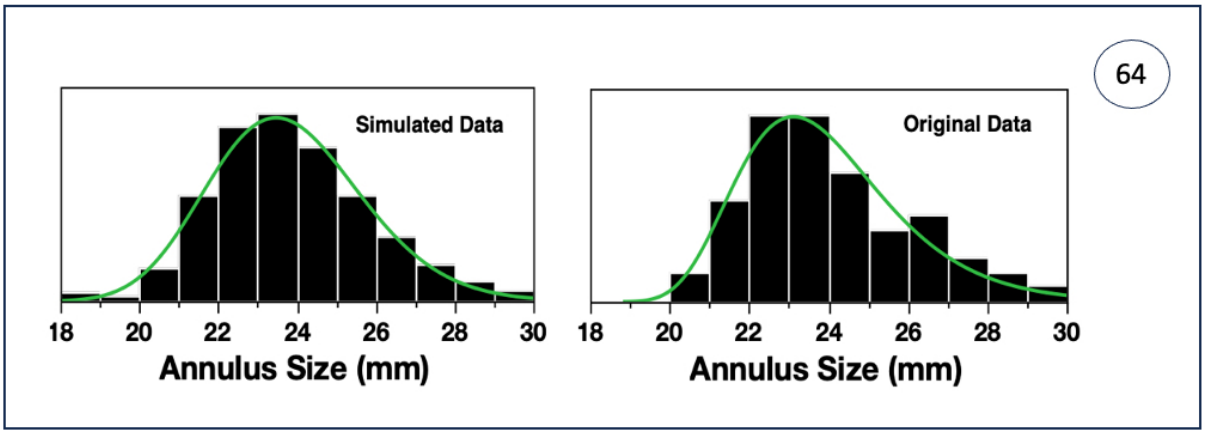


Figure 64: *A Johnson SI distribution curve was fitted to the original data set and its probability distribution used to generate a data set with 0.1mm annulus diameter increments from 18 to 30mm (extending slightly beyond the range of CT-based Perimeter-Derived Annulus sizes of 20.2 to 29.0mm).*

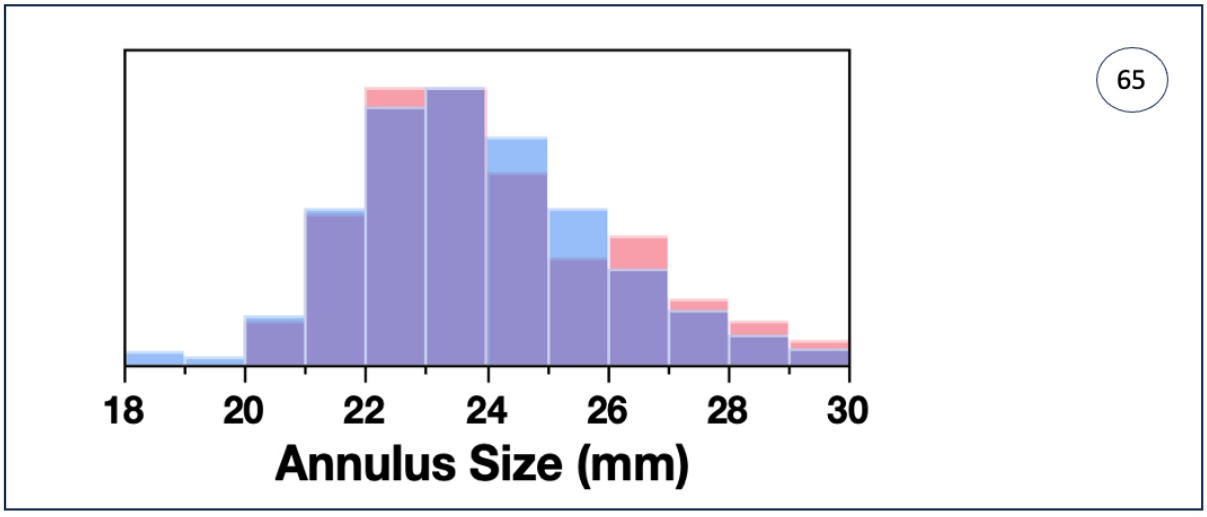


Figure 65: *The Shapiro-Wilk W test confirmed an acceptable goodness of fit (p=0.78). This data set provides a smoother transition across the set of annulus sizes. Over-layering these two distributions confirms the general similarity of the two distributions.*

Variable over-sizing approach

In contrast to the previous sizing allocation which relied on an identical 75% upper tolerance constraint for each valve size, a variable upper constraint approach was now investigated where constraints were adjusted empirically for each valve in turn.

Four SAT valves sizes were defined (the X-Large size was added to accommodate the larger annuli which were not, in turn, accommodated by the Large valve size):

VALVE	INTENDED SIZE
Small	21.7mm
Medium	24.3mm
Large	27.5mm
X-Large	30.1mm

Hypothetical SAT valve sizes were calculated using the following formula: where S, M, L and XL represented variables denoting oversizing limits.

$$\text{If}\left(\left(\frac{30.1}{\text{Annulus Size (mm)}}\right)\bullet 100-100\le \text{XL}\Rightarrow 30.1,\ \text{else}\Rightarrow \text{If}\left(\left(\frac{27.5}{\text{Annulus Size (mm)}}\right)\bullet 100-100\le \text{L}\Rightarrow 27.5,\ \text{else}\Rightarrow \text{If}\left(\left(\frac{24.3}{\text{Annulus Size (mm)}}\right)\bullet 100-100\le \text{M}\Rightarrow 24.3,\ \text{else}\Rightarrow \text{If}\left(\left(\frac{21.7}{\text{Annulus Size (mm)}}\right)\bullet 100-100\le \text{S}\Rightarrow 21.7,\ \text{else}\Rightarrow \text{else clause}\right)\right)\right)\right)$$

In contrast to methods used previously, this empirical approach specifically made adjustments to these variables in the sequence S, M, L, XL while each time simultaneously examining the ratio of over-sizing to under-sizing numbers, over-sizing and under-sizing extent and fractional distribution of allocated valve sizes.

Adjustments to the ‘S’, ‘M’, ‘L’ and ‘XL’ variables in turn affected the over-sizing extent and therefore, in the case of ‘M’, ‘L’ and ‘XL’, also the transition between allocation of the respective valve sizes.

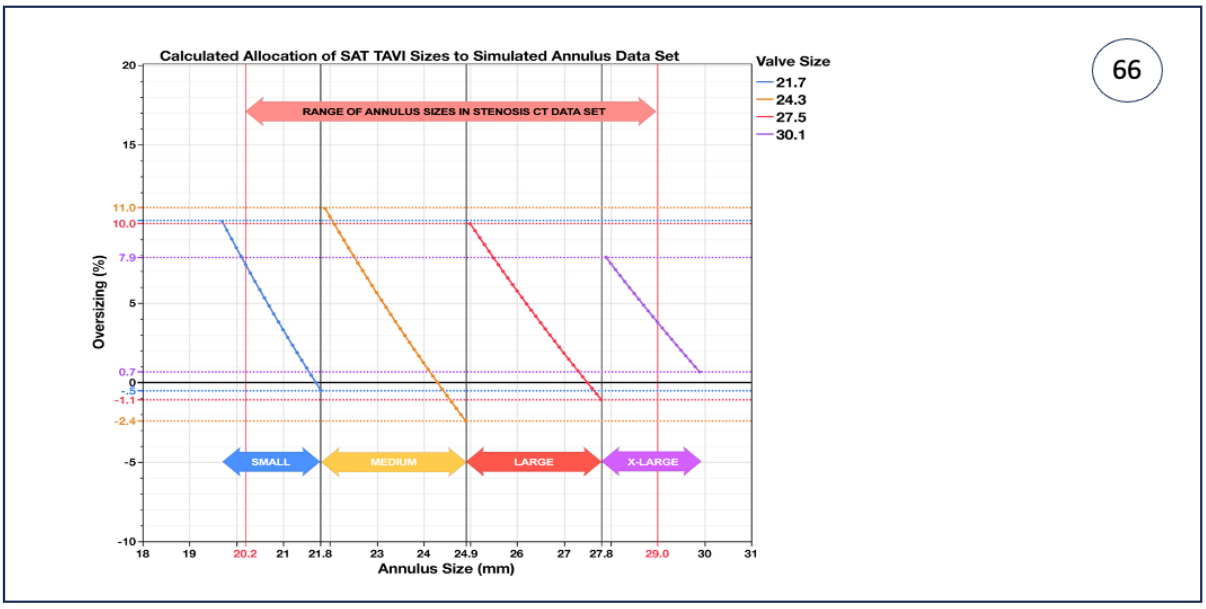


Figure 66: *Under-sizing aimed at envisaged amounts of 25% for small, 15% for medium; 5% for large and 0% for extra-large to accommodate the increased influence of mineralization with decreasing annulus size. Setting the variables as follows:* ***S=11%; M=11%; L=10%; XL=8%***

This provided an optimal solution which limited over-sizing to less than 11% and under-sizing to less than 2.4% as well as approximating the defined under-sizing ratios.

The mean annulus ranges for the simulated set allied to SAT TAVIs were as follows:

SAT TAVI	Actual Size	Minimum An	Maximum An	Mean	StdDev
Small	21.7mm	19.7mm	21.8mm	21.2mm	0.5mm
Medium	24.3mm	21.9mm	24.9mm	23.4mm	0.9mm
Large	27.5mm	25.0mm	27.8mm	26.0mm	0.8mm
X-Large	30.1mm	27.9mm	29.9mm	28.7mm	0.6mm

Over-sizing extent:

SAT TAVI	Actual Size	Over-sizing Minimum	Over-sizing Maximum	Over-sizing Mean	Over-sizing StdDev
Small	21.7mm	0.5%	10.2%	3.0%	2.2%
Medium	24.3mm	0.4%	11.0%	5.4%	3.1%
Large	27.5mm	0.4%	10.0%	6.1%	2.8%
X-Large	30.1mm	0.7%	7.9%	5.1%	2.1%

Under-sizing extent:

SAT TAVI	Actual Size	Under-sizing Minimum	Under-sizing Maximum	Under-sizing Mean	Under-sizing StdDev
Small	21.7mm	0%	0.5%	0.2%	0.2%
Medium	24.3mm	0%	2.4%	1.2%	0.8%
Large	27.5mm	0%	1.1%	0.5%	0.4%
X-Large	30.1mm	-	-	-	-

Whereas a 75% upper tolerance limit was initially defined for the hypothetical reassignment of the Edwards Sapien XT valves, the approach for the SAT valve was a variable upper tolerance to accommodate each valve size independently and permit increasing under-sizing with decreasing annulus size for the respective annulus ranges.

Reverse calculation revealed tolerance limits as follows:

SAT TAVI	Actual Size	Over-sizing Limit	Upper Tolerance
Small	21.7mm	11%	94%
Medium	24.3mm	11%	94%
Large	27.5mm	10%	89%
X-Large	30.1mm	8%	85%

Ultimately, it is not so much the tolerance limits chosen, but rather the transition annulus sizes between the valve size categories identified by the annulus ranges shown in red on the page above.

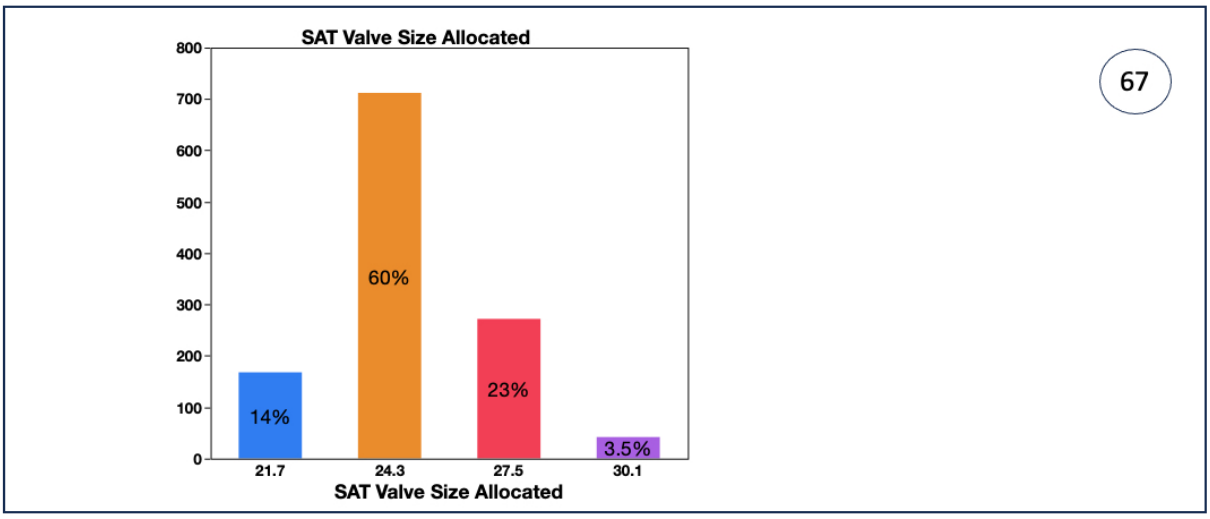


Figure 67: *Since the annulus ranges are based on data simulated from the distribution of actual clinical TAVI aortic valve replacement, they provide the most accurate estimate of SAT Valve distribution in aortic stenosis patients based on perimeter-defined annulus sizes and therefore a conservative estimate of their distribution in rheumatic patients with one caveat, namely that under-sizing is contraindicated.*

For a conservative estimate of size distributions in rheumatic patients therefore, the variables used in prediction of valves size were again modified empirically as follows:

S=11%; M=12%; L=14%; XL=10%

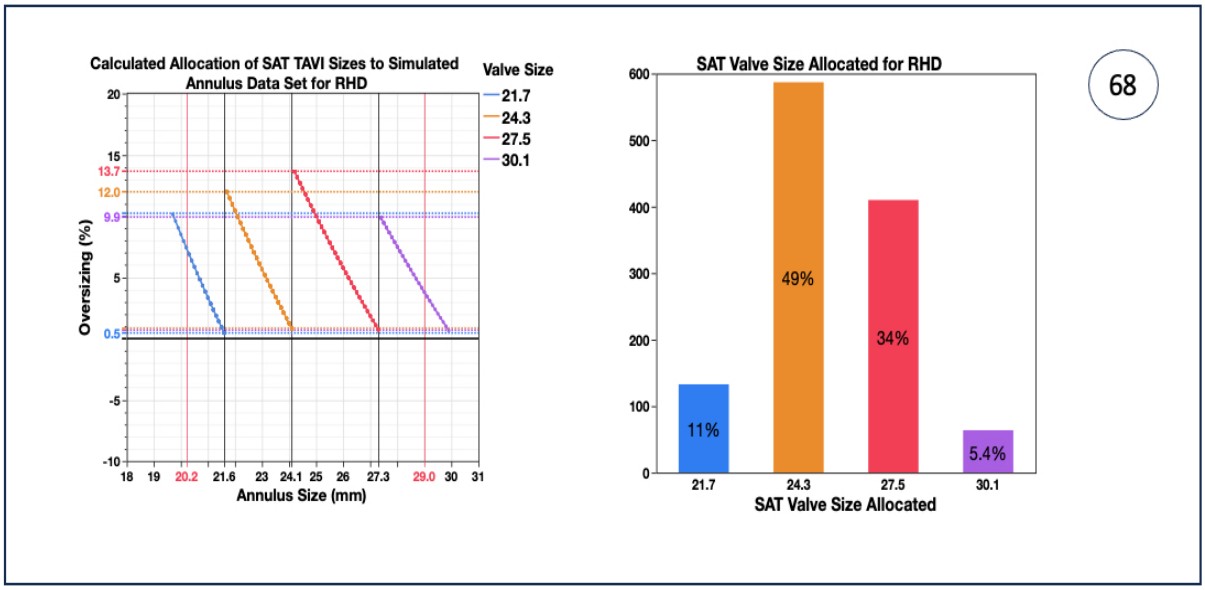


Figure 68: *Using the above chosen empirically modified variables, under-sizing was avoided but produced up to 13.7% over-sizing in the case of the large valve size and up to 12.0% over-sizing in the medium size valve.*

The only way to overcome this would be to modify the intended valve sizes (a hypothetical suggestion).

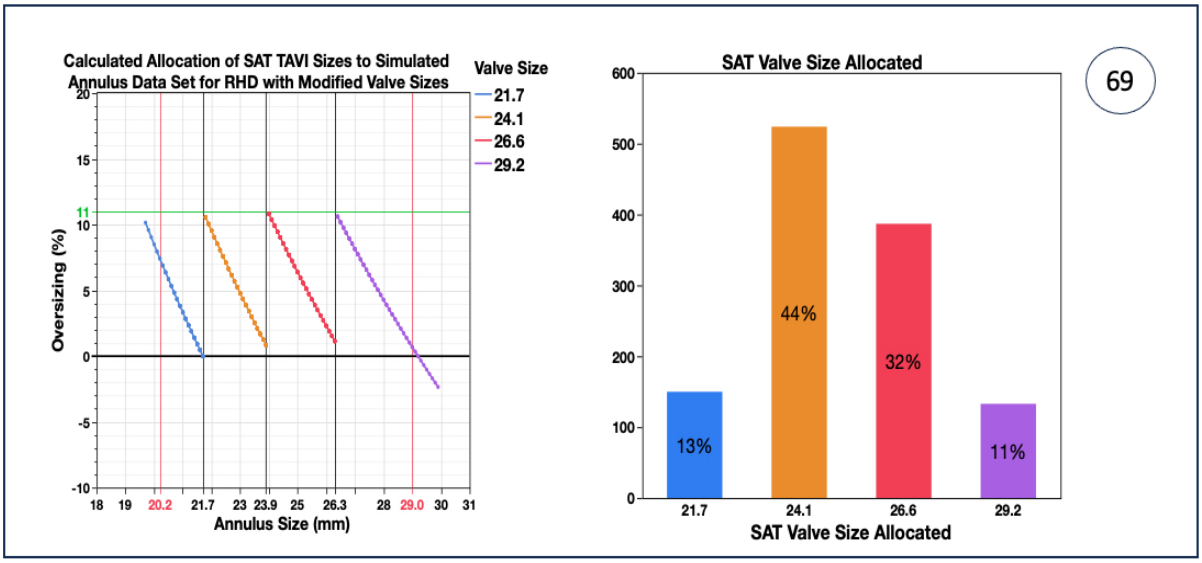


Figure 69: *By setting the over-size variables all to 11% and adjusting the valve sizes as follows: Small 21.7mm; Medium24.1mm; Large 26.6mm; X-Large29.2mm all under-sizing was avoided, provided the 29mm is seen as the largest treatable annulus diameter (this exceeds the largest annulus in the stenosis data set), and over-sizing was limited to ≤11%.*

PHASE 4: HYPOTHETICAL APPLICATION OF THE RELATIONSHIP BETWEEN THE DISTRIBUTION OF SURGICAL VALVE SIZES AND ANNULUS SIZE IN AORTIC STENOSIS PATIENTS TO THE SURGICAL SIZES IN RHEUMATIC PATIENTS TOWARDS DETERMINING THE ANNULUS SIZE DISTRIBUTION IN RHEUMATIC PATIENTS WITH AORTIC REGURGITATION

Intent:

For the purpose of hypothesizing the distribution of annulus sizes in rheumatic patients to permit the estimation of over-sizing associated with TAVI valve deployment in such patients and where only surgical valve size data in the absence of CT data was available in our cohort, an approximation was sought based on applying the relationship between surgically deployed valve sizes in non-rheumatic aortic stenosis patients and their CT-based annulus size distribution, to the distribution of surgical valves implanted in the rheumatic cohort with aortic regurgitation.

Methodology:

For determination of a conversion formula between Surgical AS and Perimeter-based Annulus data:

- Quantile for quantile (10%; 20%; 30%; etc.) was matched or density curve values (rounded to one decimal point) generated above between the two data sets to marry matching annulus and valve sizes and thereby to permit combination of the above two data sets
- A regression analysis between the surgical and annulus size data was performed to arrive at the conversion formula (Surgical on abscissa and Annulus on ordinate axis)
- An appropriate distribution curve for rheumatic AR valve size data was fitted.

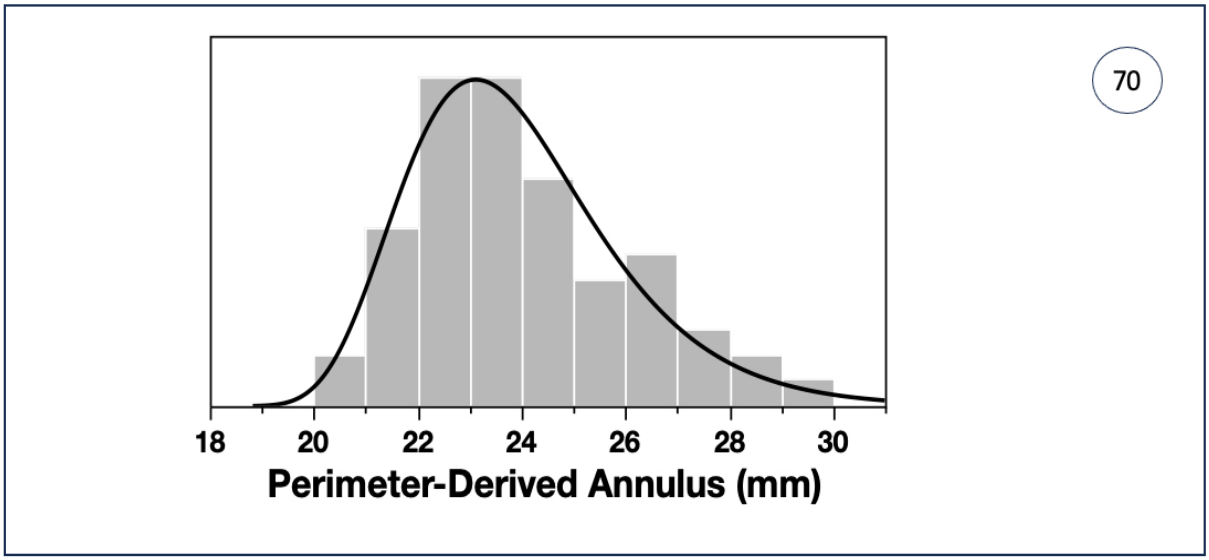


Figure 70: *A simulation data set matching density with valve size increments of 0.1mm (16.0 to 32.0mm) was created and a conversion formula between Surgical Prosthesis and Annulus size was applied to the rheumatic simulation set. The end result represents a conservative estimate of annulus distribution for rheumatic AR patients versus degenerative AS patients.*

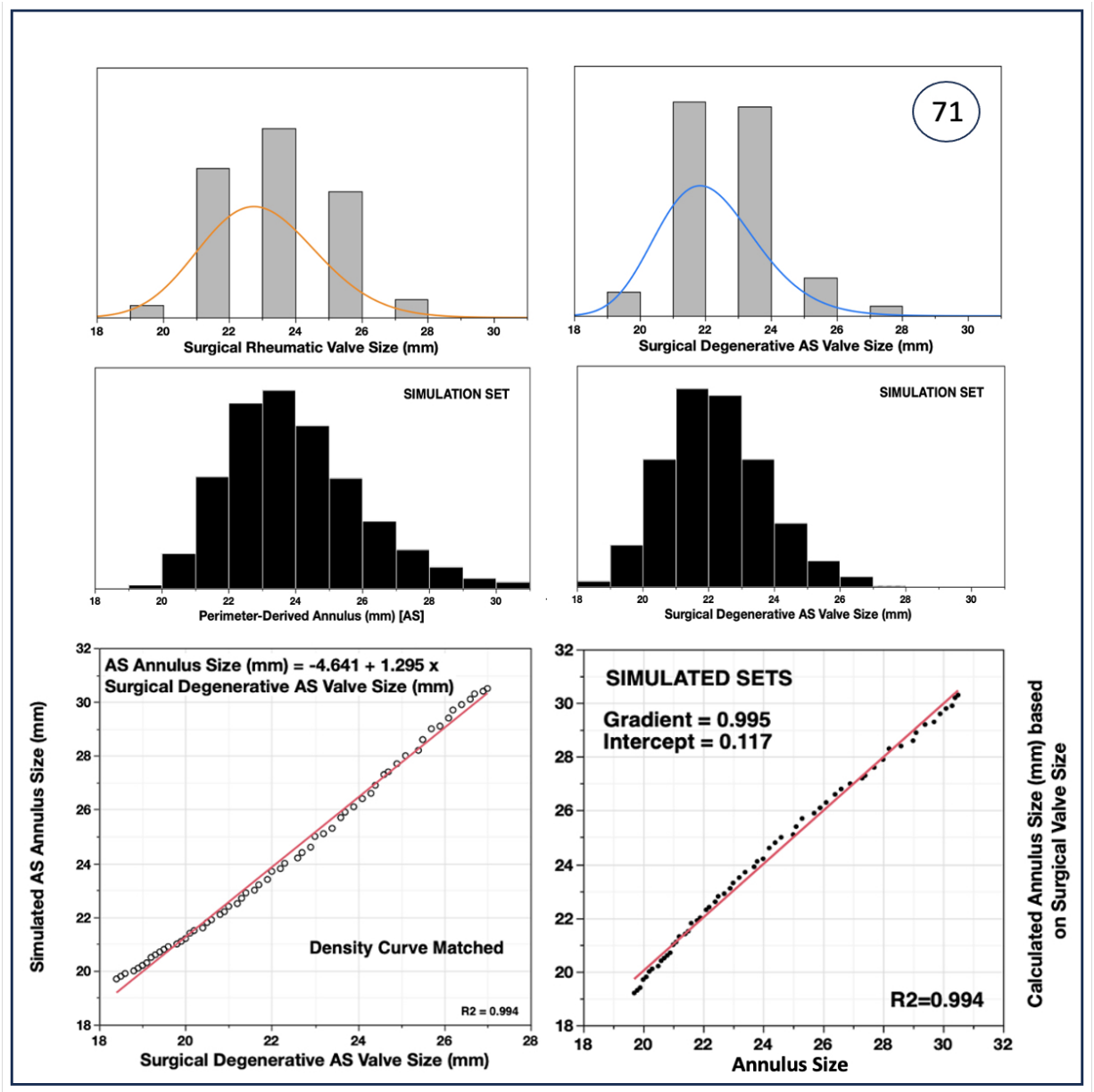


Figure 71: *Conversion from the simulated surgical size data using this linear relationship provided a distribution identical to that of the simulated annulus size data with near identity, confirming the accuracy of that conversion.*

The next step was to transform the surgically implanted valve sizes used in rheumatic AR patients into matching annulus sizes based on the relationship between the surgically implanted valves and the annulus sizes determined in aortic stenosis patients for which a relationship was now available.

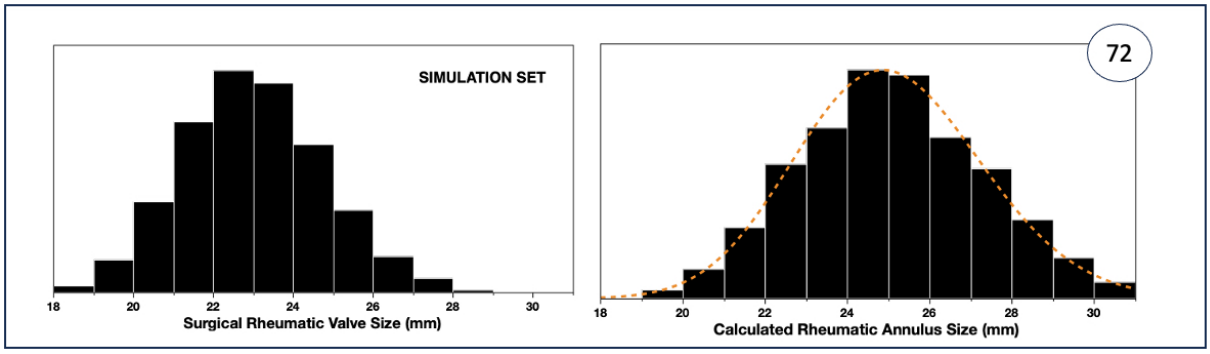


Figure 72: *the surgical valve size distribution curve for rheumatic AR patients was first used to establish a simulated valve size data set* ***(left)****. This simulated set was then transformed based*

on the above-mentioned relationship to produce a calculated annulus size distribution for patients with rheumatic AR. ***(right)***

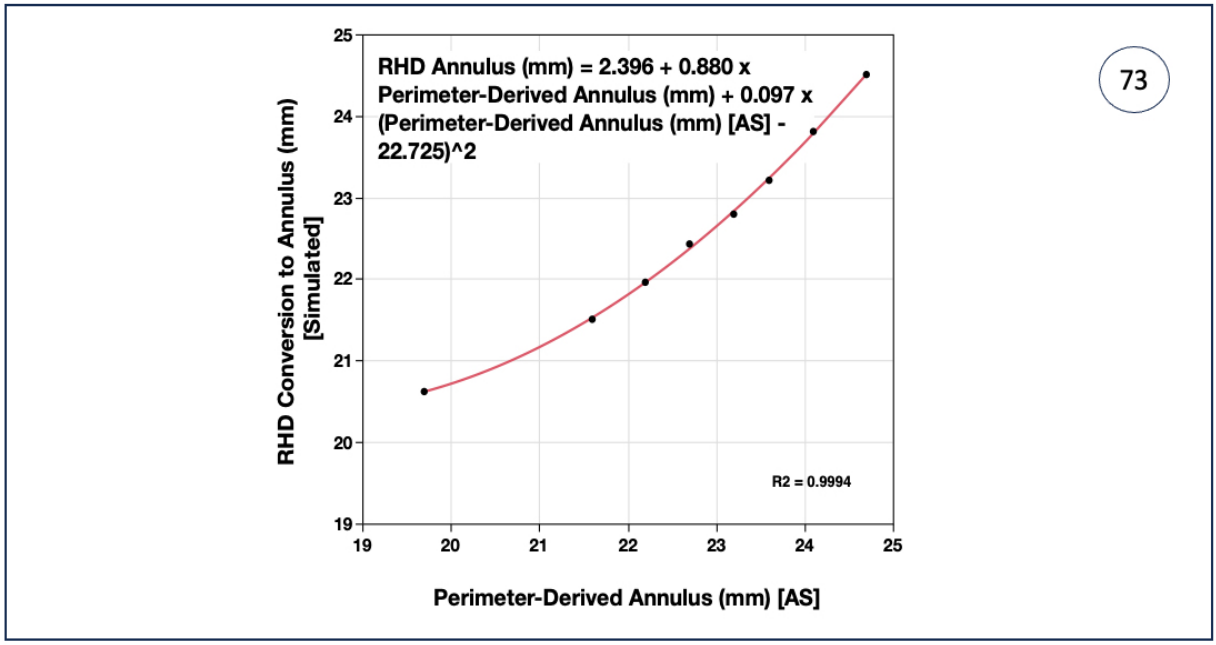


Figure 73: *Subsequent quantile matching with the simulated perimeter-derived data set for aortic stenosis patients to permit investigation of the relationship between surgical valve sizes implanted in rheumatic patients and the CT-based diameter was performed.*

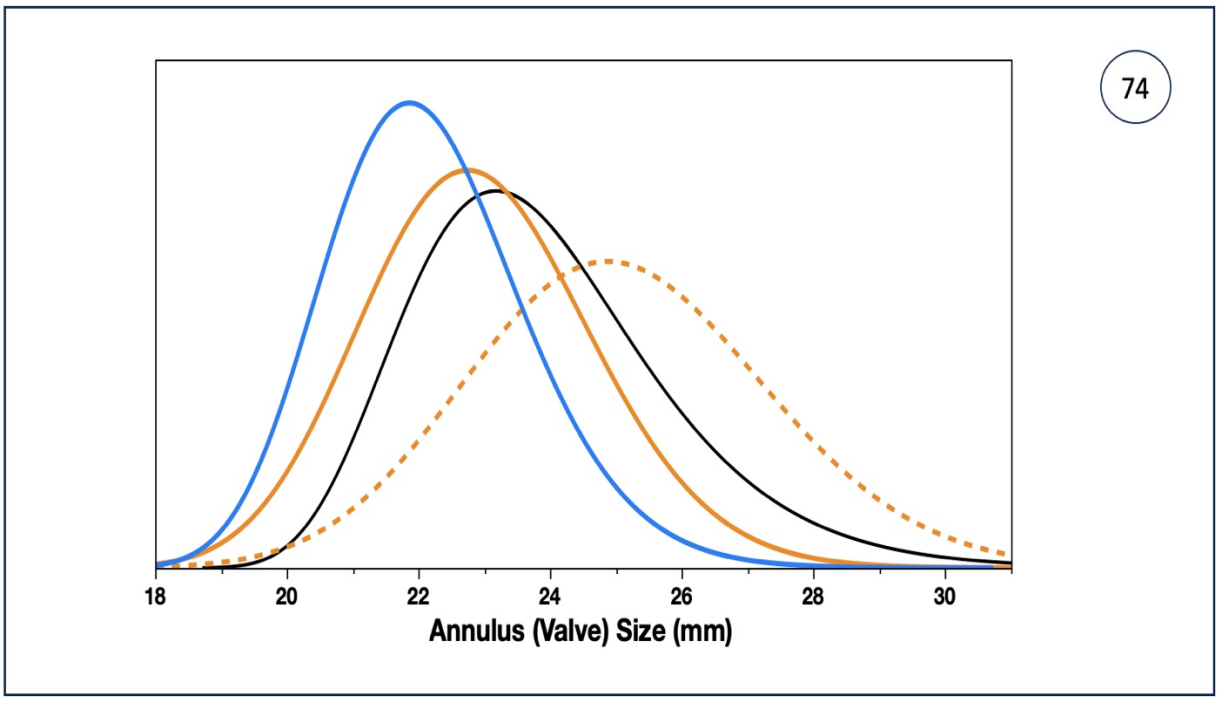


Figure 74: *shows the distribution curves for surgical valves in degenerative aortic stenosis (AS) (blue) and the corresponding perimeter-derived annulus sizes (black) as well as the distribution curves for surgical valves in patients with rheumatic AR (orange) and their anticipated annulus size (dashed orange). This latter curve represents in rheumatic AR the equivalent of the distribution of perimeter-derived annulus sizes of aortic stenosis patients. Its position lies to the right of the annulus distribution for stenosis patients (black) which is expected given the volume overload-remodelling in AR.*

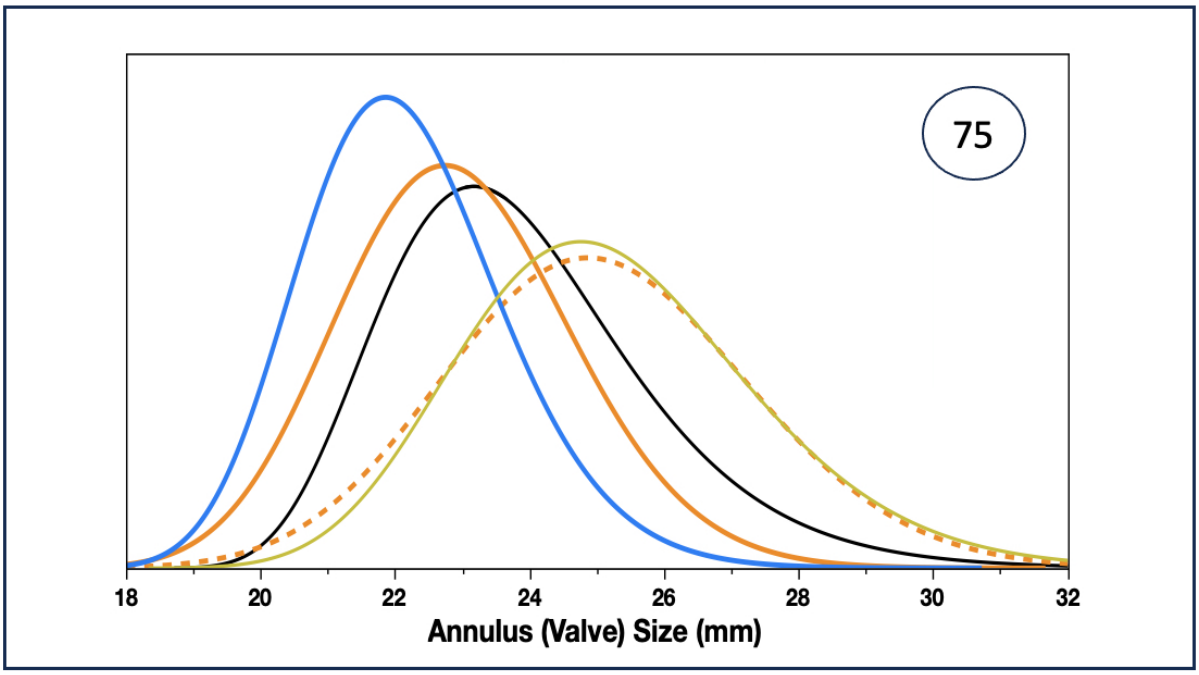


Figure 75: *additionally includes the hypothesized SAT TAVI size distribution curve (olive green) for AS annuli (black) highlighting the right-shift of TAVIs relative to the CT-based annulus size (bigger) versus the left-shift of surgically implanted valves (smaller).*

PHASE 5: EVALUATION OF THE EXTENT OF OVER-/UNDER-SIZING OF SAT TAVI VALVES AGAINST THE HYPOTHETICAL ANNULUS SIZES FOR A RHEUMATIC POPULATION AND THE APPLICATION OF PUBLISHED OVERSIZING ESTIMATES TO RHEUMATIC AR.

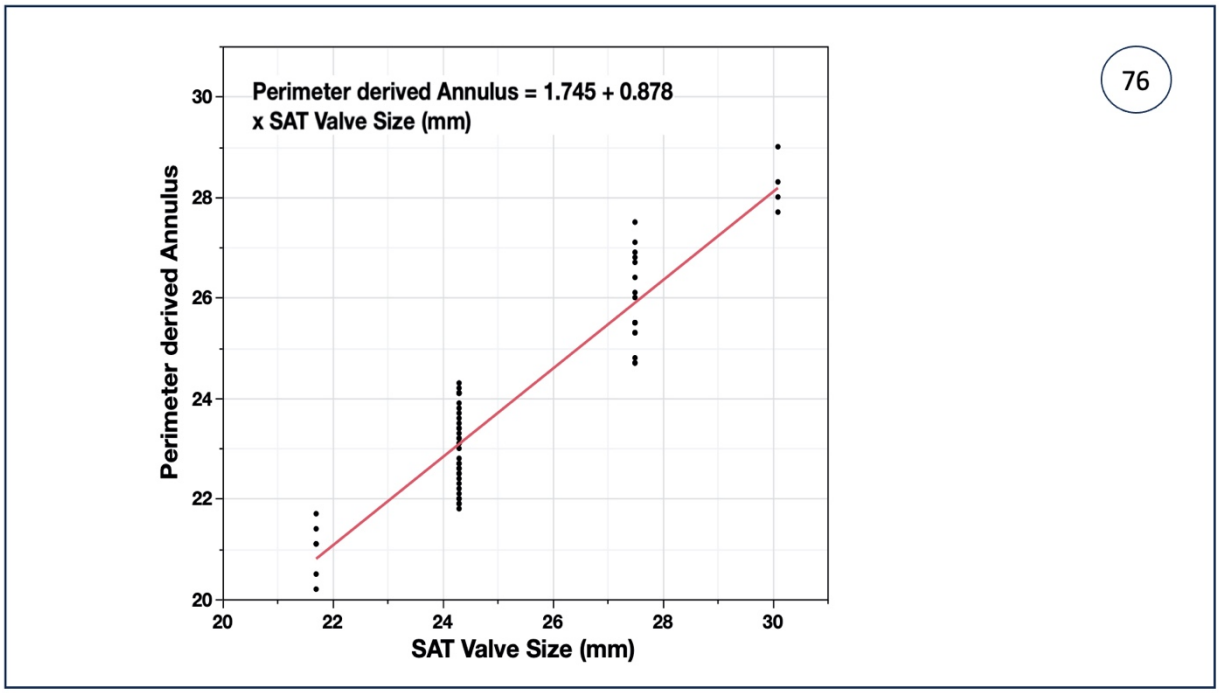


Figure 76: *Relationship provided by extrapolating the transition between CT-based Perimeter-Derived Annulus and the proposed SAT TAVI size distribution in* ***Aortic Stenosis*** *patients to the rheumatic annulus size distribution curve (orange dashed line).*

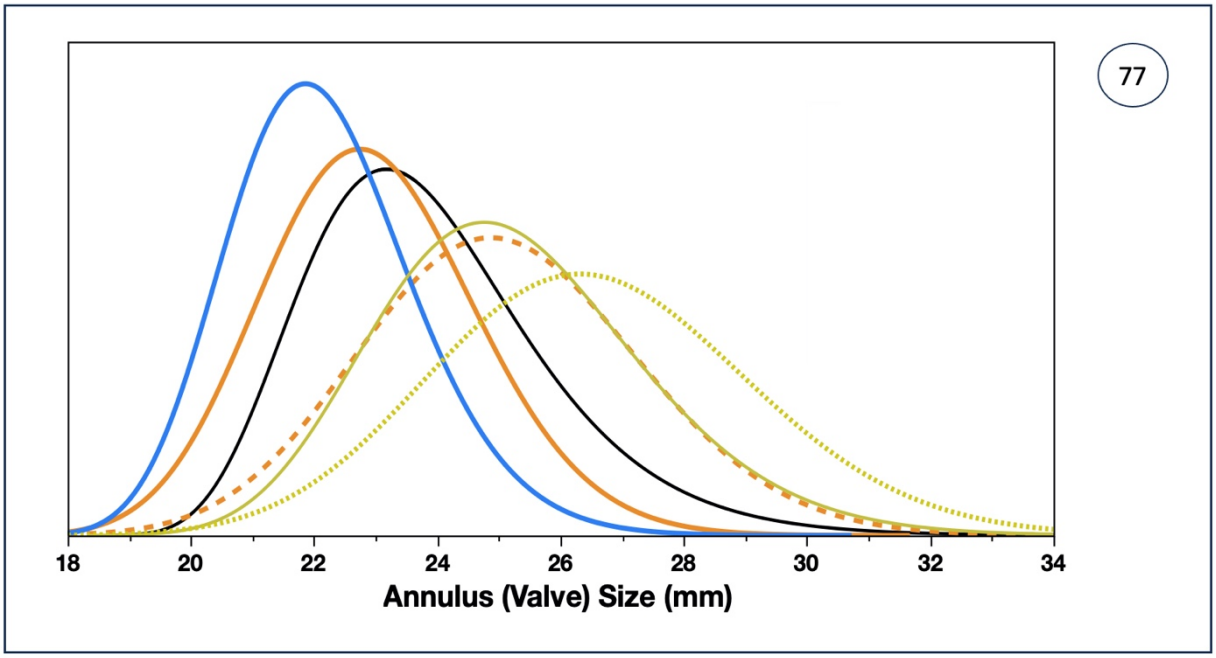


Figure 77: *Using the relationship depicted in figure 76 to convert the distribution of annuli of patients with* ***rheumatic AR*** *(dashed orange curve) allowed the calculation of a conservative estimate of SAT valve size distributions for rheumatic patients (dotted olive green).*

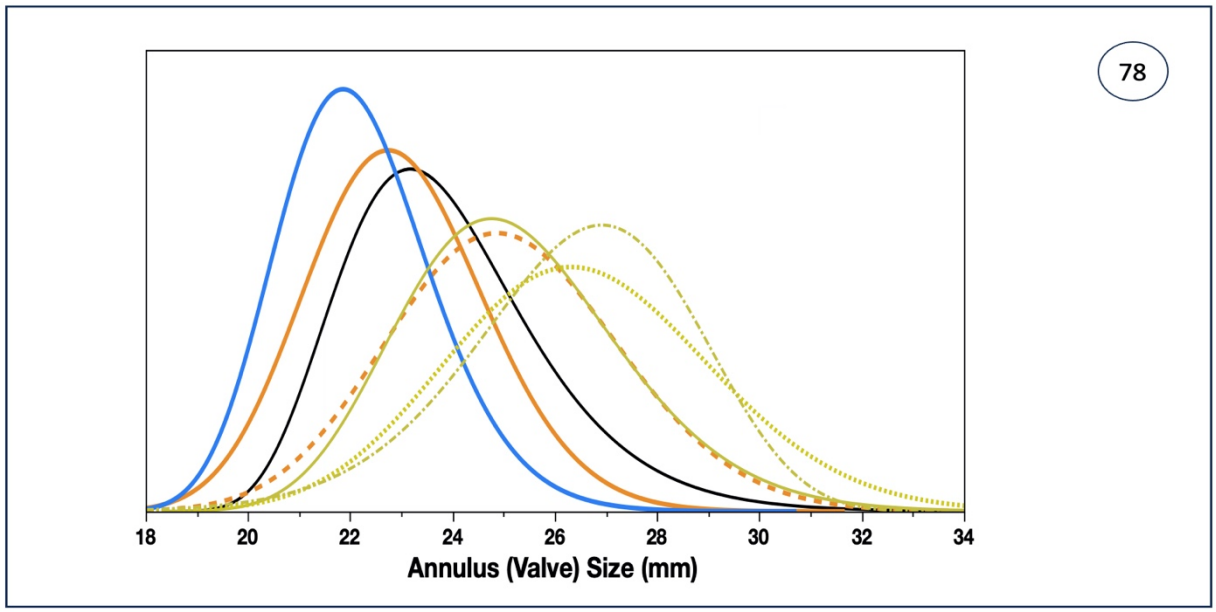


Figure 78: *Approaching this differently by reoptimizing the SAT Valve size allocations based on the new AR annulus distribution curve (dashed orange) with application of the zero-under-sizing rule and oversizing controlled to avoid dead zones (gaps) between valve sizes based on the constraints:* ***S=10%; M=11.4%; L=13%; XL=9%*** *The resulting SAT valve size distribution curve (****above:*** *dot-dashed olive green) is slightly right shifted compared to the more conservative SAT valve size curve (dotted olive green).*

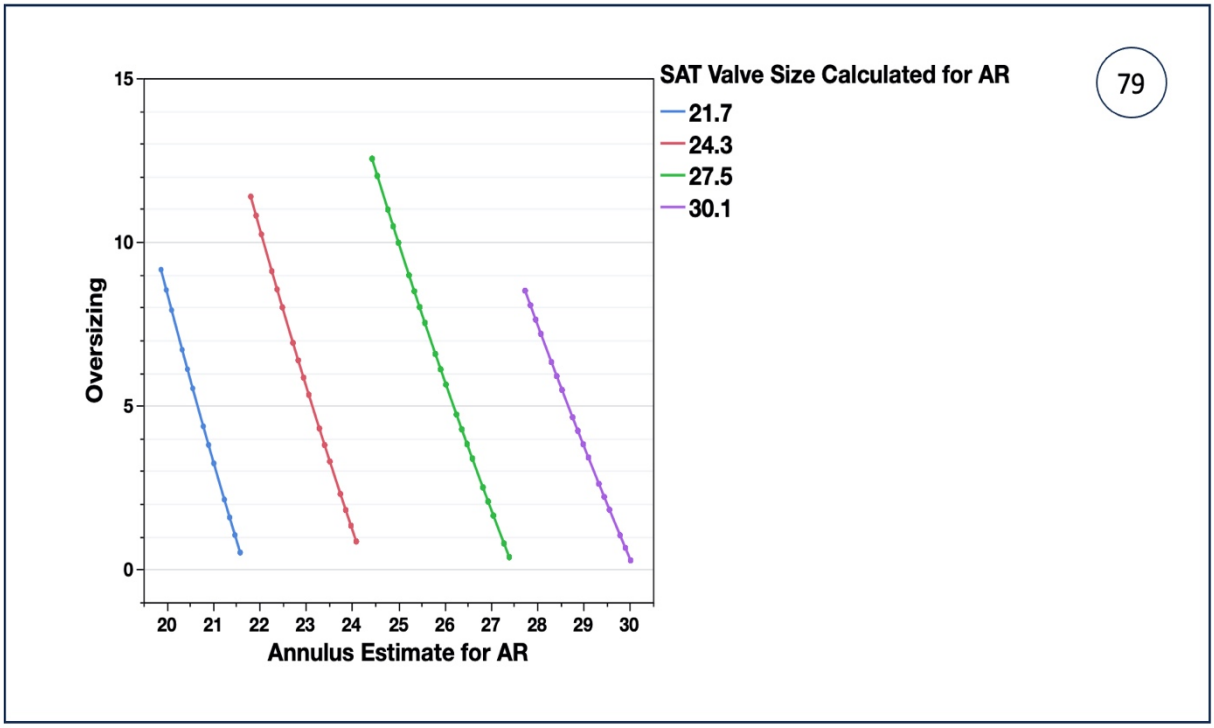


Figure 79: *Resulting SAT valve size allocations for the conservative approach based on assumed compliance equivalence in degenerative AS and rheumatic AR.*

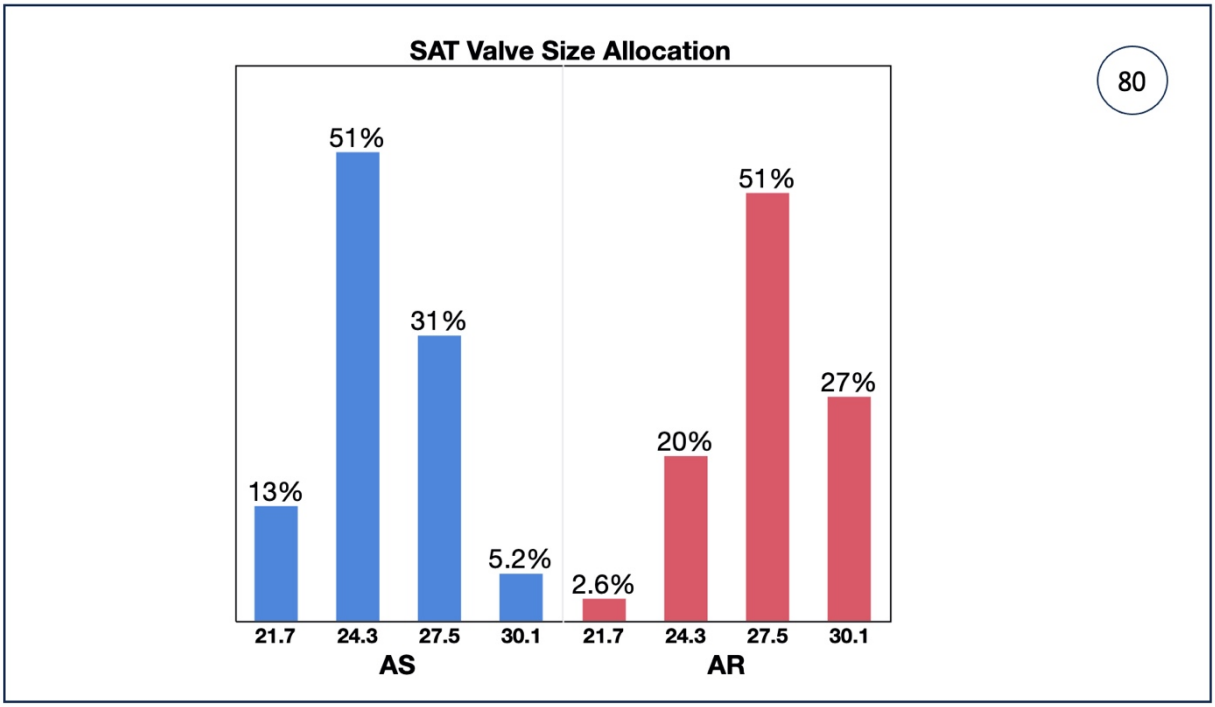


Figure 80: *Hypothetical SAT valve size assignment (conservative scenario) in degenerative AS and rheumatic AR patients shown for comparison.*

Incorporation of published 15% oversizing

Applying the following constraints:
S=23% and 8%; M=23% and 8%; L=23% and 8%; XL=18% and 8%

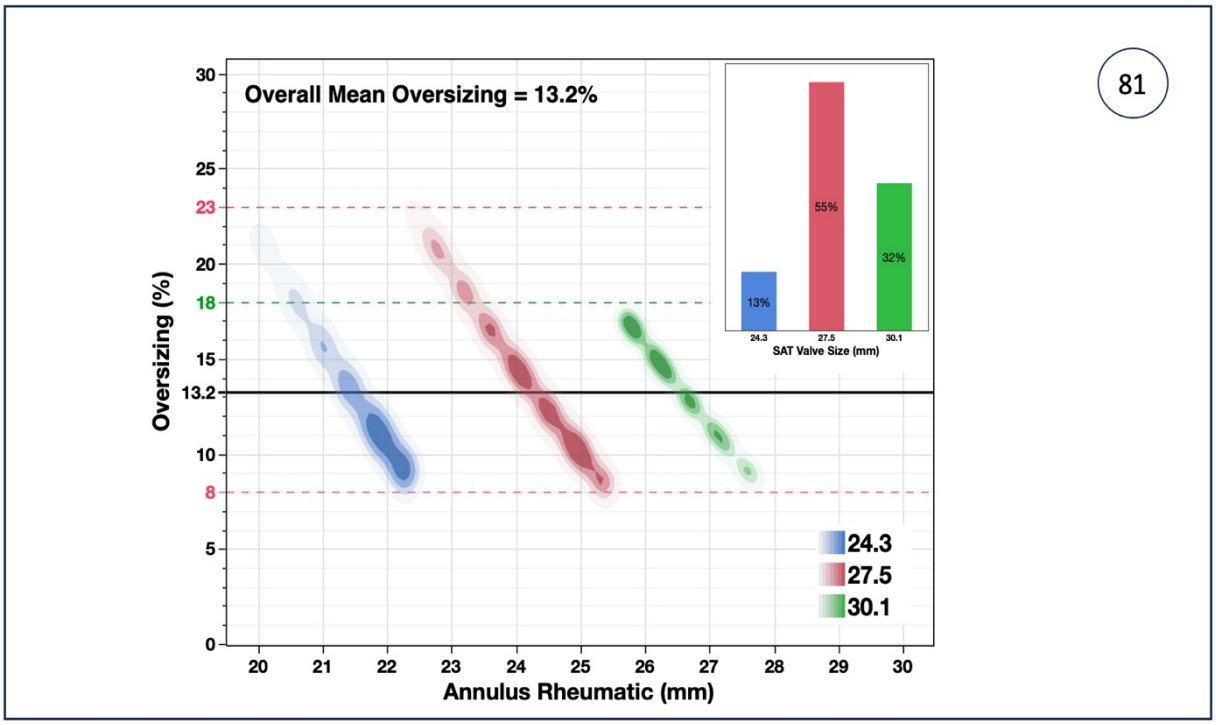


Figure 81: *Applying an overall mean oversizing of 13.2% (which approximated the reported 15% mean), while limiting oversizing to between 23% and 8%. The upper limit for the hypothetical 30.1mm valve was reduced to 18% to avoid encroachment into the allocations for the 27.5mm valve.*

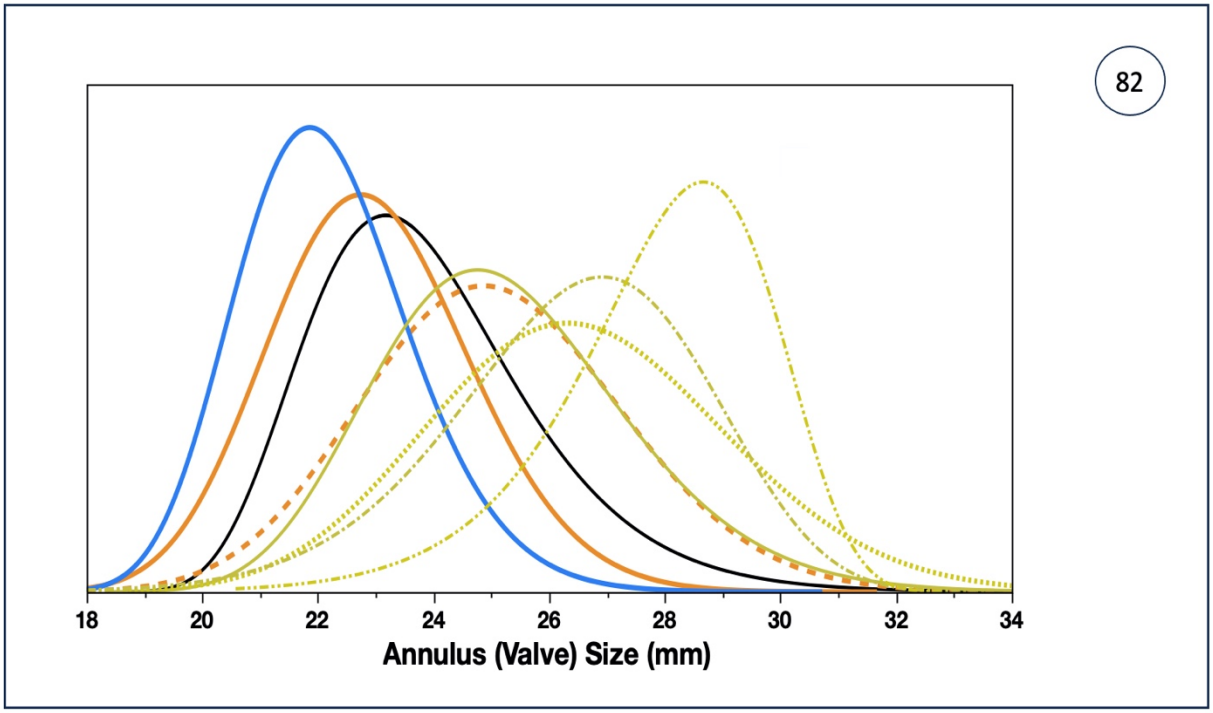
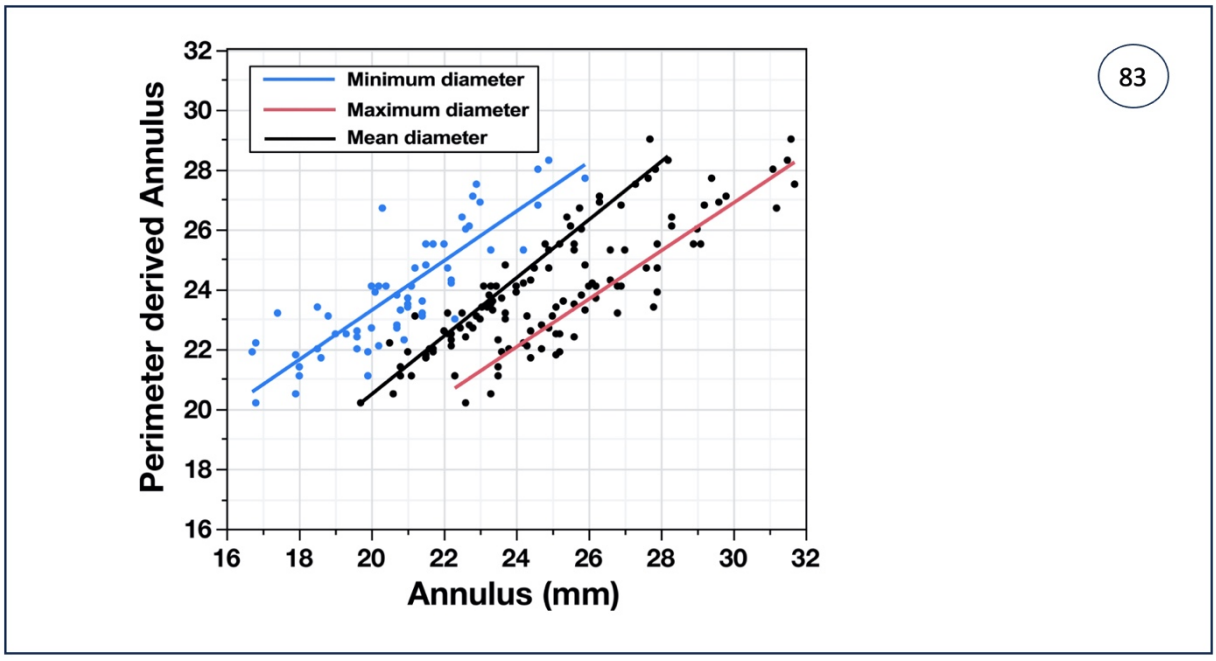
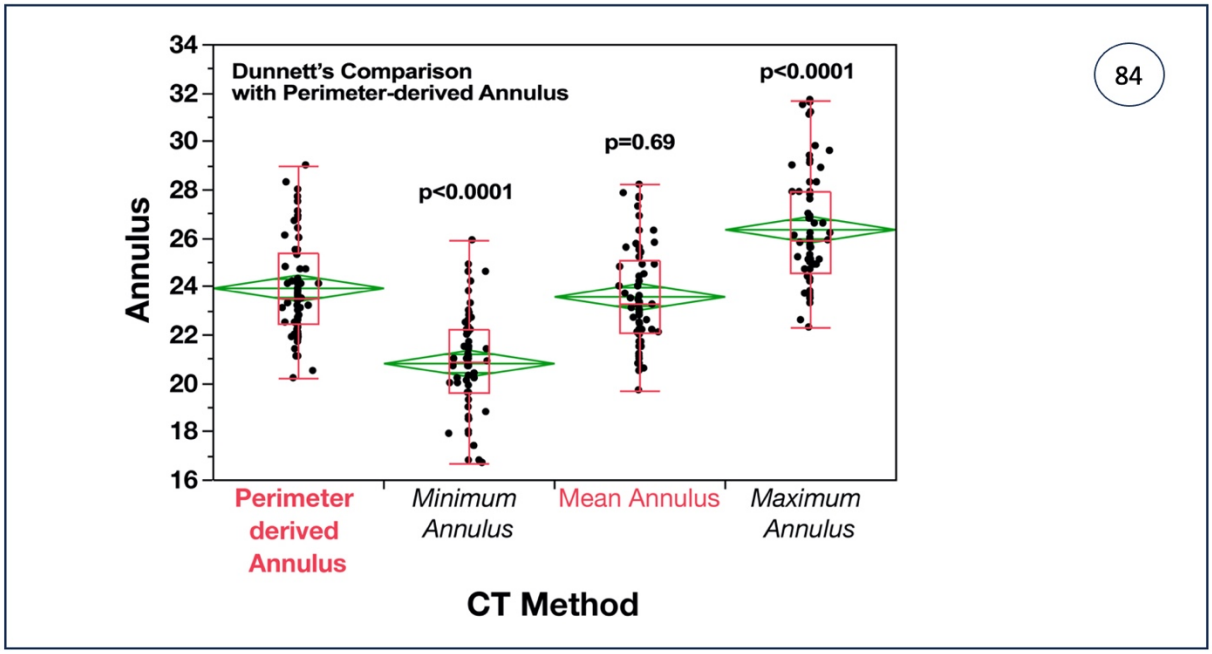


Figure 82: *The SAT valve size distribution curve representing 13.2% overall mean oversizing is now included (olive green dash dot dash).*

PHASE 6: ANALYSIS OF TAVI REPLACEMENTS OF THE AORTIC VALVE IN HEALTHY PIGS AND WHICH INCLUDED TWO-DIMENSIONAL ECHO-BASED MEASUREMENTS OF THE ANNULUS





Figures 83,84: *Confirmation of 2D Echo-Based Annulus Means as Representative of Perimeter-Derived Annulus Diameter Measured by Computer Tomography*

PHASE 7: PRE-CLINICAL IMPLANTS EMULATING THE CLINICAL APPROACH USING PRE-OPERATIVE CT

As a last step prior to commencing the 'first-in-humans' safety trial with the SAT TAVI, 10 pigs underwent CT scanning providing clinical accuracy in pre-procedural availability of dimensional root data. Avoiding multi-factorial data-scattering, animals suitable for one SAT size were selected.

Animal Characteristics: 40-43kg pigs were found to be suitable for the Medium (24.3mm SAT TAVI after a weight gain of 28-38% over the 18 day period from farm-collection to CT to implantation. At the time of the CTs the maximum annuli ranged between 22.2 and 24.6mm.

Table VI: *Dimensional Analysis of the three pre-clinical pigs that underwent pre-implantation CT for precise size assessment of the aortic root. The efficiency of the plastic deformation of the TAVI stent during deployment resulting in firm anchorage in spite of a compliant, non-calcified root allowed largely under-sizing without resulting in valve embolization or paravalvular leaks.*

Table VI

	WEIGHT			ECHO ∅ Max Ann		CT						BALLOON Filling Pressure	STENT ∅ Assumed from Standard Curve			STENT ∅ at Explant			REGURG.
	Collection from Farm	*CT (8 days later)*	*TAVI Implant (10d post CT / 18d post Echo)*	*Initial Farm Screening*	*At TAVI Implant*	*Max. Annulus ∅*	*STJ*	*Annulus : STJ*	*Sinus*	*Annulus : Sinus*	*LCO-Height*		*Bottom Arms*	*Nadir*	*Bottom Flare*	*Bottom Arm*	*Nadir*	*Bottom Flare*	
PIG 1	43	50 +16%	55 +10% +28%	24.1		24.6	25.5	0.96	32.8	0.75	8.9	14 bar	30.0	23.8	28.5	26.8	22.8	26.9	Slight PVL
PIG 2	42	52 +24%	58 +12% +38%	21.5		23.3	26.9	0.87	28.6	0.82	6.1	14 bar	30.0	23.8	28.5	26.89	22.6	27.3	Very slight PVL
PIG 3	40	44 +10%	53 +20% +33%	23.7		22.2	23.4	0.95	26.4	0.84	6.2	14 bar	30.0	23.8	28.5	27.8	23.3	28.1	None

Table VII: The 8% oversizing recommended from previous experiments could be significantly undercut. Even if the TAVI had deployed to the dimensions recorded under benchtop conditions, two TAVIs would have been undersized by 3% and only one oversized by 7%. Given the restricted expansion at implantation, two of the three pigs were actually undersized by 3 and 7% and only one was oversized by 5%.

Table VII

Sizing on Basis of max CT Annulus ∅ versus expected benchtop Nadir-∅ of the TAVI				
	Max Annulus ∅ On CT	Nadir ∅ at Benchtop Deployment	Difference in Millimetre	Percent Difference
Pig 1	24.6	23.8	-0.8	-3.3%
Pig 2	23.2	23.8	-0.6	-2.6%
Pig 3	22.2	23.8	+1.6	+7.2%
Sizing on Basis of max CT Annulus ∅ versus truly deployed Nadir-∅ of the TAVI				
	Max Annulus ∅ On CT	Nadir ∅ at Explantation	Difference in Millimetre	Percent Difference
Pig 1	24.6	22.8	-1.8	-7.3%
Pig 2	23.2	22.6	-0.6	-2.6%
Pig 3	22.2	23.3	+1.1	+5.0%

Conclusion

With left coronary ostia still only half as high as in humans the lack of coronary occlusions seen in this series of three pigs suggests that the traditionally applied distinct oversizing had perhaps unnecessarily obliterated the sinuses in our large-animal experiments. Furthermore, it clearly demonstrated that the TAVI design allows a size-matching without fearing PVLs and embolization.

3. SUMMARY: SAT TAVI SIZING

A hypothetical stepwise approach for the determination of TAVI valve sizes suitable for use in patients with rheumatic aortic valve regurgitation in the absence of clinical measurements is presented here.

This analysis relied on extrapolating the relationship between conventional surgically placed valve sizes and CT-based annulus data available from non-rheumatic aortic stenosis cases to surgical valve size data used in rheumatic cases. This extrapolation, which provided a conservative estimate of rheumatic annulus distribution, was complicated by both the need to accommodate allowances for variable under-sizing due to calcific deposits in non-rheumatic cases and to accommodate anticipated allowances for over-sizing in the more compliant rheumatic cases.

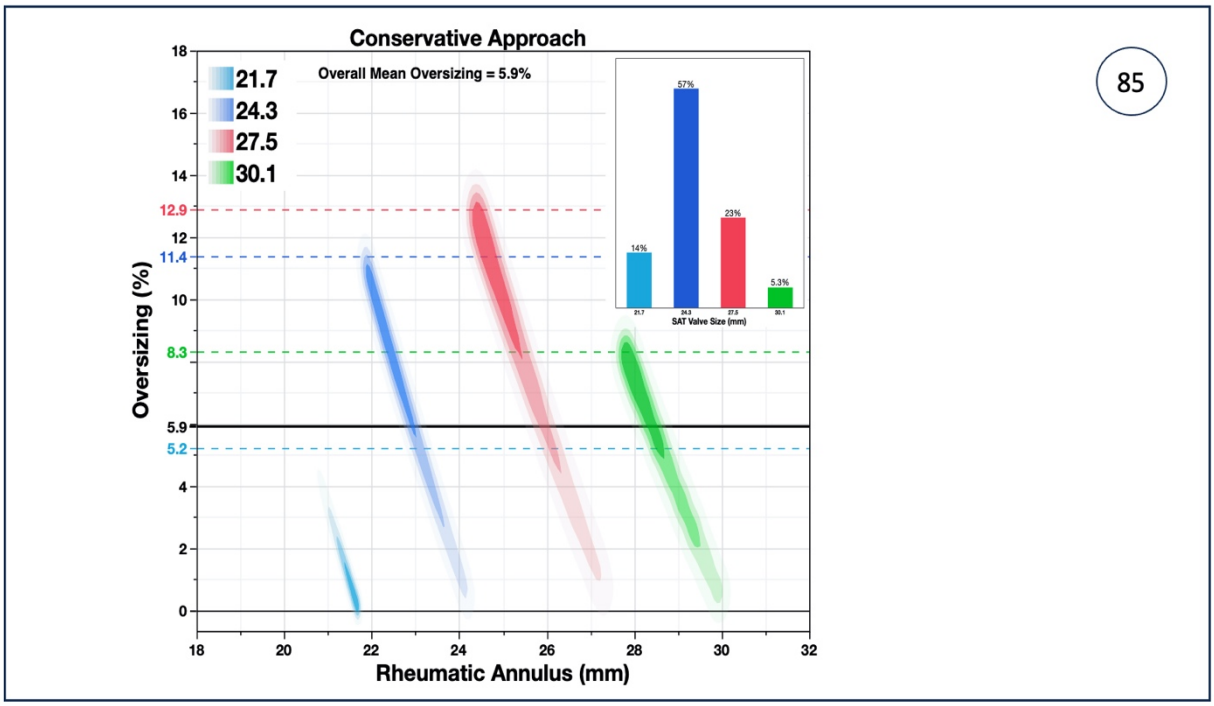


Figure 85: *Applying defined SAT TAVI valve sizes (small, medium, large and hypothesized extra-large sizes) to the extrapolated, but conservative, rheumatic annulus distribution curve, while applying a principle of zero under-sizing and fine-tuning the degree of over-sizing for each of the valve sizes to avoid 'dead zones' where annuli were unaccommodated by any of the SAT valve sizes, the estimated conservative SAT TAVI valve size distribution curve for rheumatic patients was deduced. This involved maximal over-sizing of 10.0, 11.4, 13.0 and 9.0% for small, medium, large and extra-large SAT valves respectively.*

Although the pre-clinical implant series confirmed both anchorage and lack of PVL without oversizing the data derived through statistical deduction in this chapter 10 were used to determine the expected size distribution of SAT valves in patients with pure and non-calcified rheumatic aortic regurgitation at a maximum anticipated oversizing of 15%. With an overall mean of 13.2% being achieved while avoiding under-sizing and dead-zones the main TAVI size with 56% was the 27.5mm valve as opposed to 57% falling into one size smaller group of 24.3mm if undersizing was equally avoided but oversizing was kept to the absolute minimum.

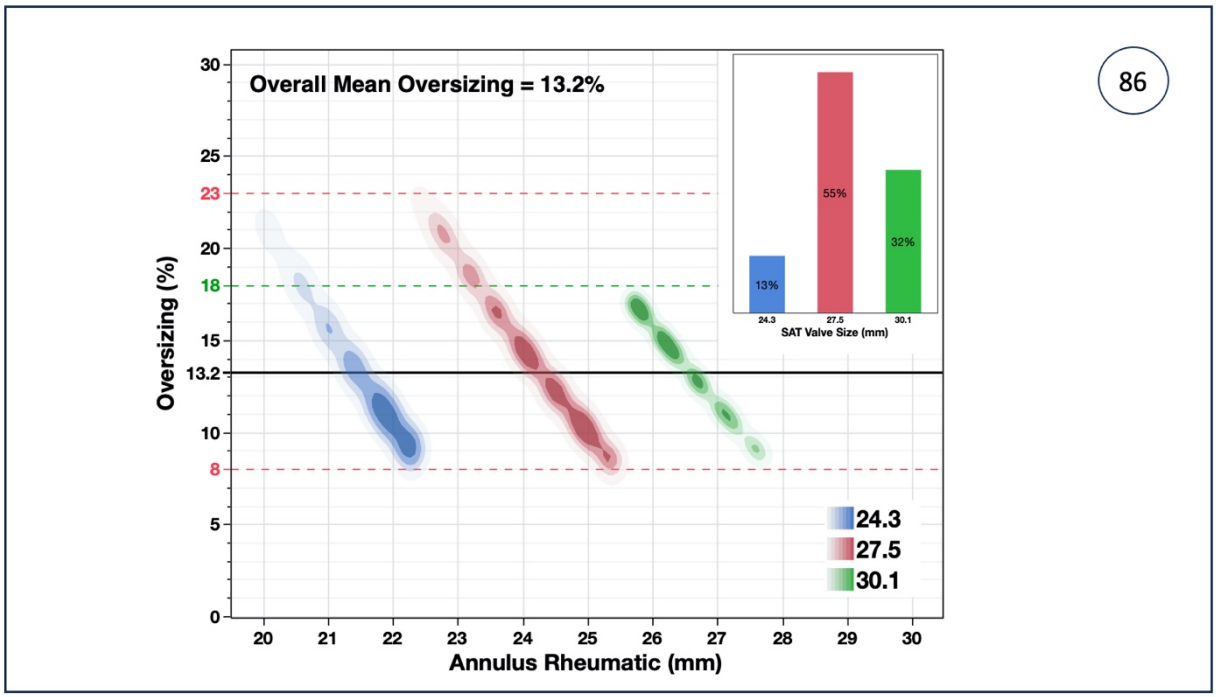


Figure 86: *At the other end of the spectrum applying a significant degree of oversizing (8 to 23% for medium (24.3mm) and large sized (27.5mm) valves and 8 to 18% over-sizing for the hypothesized extra-large valve size(30.1mm) representing SAT valve size distributions in accordance with conventional clinical AR oversizing. The small valve size did not accommodate any of the proposed rheumatic annuli.*

4. DISCUSSION

In this chapter I addressed the biggest unknown prior to the commencement of clinical implants: the lack of CT dimensional data in patients with rheumatic AR and the absence of sizing requirements.
I used a statistical approach to reconstruct a virtual Gauss-curve of CT dimensions of patients with rheumatic AR based on known parameters. These virtual CT-based dimensions together with data on surgical valve sizes allowed an estimation of expected SAT TAVI sizes for this patient group defining limits of under- and oversizing within conventional TAVI ranges that avoid size gaps for which no TAVI exists.
Finally, a pre-clinical series of animal experiments that had obtained accurate CT data prior to implantation demonstrated that there is much less need for oversizing than expected due to the excellent anchorage and seal the stent design provides.
The challenge of finding size and need approximations that will only retrospectively be confirmable once actual clinical implant data are available is amplified by changing general trends in TAVI sizing. As such, clinical sizing will play a crucial role and therefore, I summarise the state-of-the-art of TAVI sizing and its associated problems in depth in this discussion before interpreting my own sizing results with regards to the SAT TAVI in patients with rheumatic aortic regurgitation.

The first task was therefore to explore a statistical approach that extrapolates annular dimensions only known for aortic stenosis (AS) to aortic regurgitation (AR) by using the correlation obtained from an annular dimension known for both AS and AR. This known dimension was the size of surgically implanted valves. Subsequently, basic principles of TAVI sizing and assumptions of tissue compliance were used to predict the size-needs for the new TAVI.

Applying quantile matching and a variable degree of presumed oversizing, a basic correlation between the size distribution of surgically implanted valves; mean aortic annuli obtained by CT and clinically used TAVI sizes was established.

This correlation was based on typical patient cohorts undergoing valve replacement for calcific aortic stenosis at Groote Schuur Hospital / University of Cape Town. In essence, surgically implanted valves were smaller than the native annulus size may have suggested while TAVIs were larger. As such, the surgically implanted prostheses (excluding root widening procedures) were on average 1.9±2.4mm smaller than the CT-based annular diameters and 2.9±2.6mm smaller than corresponding balloon-expandable TAVIs (Edwards Life Sciences). The average oversizing of TAVIs in relation to native annular dimensions was therefore 4.8±12.5%. Differently expressed, for comparable annulus sizes, TAVIs were on average 13.7±12.3% bigger than surgically implanted heart valve prostheses (SAVRs).

The reasons why surgical prostheses were sized smaller than the natural valves could be manifold. One inevitable effect of the size increments in which replacement valves are available is that any chosen valve size is either a bit too big or too small for a given annulus. In the absence of a perfect size fit the potential consequence of needing to take out a partially implanted valve after it turned out to be too big subconsciously prompts a surgeon to rather err on the smaller than the bigger size. This is aggravated by the fact that in a teaching hospital a significant proportion of single aortic valve replacements are done by residents in training, further heightening the tendency to rather under- than oversize. This caution is underpinned by the surgical experience of a restricted annular tissue compliance in these patients which allows less stretching of the annulus than the 2mm increments in which valve prostheses are available. It is unlikely that the degree of 'downsizing' we saw in surgical aortic valve replacements (SAVRs) was just a reflection of the inaccuracy of the preoperative sizing modalities. Even if one uses annulus sizes that were obtained by Hegar sizers with their 1mm increments (363) our surgically implanted valves would still have been 5.1±4.9% smaller than their measured annulus diameter. Incidentally, the intra-operatively obtained 'Hegar'-based mean annulus diameter of 23.2±1.9mm coincided with the mid-systolic CT value of our AS patients (23.9±2.1mm), only deviating by 2.4±8.1% (90% Tolerance Interval: -18.2 to 13.5%).

This further emphasises the centrality of basing TAVI sizing on an imaging modality that reflects most accurately the biggest annulus dimension during the cardiac cycle to avoid under-or oversizing of TAVIs. Undersizing can result in patient-prosthesis mismatch, paravalvular leakage, device migration and embolisation, all of which can adversely influence prognosis after TAVI. Conversely, oversizing may lead to annular rupture, prosthesis under-expansion with subsequent risk of central transvalvular regurgitation, and conduction abnormalities due to excessive compression of the conduction system in the LVOT [(364)].

Over time, multi-slice computed tomography (MSCT) emerged as the imaging modality representing the most reliable reflection of the actual diameter of the native annulus. Yet, while MSCT is by now the undisputed gold standard for the sizing of the annulus a consensus is still evolving whether it should be area- or circumference-based. When pre-operative circumference-based MSCT sizing of the annulus was compared with intra-operative Hegar-sizing annulus diameters, it turned out to be near-identical [(365)]. To exclude the possibility that intra-operative Hegar-sizing already encompasses a degree of annular distension another study correlated Hegar sizing with CT and Cardiovascular Magnetic Resonance (CMR) – based sizing. The latter may well represent the most accurate dynamic preoperative imaging modality. The complete congruency of Hegar-based and CMR based annular diameters proved that Hegar sizing did not stretch the annuli beyond their physiological maximum diameter seen during systole. Pre-operatively obtained CT sizes again differed less than 2%

from intraoperative Hegar-sizing and CMR [365]. However, when calculating annulus sizes on the basis of CT imaging it increasingly seems crucial to base it on perimeter rather than cross-sectional area although area-based approaches have historically been used for balloon expandable TAVIs. Preferentially using a circumference-based annulus diameter is particularly justified in patients with calcific aortic stenosis as with increasing age and hypertension, the aortic annulus becomes progressively less spherical and assumes an increasingly elliptical profile in this patient population [366]. When using the area for deriving the annular diameter one needs to consider that at a given circumference, areas decrease linearly with increasing ellipticity. As this phenomenon led to a significantly smaller annulus in patients with AS when based on CT area [367] as opposed to circumference, perimeter-based sizing became a widely accepted gold standard in the self-expanding TAVI field with their lower likelihood of correcting an elliptic into a spheric annulus. Balloon expandable TAVIs, however, still tend to continue recommending oversizing on the basis of percent increase in area. Apart from geometric concerns with this approach, one needs to be alert to the fact that values are twice as high as in circumference-based recommendations. Notwithstanding total market shares, the flurry of new self-expanding TAVIs has ascertained that it is perimeter-based sizing that is increasingly adhered to in the manufacturer's sizing charts [366].

Yet, independent of whether the perimeter or the area are used, consensus needs to exist with regards to where measurements should be taken. According to Anderson et al. [368] proper values of the annular dimension can only be provided when measurements are made at the bottom of the leaflet attachments. Therefore, the level of the aortic valve annulus on CT is defined as the lowest level of insertion of the valve leaflets into the aortic root. For the Sinuses of Valsalva (SOV) the opposite applies. Their scalloped shape excludes the use of the perimeter to deduct their widest diameter. As such, the SOV diameter is measured as a line extending from each of the three commissures to the middle of the opposite coronary sinus [368].

Notwithstanding the generally recognised role of MSCT as the central pre-operative sizing modality, transcatheter heart valve replacements also rely on intraoperative imaging. There, it is crucial to be aware that certain limitations of such imaging modalities may lead to under- or overestimated annulus diameters when compared to MSCT. Particularly 2-D echocardiography is notoriously underestimating the more oval annular anatomy of patients with aortic stenosis by 1.5±2.3mm [369].

Even on TOE, annulus measurements were significantly smaller than on MSCT [370]. Similarly, when compared to intraoperative Hegar-sizing, 2D TTE and TOE resulted in 7.3% and 5.2% smaller annuli [363], respectively. Considering the limitations of 2D echo-planes to assess elliptic structures, it becomes obvious why this imaging modality is suboptimal as far as the accurate measurement of annular diameters is concerned. In the predominantly used enlarged mid-oesophageal long-axis view (approximately 110° to 140°, referred to as the "3-chamber view") the annular dimension measured on the sagittal plane is the shorter one, while that measured on the coronal plane is the longer one [371] even in a circular annulus. In an ovoid annulus the long axis aortic view additionally represents the shortest diameter of this oval, making the sizing of this structure for the implantation of a circular valve fraught with potential errors [366].

In tandem with the acceptance that 2D echocardiography (including TOE) under-sizes the annulus diameter [372], 2D analyses have increasingly been superseded by 3D imaging, which more accurately delineates a non-circular anatomy. Underlining the ability of 3D echo to assess elliptical annuli, a study from 2017 using this imaging modality confirmed two age-related characteristics of degenerative aortic stenosis: a decreasing distensibility of the aortic

root and a remodelling process that leads to an increasingly ovoid shape of the LVOT [366]. In another study confirming the accuracy and safety of exclusively using 3D TOE for the sizing of TAVIs, aortic annuli were again significantly larger on 3D than on 2D-TOE leading to 40% of TAVIs being selected larger than they would have been based on 2D echo [373].
Notwithstanding the fact that 3D echo underestimates annular sizes less than its 2D counterpart, however, there is evidence that 3D TOE still mildly under-sizes annuli in AS compared with MDCT or CMR [374]. In addition, although 2D TOE can often define the annular–ostial distance for the right coronary artery, the left mainstem ostium usually lies in the coronal plane that cannot be acquired by standard 2D imaging [375]. This is important as 3D TOE can not only measure the distance from annulus to LMS ostium but can also determine the length of the left coronary cusp which, if beyond a critical length, may occlude the LMS ostium after valve deployment. As such, improved resolutions and continuously refined software developments of 3D TOE increasingly challenge MSCT as the gold standard in in the aortic annular sizing arena [366]. Taken the likelihood into account that 3D TOE may still slightly underestimate sizes compared to perimeter-based MSCT assessments [374] 3D echo performs sufficiently robustly as a sizing modality in high-volume centres with expertise in its acquisition and application [366].

In spite of a growing role of echocardiography, however, angiography will continue to represent a key means of intraoperative aortic root assessment. In a most recent comparative study, angiography based sizing corresponded well with MSCT-based sizing in 60%; undersized in 11% and oversized in 29% [376]. Accuracy may be added to angiographic sizing by using a sizing balloon [363, 367, 377, 378]. For this procedure, an aortic valvuloplasty balloon with a diameter not more than 2mm larger than the annular diameter on TOE is chosen and the inject-volume for the TOE diameter is determined with a sterile caliper at 2 Bar. If the full volume is injected and the pressure is higher than 2 Bar, the annulus is smaller than the balloon [377]. In the absence of a waist, the procedure is repeated with a bigger sized balloon. When using balloon-sizing, however, it is again crucial to take the strengths and weaknesses of this modality into account when interpreting the results. For one, balloon sizing will inevitably cause some annular distension even in the most non-compliant, stiff roots and therefore it will anticipate part of the oversizing intrinsic to TAVIs. This slight overestimation of annulus diameter with balloon-sizing was confirmed in a study where open surgical balloon sizing exceeded standard surgical sizing in more than 90% [363], although the calcified leaflets had been left in place prior to balloon sizing while the surgical valve sizing happened after excision of the leaflets. Similarly, when aortic valvuloplasty balloons (BAV) were used for TAVI sizing aortic annuli were >6% bigger than on 2D TOE [377]. This correlated well with the difference between open surgical Hegar-sizing and 2D TOE [363] indicating a similar mild degree of procedure-related annulus distension when using BAV for sizing. At the same time, balloon sizing takes significant leaflet calcification better into account than MSCT-based perimeter-derived annulus sizing which circumnavigates the calcium deposits on the outside. Accordingly, in a most recent study from 2020 using balloon sizing, only 50% of TAVI sizes chosen on the basis of pre-operative MSCT dimensions were verified intraoperatively while almost the same proportion (46%) was downsized without detrimental effect on PVLs. This confirmed a previous TAVI study where balloon-sizing resulted in only 52% of patients receiving oversized TAVIs. As a positive consequence of this fine-tuned approach to sizing, there was a 100% freedom from adverse events [377]. These observations indicate that balloon-sizing may take better care of ‘real life’ circumstances, leading to up-sizing in compliant roots and downsizing in the presence of severe calcification.
It is therefore important to factor in a sensible moderation of pre-operatively assessed annular sizes when choosing a TAVI on the basis of intra-procedural balloon-sizing. However, in view of the wealth of experience using modern imaging modalities for TAVI sizing, balloon

sizing should be seen as a last resort [1] when there is a major discrepancy between the non-invasive imaging methods; [2] in borderline annulus sizes of 21-22mm and 24-25mm; [3] in massive and/or eccentric calcification and [4] in bicuspid aortic valves [(378)].

Apart from the specific size-bias associated with each imaging modality there is also a dynamic variability of dimensions throughout the cardiac cycle [(139, 379)]. Selecting the cardiac phase in which the annulus is largest was shown to prevent prosthesis under-sizing [(365, 371)] and thus the risk of embolization or paravalvular leak (PVL). As it is physiologically plausible to expect root dimensions to be maximal and most circular during early [(371)] or mid-systole it is widely believed that ECG-synchronized systolic image acquisition is a sine-qua-non for the assessment of maximal annular dimensions and minimum distances from annulus to the coronary ostia. Largest circumferences are usually observed at 20% of the R-R interval [(380)]. Yet, when ECG-gated MSCT reconstructions were done at each 10% of the cardiac cycle in a cohort of healthy middle aged individuals the aortic valve annulus (AVA) was oval (defined by > 3 mm difference between minimum and maximum cross-sectional diameter) during both systole and diastole in 70% of cases and only during diastole in 18% [(379)]. Although most of the healthy subjects still had the largest dimensions during systole, some did have larger diameters during diastole. While the mean dimensions did not show any significant difference between systole and diastole the individual dimensions could be more than 5mm greater in diastole than in systole [(381)].
This variability was independent of gender, age, height and weight demonstrating a significant individual dynamic change in the dimensions of the aortic root. In aortic stenosis, these dynamic changes resulted in 7.3±2.1% differences in minimum and maximum perimeter-derived diameters [(380)].

In the context of this PhD the two main challenges of an evolving, incomplete sizing platform for a new clinical indication for TAVIs are the validation of available dimensional data against the literature and the identification of parameters by which the new indication may differ most significantly from the established one. We hypothesised that tissue compliance may influence prosthesis sizing more than any other parameter in the extrapolation of dimensions from old patients with calcific aortic stenosis to young patients with non calcified aortic regurgitation. Moreover, as the gold standard of MSCT dimensions will not be routinely available for young patients with rheumatic aortic regurgitation as long as surgical aortic valve replacement remains its treatment of choice, a realistic interpretation of echo-data becomes even more crucial.

Notwithstanding - as far as validation is concerned - the central role of MSCT in the preoperative sizing of aortic annuli was confirmed in our analyses. A mean MSCT-based diameter of 23.9±2.1mm was found in our racially mixed population with ***degenerative calcific AS.*** It correlated well with the 23.2±1.9mm measured intraoperatively in a North American series [(363)] and the equally CT-based 23.8±2.2mm described in a European cohort [(382)]. Our surgically implanted valves for calcific AS had a mean diameter of 21.9mm and as such were 1.2mm smaller than the native valves on CT. Whether the slightly bigger valve sizes implanted in European studies [22.9±1.7mm [(383)]] were due to racial differences or to the fact that residents usually start their operating experience with single valve replacements in Cape Town while in Europe a majority of these cases is done by experienced staff surgeons remains unclear. The intuitive expectation that the relatively younger patients with non-calcified ***rheumatic AS*** may require larger prostheses than the typically elderly patients with degenerative AS was not confirmed. At our own institution there was no difference in the size of implanted valves between patients with calcific and rheumatic aortic stenosis (21.9±1.6mm).

In patients with aortic regurgitation, in contrast, valve sizes were expected to be bigger than in stenosis. As patients typically tolerate AR well for prolonged periods of time they may only become symptomatic decades after diagnosis. At that stage the remodelling process has often led to distinct eccentric myocardial hypertrophy, fragile thin aortic walls and chamber dilatation. In two European TAVI-studies for ***pure degenerative AR*** MSCT-based valve sizes were indeed bigger than in degenerative AS [24.7±1.5mm (350)] and [25.2mm [(384)]]. Given the relatively young age of patients with rheumatic AR, current guidelines for high income countries prescribe surgical aortic valve replacement as the default position. As such, no MSCT-based native valve sizes are available. Considering the remodelling dynamics of the aortic annulus in regurgitant valves as opposed to aortic stenosis this lack of MSCT data is aggravated by the fact that reliable echo-dimensions are also scarce. As such, the development of a transcatheter solution for younger patients with rheumatic AR could not rely on the wealth of existing data on size-distributions that exist for degenerative AS. In order to allow R&D on the basis of highest probability, we developed a statistical reverse analogy approach to generate virtual MSCT-based annular dimensions for patients with ***rheumatic AR*** on the basis of extrapolating available cornerstone data such as surgically implanted valve sizes. In doing so, the CT-equivalent obtained provided a mean annulus diameter of 24.8mm for rheumatic AR as opposed to 23.9mm mean size for the selected valve prostheses. Compared to the annular CT dimensions reported for pure degenerative AR the difference between degenerative and rheumatic AR was again negligible in spite of the distinct age difference between these two patient groups. Yet again, similar to degenerative aortic valve disease, annuli were 1.7mm bigger in patients with rheumatic AR than rheumatic AS.

These correlations need to be seen in a dynamic way as progressive tissue remodelling in AR leads to increasing annular diameters over time. As such, the stage at which a patient is being diagnosed as needing a heart valve replacement for rheumatic AR indirectly affects the prosthesis size. This trend was confirmed in a study from the All India Institute (AII) in Delhi where a strong correlation of large annulus sizes with poor ventricular function and large ventricular dimensions was found in patients undergoing aortic valve replacement for rheumatic AR [(385)]. As the annulus dimensions of our patients with rheumatic AR were smaller at the time of surgery than those described by the AII India Institute, the obvious explanation is that patients presented for aortic valve replacement at an earlier stage in Cape Town than in Delhi. This gradual increase in annular diameter accompanying increasing ventricular dimensions and decreasing ventricular function does, however, also mean that **TAVI sizes will need to be bigger the more progressed the disease is.**

The consistent observation of larger annuli in AR than in AS – regardless of the aetiology – was matched by higher tissue compliance in AR than in AS. Even in elderly patients with degenerative AR the difference between diastolic (23.9mm) and systolic annulus diameter (25.4mm) was 1.5mm or 6.3% [(386)] compared to degenerative AS where compliance was described to be a quarter to half of these values [0.15-0.82mm [(387)]; 0.6mm (23.7±2.1mm vrs 23.1±2.1mm) [(388)] and 0.9mm or 3.7% [(389)]].

Summarising the main insight we gained regarding the annular dimensions of both stenotic and regurgitant aortic valves in patients with rheumatic and degenerative pathologies the modelling approach produced the following key findings:

- In our patients undergoing surgery for symptomatic aortic stenosis, there was no difference in CT-based annular sizes (actual and virtual) between degenerative calcific or rheumatic aetiologies although our overall dimensions (21.9±1.6mm) were smaller than in Caucasian cohorts (23.0-23.9mm) [(363, 382)].

- Similarly, the annular size reported for patients with degenerative aortic regurgitation (24.7-25.4mm) [386] was again not significantly different from the one in rheumatic aortic regurgitation in spite of the younger age of the latter. In this pathology, our dimensions of 24.8 mm were similar.
- In contrast, annuli in patients with AR were in average 1.7mm or 7% bigger than those of patients with AS. In European studies, pure ***degenerative AR*** had a mean annulus size of 25.0mm [350, 384] as opposed to 23.6mm observed in degenerative AS [363, 382]. This difference further increases in patients with decreasing ventricular function.
- Even in old patients with degenerative aortic valve disease, the compliance during the cardiac cycle ranges between being identical and 2-3 times higher in patients with AR than AS suggesting the validity of applying baseline characteristics of aged patients with degenerative AR to young patients with rheumatic AR.

To correctly size TAVIs on the basis of annular dimensions confronts us with an even bigger challenge than the 2mm increments at which surgically implanted valves are available. In surgical valves, our analyses showed that prostheses were in average 1.9±2.4mm smaller than their corresponding MSCT-based annulus would have suggested. In TAVIs, the sealing effect of surgical sutures pulling the annulus towards the sewing ring does not exist and the presence of often large calcium conglomerates further thwarts a smoothly sealing tissue grip of the valve . As such, downsizing as is customary in routine surgical aortic valve replacements would inevitably lead to leaking and insufficiently anchored TAVIs in AS. Together with the larger size increments of 3mm at which TAVIs are available, oversizing rather than under-sizing is a sine qua non in order to avoid the risk of embolization and paravalvular leaks (PVLs).

In the early experience with TAVIs the recommendation was to select a TAVI >2mm larger than the annulus [122, 363, 390, 391]. This would translate into an average up-sizing of 9% of the mean CT based annular diameter [122, 390, 391] and only marginally less if based on Hegar diameter during SAVR [122, 390, 391]. Later TAVI guidelines for aortic stenosis continued to propose oversizing the valve by 5-13% in relation to the CT-based diameter of the native aortic annulus [381]. Naturally, oversizing was more moderate in the presence of significant calcification but rarely led to under-sizing. This is reflected in the 'optimal' cut-off sizes of 22.8mm and 26.1mm between the small (23mm), medium (26mm) and large (29mm) Edwards TAVI sizes [367].

Overall, each indication and each device needs to find the optimal balance between sufficient oversizing for minimising PVLs and detrimental overstretching leading to annular rupture and permanent pacemaker (PPM) implantation. While the degree of oversizing is known to be inversely related to PVLs [392] it is accepted that oversizing should not exceed 20% in calcific AS to avoid a significant risk of annular rupture or conduction defects [393]. As such, there is a relatively narrow bracket for oversizing. Going beyond 12% eliminated PVL but led to a high incidence of permanent pacemaker implantation. Remaining below 7% led to a high incidence of PVL. As such, 7-12% oversizing seems to have provided the best risk-benefit ratio for calcific aortic stenosis [394]. With 9.3% annular oversizing (relative to MSCT mean diameter) no annular rupture and low incidences of post op PVLs were observed [394]. Unfortunately, given the 3mm size increments of TAVIs only 1/3 of patients fitted into this group [394].

In our TAVI patients, size-match ranged between -2% and +14%. Yet, 88% of patients received a TAVI that fell into the 75% upper tolerance interval of 7.9% oversizing for 23mm Edwards Sapien XT TAVIs; 10.7% for 26mm and 11.8% for 29mm. This 75% tolerance interval even coincidentally accepted cases with modest under-sizing.

Although no TAVI has been registered for AR except for the Jena valve, existing TAVIs have been used off-label for primarily regurgitant non-calcified valves [350, 384, 395-398]. Yet, the lack of calcium in aortic regurgitation poses a significant challenge for the application of conventional TAVIs. The absence of a circular, rigid frame of calcium at the annulus, commonly seen in AS, increases the risk of TAVR device dislodgement, malposition, and embolization [376, 399] as well as higher rates of PVL compared to AS [384]. Additionally, AR roots are more compliant than in AS and can expand to a greater degree during valve deployment. Standard sizing calculations may therefore leave devices significantly undersized. Accordingly, TAVI devices in AR are typically more aggressively oversized to accommodate for the greater stretch in the valve. Besides, annuli in pure AR are distinctly bigger than in AS and larger annuli further increase the risk of dislodgement, malposition and embolization [400]. Accordingly, Markham et al [399] recommend 15-20% oversizing to accommodate for the lack of calcium and the more expansive aortic regurgitant valve. They also suggest placing 2 pigtail catheters in the root to provide a clearly defined fluoroscopic coplanar annular view [399]. Yet, although one registry involving 40 centres and >330 patients showed a lower failure rate in off-label use for pure AR when new-generation TAVIs were used [384] a recent meta-analysis still shows a 20% failure rate (eg the need for a second valve implantation) and moderate to severe PVLs in 7% [395].

Summarising our own TAVI experience in calcific AS as well as the modelling of acceptable oversizing brackets for the SAT TAVI we conclude that:

- In our series of degenerative, ***calcific AS***, the pre-operative annular CT dimensions based on perimeter were 23.1mm; the average surgical valve size was 21.9mm and the mean Edwards TAVI size used was 25.0mm. As such, the average oversizing of TAVIs was 8.2% in this population group. The resulting size distribution of TAVIs was 48% for 23mm valves; 36% for 26mm valves and 16% for 29mm valves. This coincided with the less aggressive oversizing strategy of contemporary series as opposed to old reports where two thirds of Edwards Sapien TAVIs were medium sized [367].
- As such, surgical prostheses were in average downsized by 5.2% while the Edwards TAVIs were upsized by 8.2%.
- Our modelling also showed that the size distribution of SAT TAVIs would be 13% for the 23 (21.7)mm valve; 51% for the 26 (24.3)mm valve; 31% for the 29 (27.5)mm valve and 5% for the 32 (30.1)mm valve in the same patient population of calcific, degenerated AS. Oversizing was postulated to not exceed 11%.
- In ***rheumatic AS***, our average surgical valve size was 21.9±1.6mm and as such comparable to the degenerative group. Under the assumption of no under-sizing and a 14% over-sizing limit, the size distribution of SAT TAVIs in this patient group would be 11% for the 23 (21.7)mm valve; 49% for the 26 (24.3)mm valve; 34% for the 29 (27.5)mm valve and 5% for the 32 (30.1)mm valve.
- For pure ***rheumatic AR***, the average surgical prosthesis size was 23.9mm and the calculated, corresponding CT-based mean annulus diameter was 24.8 mm. Presuming a limit of 8-23% to oversizing (mean 13.2%), the predicted size distribution for the SAT TAVI would be 13% for the 26 (24.3)mm valve; 55% for the 29 (27.5)mm valve and 32% for the 32 (30.1)mm valve.
- Most importantly for the purpose of this thesis, the initial hypothesis that overcompliance of aortas in patients with rheumatic AR will require disproportional oversizing of TAVIs does not seem to hold. Degenerative aortic valve disease showed a right-shift of the CT curve from aortic stenosis towards aortic regurgitation by 1.7mm. As a similar right shift was seen in the sizes of surgical valves between rheumatic stenosis and regurgitation, the

higher compliance should already be corrected for when using CT images taken at 20% of the R-R interval (mid systolic).

The higher degree of oversizing in AR, however, potentially increases the risk of coronary occlusion. In TAVIs, the native leaflets together with calcium agglomerates are simply displaced and at times crushed by the trans-catheter heart valves. This harbours the risk of coronary occlusion, in particular if the coronary arteries originate low within the sinus of Valsalva. This is further augmented by small sinuses and long leaflets with bulky calcifications. In calcific AS coronary occlusion happens in less than 1% of cases. In 98% it is due to displacement of native, calcified leaflets; in the remaining 2% due to impingement by the scaffold of the TAVI or its leaflets [(401)]. The distance from the aortic annulus plane to the coronary ostia can easily be assessed by MSCT. In a study of 100 patients with aortic stenosis undergoing CT, the average distance of the left and right coronary ostia was 15.5±2.9mm and 17.3±3.6mm, respectively [(402)]. Anatomic risk factors are a low take-off of coronaries (<10mm) (403) sinus of Valsalvae (SOV) dimensions of < 30mm (403) and a narrow sino-tubular junction (STJ) [(404, 405)]. In particular when using balloon-expandable devices in low STJ height anatomies, STJ diameter should be compared to the anticipated THV size in order to identify anatomies with smaller STJ diameter than THV diameter, which would be indicative of increased risk for STJ injury [(403)]. Thus, coronary ostial height should not be considered as an isolated measure of risk of occlusion. In >25% of cases of coronary occlusion, for instance, the coronary height was >12mm [(404, 405)]. Rather, the derived values for coronary height and sinus of Valsalva width should be interpreted in the context of annular dimensions, overall root dimensions and the anticipated TAVI size. Struts may also overlay the coronary ostia, in particular in patients with low sinus heights but this does not necessarily imply ostia occlusion, as the upper third of the TAVIs are not covered by a sealing cuff [(369)].
For patients falling below the two main anatomical coronary occlusion criteria (ostial height <12mm; SOV < 30mm) the additional parameter of distance between leaflet and coronary ostium (between 0.9 and 13mm) [(406, 407)] may help if indexed against the diameter of the left coronary artery on CT (2.7-5.7mm). If this index increases beyond 0.7 (in the direction of 1.0) the risk increases steeply. Between 0.45 and 0.7 it is mildly increased (around 5%) whereas below 0.4 there was a 100% success rate in spite of fulfilling the other two risk criteria of coronary height and SOV width [(408)].

Overall, the statistical modelling based on our own patient series and correlations with major series in the literature allowed us to make certain predictions for the use of the SAT TAVI system in patients with rheumatic aortic regurgitation.

- If potential TAVI patients would mirror those who received a surgical aortic valve replacement for aortic regurgitation at our institution, an upwards shift of one whole TAVI size would be required compared to patients with AS: while half of the patients with AS (49%) would receive a size 26 (at annulus level 24.3mm), more than half of the patients with AR would receive a size 29 (at annulus level 27.5mm). Similarly, one third of patients with AS (34%) would receive a size 29 (27.5mm at annulus level) while a similar third (32%) of patients with AR would receive a size 32 (30.1mm at annulus level).
- Given the narrow restriction of first in man implants to nearly inoperable patients with end systolic ventricular diameters $\geq$ 55mm an even larger annulus dimensions must be expected with a further upward shift towards bigger TAVI sizes.
- Individual sizing guidelines would be applied defining oversizing at 13% not exceeding a bracket between 8% and 23%.
- If patients meet the exclusion criteria of ostial heights of <12mm; SOV < 30mm or Annulus: SOV ratios of > 0.82 the additional parameter of distance between leaflet

and coronary ostium (between 0.9 and 13mm) [406, 407] shall be indexed against the diameter of the left coronary artery on CT (2.7-5.7mm). If this index increases beyond 0.7 (in the direction of 1.0) the risk increases steeply. Between 0.45 and 0.7 it is mildly increased (around 5%) whereas below 0.4 one should expect 100% success.

While these results represent rationally derived predicted TAVI sizes and associated levels of implant-oversizing, our model will need to be continually updated and corrected as first actual clinical dimensions will begin to emerge. Similar to the early days of TAVIs for calcific aortic stenosis early data will be extreme due to the initial selection of late-stage patients.

CHAPTER 11

CONCLUDING DISCUSSION

The arc of my thesis reached from the rational for a tailor-made trans-catheter solution for patients with rheumatic heart disease in low- to middle-income countries to the de-novo establishment of meaningful animal models to the definition of anatomical exclusion criteria and a pre-clinical verification. I covered the broad complex of the surgical treatment of symptomatic rheumatic aortic valve disease from patient characteristics to patient needs and from the definition of anatomical implantation-criteria to the pre-clinical testing in large animals. In this chapter I summarise the essence of the results of my studies.

On the basis of this PhD thesis, the ethics committee of the University of Cape Town has approved a first-in-man safety study with the UCT/SAT bioprosthetic TAVI at Groote Schuur Hospital.

In my thesis, I evaluated a novel trans-catheter heart valve system as a capacity expanding, tailor made solution for hundreds of thousands of patients in low- to middle income countries with symptomatic rheumatic heart disease. While specifically focusing on an easy-to-place deployment- and heart valve system for the aortic valve, the introduction of a trans-catheter approach to the unique pathology and socio-economic circumstances of patients with rheumatic heart disease certainly broke new ground in a wider sense. For one, carrying the enabling technology of transcatheter heart valve surgery for these patients to a point of clinical trials has paved the way for a paradigm change that could make new life-saving therapies amenable for patients who were previously doomed to die. Independent of the trans-catheter path of implantation, by pioneering a soft-leaflet replacement valve that has shown manifold longer durability than conventional bioprostheses, a second paradigm change away from mechanical valves may occur. I have clearly concluded in ***chapters three and four*** that such a paradigm change will be a sine-qua-non for providing adequate surgical therapy for RHD in LMICs.

My PhD thesis covered the surgical aspects of a major multi-facetted undertaking spear-headed by the University of Cape Town (UCT) that addresses the unsatisfying current situation that LMICs depend on technologies, infrastructures and heart valve prostheses that were developed for entirely different pathologies, patients and circumstances. As such, the thesis covers the clinical translation of a unique initiative of a South African tertiary institution towards a comprehensive, tailor-made African answer to a global health problem affecting indigent patients outside the industrial world. While both long-lasting heart valve leaflets and the development of a trans-catheter system suitable for a low-tech environment have been successfully realized by UCT institutions closely associated with my clinical home department, my thesis conducted the necessary clinical needs assessment to provide the clinical facts for the implementation. It also carried technologies that were emerging on the basis of desk-top engineering and small animal studies to the point of readiness for first-in-human studies.

All this happened against a background of high-profile research that has been conducted by world renowned scientists who made UCT a global hub for research on rheumatic heart disease over the past two decades [1, 2, 5, 9, 11, 14, 318, 362, 409-413]. Following Prof. Mayosi's Drakensberg Declaration [409]; Prof.Sliwa's 'Heart of Soweto' study [5] and Prof.Zühlke's 'REMEDY' study [414] which together defined the scope of the challenge of RHD in low- to middle-income countries, the Chris Barnard Department to which I belong pioneered awareness and potential solutions for those patients in need of surgery. The Cape Town Declaration [1, 12, 14, 415] signed at the celebration of the 50th anniversary of the first heart transplant in Cape Town gave rise to the global 'Cardiac Surgery Intersociety Alliance' (CSIA) [12] and to a multi-national assessment of cardiac surgical needs for RHD [1, 2]. These analyses for the first time correlated the prevalence of silent rheumatic valvular disease with that of cardiac failure and death caused by the disease allowing conservative estimates of the need for cardiac surgery. Although these indirect deductions will remain estimates until such time when well established cardiac services provide firm data, they for the first time allowed an approximate assessment of two core questions, namely how many cardiac operations should one expect to be needed in a low income country per million population and how much do the needs for cardiac surgery differ between LICs and HICs. The studies conservatively narrowed the range to 100-300 operations per million population needed in low income countries [1, 2].

As both underlying pathologies and the socioeconomic circumstances of significant parts of the population of LMICs remain distinctly different from HICs neither established hospital

systems nor surgery itself can be uncritically mirror-replicated from industrialized countries [(1)]. Therefore, the task of providing cardiac surgery in low- to middle-income countries involves much more than establishing expensive infrastructure and scarce skills [(1)]. Surgery for RHD in particular is in a difficult situation: heart valve replacement often stands at the beginning of a program, but the cost of prostheses is often prohibitive, and poor outcome [(78, 81, 83, 183, 184, 237)] makes repair rather than replacement even more desirable than in high income countries (HICs) [(416-422)]. Yet, valve repair is a skill that builds on the experience of a seasoned team, and, as such, is often absent where it is needed most. High unmet needs, population growth and the ongoing epidemiologic transition will further escalate the situation requiring a dedicated prioritisation of cardiac surgery both in LICs an MICs, something that will remain outside the economic capabilities of most of the affected countries. LICs are particularly vulnerable. Upheavals in the world economy will hit the weakest most and make perceived 'luxuries' like heart surgery the obvious targets of forced austerity. At least a new level of awareness of the scope and magnitude of this problem has begun to emerge in these countries [(1)]. The commitment of LICs towards the establishment of independently operating cardiac surgeries on the one hand and signs of a new dawn of awareness in HICs such as the 'Cardiac Surgery Intersociety Alliance' (CSIA) [(12)] are promising glimpses of hope. It is additionally encouraging that the unique position of MICs has given rise to the realisation that they are in a perfect position as a site for the development of home-grown solutions. Being much more affected by the need for next-generation, better-suited tissue valves (surgical or trans-catheter) [(22, 175, 423)] than high income countries with their aging population, the high levels of technological capabilities that have emerged in MICs over the past two decades makes them the logical development site for long-lasting bioprosthetic heart valves. This will eventually also benefit rich countries not least because it will lower the age limit for TAVIs.

In my background assessment of the suitability of existing heart valve prostheses for patients with RHD in chapter 2 it became obvious that independent of the limited access of LMICs to cardiac surgery, the threshold for using bioprosthetic valves is often wrongly higher than the anticipated life expectancy of a patient. I therefore concluded in this chapter that ill-informed decision making processes between bioprosthetic and mechanical valves have been contributing to the poor results in LMICs. At the root of this problem lies the continual uncritical implementation of Western guidelines with their 'supremacy' of the chronological age over other aspects such as socioeconomic circumstances and life expectancy. As a consequence, mechanical valves are still being implanted into patients who are often not able to deal with anticoagulation while bioprosthetic valves may be overly shunned for fear of reoperations. Behind this over-implementation of first-world guidelines is an often limited comprehension of the fact that contemporary replacement heart valves were developed for the patients of industrialised countries with their advanced medical systems. As a prerequisite for keeping the complication rates of such valves within an acceptable range, mechanical valves need reliable anti-coagulation monitoring and bioprosthetic valves should preferentially go into older patients. Both these preconditions are insufficiently met in low- to middle-income countries (LMICs) where the dominant valve pathology is rheumatic rather than degenerative [(1, 2, 8, 58, 80, 81, 98-104)]. Unsurprisingly, even if patients have access to cardiac surgery, clinical results are disappointing. Low anticoagulation compliance due to socioeconomic and cultural circumstances leads to a high incidence of lethal or debilitating thromboembolic complications in patients with mechanical valves [(78, 83, 183-186)].
I concluded that the quest for longer lasting tissue valves and anticoagulation-free mechanical valves of young patients of HICs who are eager to live an active life may add weight to the efforts of middle-income countries addressing the needs of their patients with

RHD. As such, the realization that better suited tissue valves may hold one key to the surgical treatment of RHD in LMICs provided further impetus for the translation focus of my thesis.

Proving the point that promising research data on modern 'soft leaflet' materials are opposed by poor clinical results in a MICs, I conducted a long-term follow-up study in ***chapter 4*** analysing the 10 year outcome in patients with RHD who underwent single aortic valve replacement with a mechanical valve at our institution. Indication for this valve choice was young chronological age defined as younger than 60 years. As the subgroup of patients with obvious compliance problems at the time of surgery would have received a tissue valve in the first place, the result of every fourth patients either having been dead or having had a stroke after 10 years of implantation showed in an alarming clarity how important it is to replace the 'supremacy' of the chronological age of a patient by a more comprehensive assessment of his/her circumstances and a lower threshold for soft-leaflet valves - provided modern materials are used.

Unknown to many, much progress has already been made in the field of bioprosthetic leaflet material in recent years and much of the insight has been implemented in the UCT TAVI for rheumatic patients. Calcific bioprosthetic degeneration of tissue valves had been shown to hinge on remnant immunogenicity [(19)]. Better immune-suppression through alternative crosslinking approaches [(22, 23)] and/or decellularization [(260, 262)] were shown to mitigate calcification. Alternatively, alpha-gal receptor-depleted trans-genic pigs were suggested as tissue source [(297)]. As a first step towards clinical implementation, cell membrane extraction through alcohol-based lipid wash-out [(258, 259, 261)] was partially introduced to commercial valves [(263)]. Complete decellularization with the goal of extracting the main antigen carriers from the tissue was clinically successfully demonstrated in allografts [(298)]. Decellularization of xenografts tissue [(260)] was a logical next step. While some successfully used it [(302)] as non-crosslinked patches for valve reconstruction [(303)] in order to allow tissue regeneration decellularization without crosslinking led to poor clinical outcome in other studies [(299)] suggesting that unmasked/non-crosslinked extracellular matrix may still be sufficiently immunogenic to trigger an inflammatory xenograft response. Recently, a consensus emerged that engineered crosslinking on top of decellularization near-eliminates bioprosthetic calcification [(15)]. Following two decades of conclusive research, decellularized tissue valves potentially combined with engineered crosslinking [(15)] will undoubtedly introduce a quantum leap into bioprosthetic heart valve developments. In its wake, one can expect a dramatic downward-shift of the age from which onwards tissue valves may be used. Unsurprisingly, MICs like Brazil and South Africa [(175)] and HICs with a significant burden of RHD like Australia [(301)] are currently pioneering such prostheses.
Alternatively, polymeric leaflets have been pioneered as alternative materials for 'soft-leaflet valves'. They are immune-quiescent but had previously experienced calcific degeneration due to polymer degradation and imperfect production [(304)]. Once these issues had been addressed, Daebritz and Jansen had shown the potential of such polymer valves in the challenging calf model [(305, 306)]. Momentum for polymer leaflets has additionally built up in recent years [(31, 424)] culminating in first-in-man implants in 2019 [(307)]. Accordingly, I tested the UCT TAVI for the relatively young patients with RHD with both a decellularized pericardium undergoing post-decellularization engineered cross-linking and polymer leaflets. Both were shown to have completely abolished calcific degeneration in the subcutaneous rat model.

In ***chapter 5***, I introduced the SAT TAVI system at its refined stage, 11 years after this UCT based project began to grow into an enterprise of > 60 engineers and technologists. The core element of the system is a self-homing deployment device for a balloon expandable valve; a stent that undergoes a shape-change during deployment that creates anchoring arms for non-calcific aortic valve disease and degradation- and calcification-resistant leaflet materials.

In general, apart from cost-effectiveness, TAVIs need to address very different requirements in middle- and high-income countries. The specific requirements in MICs include independence from sophisticated imaging equipment, the ability to locate and anchor the valve in the absence of calcification, the acknowledgement of resource limitations that necessitate single-staged procedures and are near-prohibitive for potential downstream interventions such as permanent pacemaker (PPM) implantations and the appreciation of the predominance of rheumatic aortic regurgitation rather than aortic stenosis with its associated fundamentally different hemodynamics, and the need for long-lasting leaflet materials for use in younger patients.

Chapters 6-9 cover the in-vivo translation of the technology which I developed over several years of this PhD first refining the animal model ***(Chapter 6)*** and the surgical technique ***(Chapter 7)*** before showing in acute implants ***(Chapter 8)*** that the above listed specific requirements are being addressed by the purpose-designed transapical balloon-expandable TAVI system developed at UCT [(423, 153)] confirming the ability of the delivery system to deploy a balloon-expandable TAVI without the need for rapid pacing and with ejection maintained throughout cardiac systole [(175)]. The subsequent chronic study ***(Chapter 9)*** demonstrated that tactile placement allows accurate positioning. As the positioning trunks consist of smooth yet bend-resistant 4mm balloons, they do not have the traumatising potential of metal arms which may cause dissections [(357)]. The trunk retrieval through invagination at the end of the procedure guarantees a friction-free withdrawal preventing dislodgement of the deployed valve. An extremely tight aortic root model such as the sheep also demonstrated the ability of the balloon trunks to maintain sufficient inflow spaces to the coronary ostia when the helical deployment balloon was fully inflated. Despite tightly stretching the sino-tubular junction, the fully inflated balloons did not cause any signs of ischaemia. Confirming ex-vivo tests, this additional safeguard of coronary perfusion warrants sustained maximal balloon inflation at the conclusion of the deployment, thereby potentially minimising paravalvular leaks and ellipticity. The hollow balloon itself providing a luminal cross-sectional area of 1.8cm^2 for a 23mm valve and an effective backflow valve that maintains sufficient diastolic pressures for coronary perfusion was hemodynamically almost 'invisible'.

In the chronic implants of chapter 9 the supra-annular stent arms resting on the ventricular side of the leaflet nadirs were proven to be firm and effective anchors in the compliant non-calcified roots of sheep. Once deployed, none of the valves migrated, dislodged or embolised. More than in pigs or calves, the over-elastic annulus of sheep had previously been shown to lead to device migration and paravalvular leaks unless stiffening reinforcement-rings were pre-implanted [(358)]. Our self-elevating stent arms added an essential feature to balloon expandable TAVIs that has, until now, only been achievable with self-expanding valves. Purely on the basis of expansion-deformation of the cobalt-chromium stent, the radius of the fully deployed arms exceeded the annular stent diameter by 25% creating a secure anchorage against dislocation.

The scalloped attachment struts for the leaflets were designed to deploy to their perfect pre-crimping shape. This was confirmed on implantation fluoroscopy. Before using it with pericardial leaflets in the chronic study, I had shown in the acute study of chapter 8 that this scallop-design also allows the continuous attachment of durable polymeric leaflets in vivo [(423)]. Particularly for the polymer leaflets, optimization of strain through avoidance of excessive oversizing made a balloon expandable concept additionally preferable. The de-facto under-deployment of valves in the sheep study was at a modest 5%, preserving near-perfect leaflet geometry.

For size reasons, I used 10-12 months old sheep in the chronic study. As the sheep ceases to be a calcification model once older than 4 months, the study was not expected to provide a validation of the tissue preservation process with regards to calcification. Yet, the pristine histomorphology of all explants, and the complete absence of inflammatory cells at both the surface and inside the decellularized pericardium, suggested an absence of a significant immune response of the TAVI pericardium. With the choice of Perimount surgical valves as controls, a latest generation tissue valve was selected. Other than the thinner pericardium used in these control valves, the two groups barely differed in their explant macro-morphology, neither in their aperture-like sub-valvular tissue shelf nor in the platelet microthrombi on the ventricular side. Neointimal outgrowth was more pronounced on the TAVIs covering the entire aortic side of the leaflets. This may have had its reason in the healing ability of the electrospun skirt that facilitated complete transmural vascularization in areas of direct tissue contact with the aorta or myocardium. The greater leaflet thickness only had a mild and not-significantly effect on pressure gradients across the valve. I believe that the unprecedented transmural endothelialisation through the skirt may hold a key to future tissue regenerating TAVI concepts, as transmural ingrowth was recently shown to be the only significant source of prosthetic surface endothelialisation [(361)] other than transanastomotic pannus outgrowth [(362)].

The most challenging part of my translational thesis was the establishment of a meaningful large-animal model suitable for the testing of a balloon-expandable TAVI in a compliant, non calcified aortic root without the pre-implantation of a reinforcement ring emulating the stiff landing zones of patients with aortic stenosis and the prediction of sizing requirements. The challenges centred on three major questions were therefore:

[1] Does the compliance of the non-calcified aortic roots of relatively young patients with rheumatic aortic regurgitation require a degree of annular overstretching for TAVI placement that may jeopardise coronary inflow?

[2] Is the known under-development of the sinuses of Valsalva in the conventional animal models – particularly in the sheep – associated with a high coronary occlusion rate and can anatomical minimum dimensions be defined which will allow safe insertion?

[3] Does a correlation of clinical dimensions of patients with rheumatic aortic regurgitation with a regression curve resulting from our clinical data on surgical and trans-catheter aortic valve replacements in patients with aortic stenosis allow a prediction of TAVI sizes needed for patients with rheumatic aortic regurgitation?

After establishing the animal model to a point where exclusion criteria for SAT TAVIs could be defined, I correlated our clinical cohort of TAVIs implanted for aortic stenosis with a cohort of an age-matched group of aortic stenosis patients who received a surgical aortic valve replacement. This provided the most conservative baseline degree of up-sizing required for trans-catheter valves in rigid aortic roots as opposed to conventional surgical valve replacements.
To determine a most extreme counter-scenario for non-calcified, over-compliant aortic roots, the degree of upsizing required in healthy sheep and pigs was determined. Eventually, an interim value between the upsizing requirements for human aortic stenosis patients with rigid, calcified roots and those for sheep and pigs undergoing TAVI implants in healthy animals with over-compliant roots was rationally deducted. While the inaccuracy resulting from the assumed equivalence of valve dimensions assessed by intraoperative sizing, pre-operative echo-, angiography or CT was acknowledged as well as the difficulty to estimate

where the correlation line between surgical dimensions and TAVI dimensions will eventually lie for patients with rheumatic aortic regurgitation, it provides at least a most rational framework for the decision making process for a new surgical treatment in the absence of any pre-existing data. Moreover, the linear correlation curve will slowly replace the approximations based on animals with real values obtained from echocardiographic intraoperative assessments of diastolic versus systolic annular dimensions in patients with rheumatic aortic regurgitation. The last pre-clinical animal series prior to FIMs hast given me strong assurance that the special design of the SAT TAVI allows us to further cut back on the degree of oversizing.

Equally important was the deduction of anatomical cut-off dimensions for the sinuses of Valsalva and the ratio's of anulus to sinus diameters as a means of defining safe spaces for coronary blood inflow post placement of a TAVI with supra-annular anchorage arms.

CONCLUSION

My thesis covered the entire clinical translation phase of a novel and lateral solution for patients of low- to middle-income countries who suffer from symptomatic rheumatic aortic valve disease and are in need of a surgical therapy.

This translation rests on a needs assessment of patients with rheumatic heart disease for replacement valves under circumstances which do not support repairs. The ***needs assessment*** comprised a major clinical study in which I demonstrated the poor long-term results after aortic valve replacement with mechanical prostheses in indigent patients suffering from rheumatic aortic valve disease. The key take-home messages of this preceding field study were:

- In LMICs with their high burden of RHD the underlying pathology, socioeconomic embedding, or patient age create fundamentally different conditions for the longevity and performance of replacement valves.
- Socioeconomic circumstances prevailing in areas endemic for RHD concur with poor anticoagulation compliance in patients with mechanical heart valves. In LICs like the Fijis the ten year mortality for mechanical heart valves (mean age 26 years) was 24% with death occurring 3.2 years after surgery and in Cameroon (mean age 28 years) the 6-year mortality with mechanical valves was 21%. In a MIC like South Africa every one in four relatively young patient post mechanical AVR was either dead or had a major thromboembolic stroke or major bleeding event in a consecutive series at Groote Schuur Hospital.
- The mean age of these patients at the time of surgery has gradually increased as a consequence of urbanisation and affluence - in South Africa from 22 in the early 1980s to 44 in 2020 further lowering the threshold for using soft-leaflet valves.
- Fear of reoperations has deadlocked discussions around valve choices on the level of evidence rooted in the 1980s. Yet, decellularization and engineered crosslinking have created rationally rooted approaches that fundamentally improved the degeneration resistance of biomaterials.
- On top of the fact that valve patients live generally shorter, even in HICs, in developing countries, patients from rural back- grounds and low socioeconomic status very often present with advanced disease. Hence, despite being young in age, the life expectancy of these patients is much lower than that of Western populations. As such, the assessment of life expectancy, based solely upon chronological age, is erroneous and age-related Western cut-offs are not valid. As such, it should be the individual life expectancy of a

patient that is the final determinant in the choice of the least detrimental valve prosthesis.

- Last not least, lack of cardiac surgical capacity is not only a big challenge for LICs but also for MICs outside the urban reach. In the likely continuation of resource scarcity in LMICs and the resulting inability to significantly expand the capacity of conventional open heart surgery, lateral deployment solutions will need to go hand in hand with improved leaflet materials.
- Therefore, a combination of easy-to-place trans-catheter technologies tailor-made for non-sophisticated medical facilities and suitable for the often compliant, non-calcified valves of patients with RHD with durable leaflet material may introduce replacement valves that eventually address the "needs of the many"

Based on large series of acute pig implants I performed in close interaction with the engineers who developed the UCT SAT valve, a reliable and safe device version eventually emerged from the iterations. I proved the ***reliability and performance*** of these devices during implantation after having developed an optimal deployment technique. As a next step I confirmed the excellent benchtop and accelerated fatigue results with further series of pig and chronic sheep implants. The key take-home points of these pre-clinical in-vivo trials were firstly technical validations:

- We proved the ability of locating the aortic valve nadirs in the absence of a hydroxyapatite footprint and sophisticated imaging equipment through a self-homing, non-occlusive deployment system purely based on tactile feed-back.
- Obviating the need for rapid ventricular pacing during implantation it allowed for a slow, controlled implantation of the TAVI prosthesis while physiological pressures were maintained throughout the implantation of the non-occlusive balloon-expandable TAVI prosthesis.
- Self-homing locator arms do not need to be part of self-expanding stents but can be balloon-based and be part of the dilatation balloon. By retraction through invagination, I proved that they can resist pinching even under the extremely tight conditions of the sheep model.
- Elevating stent structures required for the anchorage of TAVI valves in compliant non-calcified annuli do not need to rely on the shape-memory feature of self-expanding stents or two-component designs. By plastic deformation of a cobalt-chromium stent during balloon inflation, firm anchorage was achieved in the hyperelastic sheep aorta without excessive oversizing.
- Rapid pacing does not need to be an integral part of balloon expandable TAVIs. By utilizing a widely open helical balloon, the TAVI deployment was possible at the required radial forces, with continuing unimpeded ejection.
- Once deployed, none of the last-generation valves migrated, dislodged or embolised.
- The integration of scallops into cobalt-chromium stents, and the direct attachment of the leaflets to these scallops, does not result in an uneven post-crimping shape and detrimental stress concentrations. The structural integrity of the leaflets after 5 months in the sheep confirmed fatigue test data of >800 million cycles.

Importantly for implantation in potentially younger patients, I saw the same degree of pericardial resilience towards calcific degeneration of the decellularized, engineered-crosslinked bioprosthetic leaflet material that our department had proven in a methodical comparison in the rat model [(15)] but this needs to be seen in the context of a sheep-age that was not primarily chosen for a calcification study. The degree of transmural

endothelialisation, enabled by our novel, electro-spun skirt with its deliberate ingrowth spaces was particularly rewarding given the low socio-economic circumstances of LMICs and the high threshold for anticoagulation. The key points learned in this regard were:

- The presence of a 'shielding' cloth-skirt for heamodynamic sealing purposes does not preclude tissue ingrowth from the surrounding tissue as long as it has sufficient porosity. The electro-spun skirt allowed full transmural vessel ingrowth and may have facilitated the complete neointimal coverage of the adjacent leaflets.
- The pericardium was pristine after 25 weeks of sheep implants and largely endothelialised.

The remaining step prior to translation into clinical implants was to deduct from all available clinical and pre-clinical data both the anatomical exclusion criteria and an initial translation factor for choosing the correct TAVI size for patients with rheumatic aortic incompetence on the basis of pre-operative CTs. The key anatomical exclusion criteria can be summarised as follows:

- An aortic annulus to STJ ratio of >1.1 and an annulus to SOV ratio of >0.82 will be part of the implant instructions for SAT TAVIs.
- In view of an annulus to sinus ratio of <0.70 in patients with aortic regurgitation (AR) and systolic annulus to STJ ratio of 0.77 - 0.86 with extremes of 0.69 and 0.66 in patients with AR, these exclusion criteria can be considered to be extremely stringent safety measures for clinical implants.
- Clinical cut-off heights of <10.0mm for left coronary ostia in TAVIs for aortic stenosis can be carried over to patients with aortic regurgitation receiving a SAT valve. The proof of 100% survival even in pigs with their coronary ostia being as low as 5-6mm if based on CT-based sizing makes this again a very safe and conservative exclusion criterium.

I conclude, that the comprehensive scope of my PhD thesis has not only provided deep and up-to-date insight into the specific needs and circumstances of patients needing aortic valve replacement for RHD but also validated in vivo the UCT/SAT trans-catheter concept for a novel trans-catheter replacement valve that will significantly expand the access of patients to heart valve replacement. The years of intensive laboratory based research I conducted in the course of my PhD puts me into a confident position towards the next big step, namely safe 'First-in-Man' implants.

APPENDIX 1:

PhD Candidature approval letter

DOCTORAL DEGREES BOARD
UNIVERSITY OF CAPE TOWN
Masingene Building,
Private Bag X3, Rondebosch, 7701
Tel: **+27 21 650 2202**
E-mail: **ddb@uct.ac.za**

7 June 2018

STRICTLY CONFIDENTIAL

J Sherman
SCHJAC015@myuct.ac.za

Dear J Sherman

APPLICATION FOR REGISTRATION AS A PhD CANDIDATE

I am pleased to inform you that the DOCTORAL DEGREES BOARD has approved your admission as a candidate for the PhD under the supervision of **Professor P Zilla.**

The University requires that you are registered for a minimum period of two years, provided you maintain unbroken registration and comply with the rules for the degree. If you first register for the degree after 1 May, you may not count the remainder of the year as part of the minimum prescribed period of study for the programme. Provided you have met with these requirements, the earliest date on which you will be able to graduate is therefore two years after your first registration. I would like to remind you that you must renew your registration every year, not later than the last day of February.

Senate has adopted a set of guidelines for supervision for the information and use of candidates and supervisors. A copy of this is attached and we hope it will be useful.

The rules for the PhD (copy enclosed) give the dates by which you must notify this office of your intention to submit a thesis for examination. Early notification alerts the DDB to prepare for the examination process by getting examiners nominated, approaching them and obtaining their agreement before your thesis arrives. When advising of intention to submit, include the following information - student number, full names, postal address, thesis title, department and name of supervisor/s where any supervisor is not in the same department or at another university please indicate this.

Please note that there is an upper limit of 80 000 words on the main text of your thesis. Any request to exceed this limit must be discussed with the supervisor and final approval must be obtained from the Dean.

We wish you well with your research.

Yours sincerely

UNIVERSITY OF CAPE TOWN
Isaacs
DOCTORAL DEGREES BOARD

Janine Isaacs (Mrs)
Doctoral Degrees Board Office
Cc Supervisor: Professor P Zilla (Cardiothoracic Surgery)
FACULTY OF HEALTH SCIENCES
Ref: CC022018
Attachment

APPENDIX 2:

Approval letters to conduct the first-in-man clinical study at the University of Cape Town, Groote Schuur Hospital

a. UCT FHS Human Research Ethics Committee (HREC) approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

E52-Room 46, Old Main Building
Groote Schuur Hospital
Observatory 7925
Email: hrec-enquiries@uct.ac.za
Website: https://health.uct.ac.za/home/human-research-ethics

29 March 2023

HREC REF NO: 223/2018

Dr Jacques Sherman
Chris Barnard Division of Cardio-Thoracic Surgery
Groote Schuur Hospital
Observatory
7925
Email: Jacques.scherman@uct.ac.za

Dear Dr Scherman

PROJECT TITLE: EVALUATION OF THE SAFETY AND PERFORMANCE OF THE STRAIT ACCESS TECHNOLOGIES' SAT PERICARDIAL TAVI SYSTEM
PROTOCOL NO. SAT-TF-BP-07-09-02

Thank you for your feedback dated 10 March 2023 submitted to the Faculty of Health Sciences Human Research Ethics Committee (HREC) regarding Criteria 3 that the HREC requested include symptomatic patients (NYHA III, IV) older than 60 years. The HREC note that this has been included.

The HREC has approved Amendment (SAT-TF-BP-012 TAVI CIP Rev 06 Dated 06 March 2023) that includes SAT-TF-BP-011 PICF Rev04 dated 14 November 2022.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF number 223/2018 in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCE HUMAN RESEARCH ETHICS COMMITTEE

b. SAHPRA approval letter

SAHPRA
South African Health Products Regulatory Authority

SAHPRA Head Office
Building A
Loftus Park
2nd Floor
Kirkness Road
Arcadia
0083

Enquiries: Khanyisile Nkuku
Tel: N/A
Email: Khanyisile.nkuku@sahpra.org.za
Ref: MD20190501

ACRO (PTY) Ltd
Phase III, 2nd Floor Offices,
Centurion Science Park
1011 Pretorius Ave
Lyttelton Manor,
Centurion
0157

Dear Lize Schütte,

RE: APPLICATION TO CONDUCT A MEDICAL DEVICE CLINICAL TRIAL (Protocol Amendment)

Protocol Number:	SAT-TF-BP-012
Protocol Title:	Evaluation of the safety and performance of the Strait Access Technologies' SAT Pericardial TAVI System
Reference Number:	MD20190501
Applicant :	ACRO (PTY) Ltd
Investigational Product:	SAT Pericardial TAVI System (TAVI Bioprosthetic Valve ,TAVI Delivery System ,TAVI Crimper)
Risk Classification	Class D

SAHPRA
South African
Health Products
Regulatory Authority

SAHPRA Head Office
Building A
Loftus Park
2nd Floor
Kirkness Road
Arcadia
0083

In view of the promulgation of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) on the 1 June 2017 and the publication of the Medical Device Regulations on the 9 December 2016, approval of this clinical trial, by the South African Health Products Regulatory Authority, as well as the relevant Ethics approval, must be obtained, prior to commencement of the clinical trial.

The application for a medical device clinical trial protocol amendment , dated 28TH of January 2023 received by the Medical device Unit refers:

1.RESOLUTION AND APPROVAL

The South African Health Products Regulatory Authority (SAHPRA) resolved that the application for the clinical trial protocol amendment , noted above, be approved.

- Changes that result in the extension of duration of a trial (e.g affect safety, study design/statistical component)
- Change of inclusion/exclusion criteria

2.BEFORE COMMENCEMENT OF TRIAL

Please Note: Copies of written Ethics Committee approval/(s) must be submitted to SAHPRA before the commencement of the trial.

3.THE AUTHORISATION OF THIS CLINICAL TRIAL IS SUBJECT TO THE FOLLOWING PROVISIONS:

3.1 The Clinical Trial shall be conducted in accordance with the Protocol submitted to and approved by the Authority;

3.2 The Authority must be notified of any proposed amendment(s) to the Protocol and any amendment(s) to the Protocol must be approved by the Authority prior to implementation;

3.3 All Clinical trial must be conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and the South African Clinical Trial (SACT) Guidelines;

3.4 The Authority shall be informed immediately of any toxic effects or death, which may occur during the Clinical Trial and of any data received which, might cast doubt on the validity of the continuation of the Clinical Trial;

3.5 The Authority shall be notified of any decision to discontinue the Clinical Trial and the reason for such cancellation shall be stated;

3.6 The medical device(s), authorized for use in trial, may only be used for the purpose of this trial;

3.7 The medical device(s) shall be only be used by or under the direction of the authorized Trialist. In the events that the Trialist permits another Medical Practitioners to use the medical device(s), the Trialist shall remain responsible for any eventuality arising from such usage;

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South African
Health Products
Regulatory Authority

SAHPRA Head Office
Building A
Loftus Park
2nd Floor
Kirkness Road
Arcadia
0083

3.8 Approval by the Authority must be sought prior to the addition of a new Trialist. In the event that a Trialist, who was not authorised in the initial Clinical Trial Protocol Authorisation, is requested to participate in the Clinical Trial, the Curriculum Vitae (CV) of the additional Trialist must be provided to the Authority. The CV of the additional Trialist must be prepared using the relevant SAHPRA Curriculumn Vitae Format and must include the full names, address and qualification of the proposed Trialist; and

3.9 In the event that an authorized Trialist ceases to participate in the Clinical Trial, the Authority shall be informed and the reason for such cessation shall be given

4. PROGRESS REPORTS

The Authority must be furnished with signed, six-monthly Progress Reports, from each Trialist, including a report of the final results of the trial.

5. INFORMED CONSENT

In line with the relevant regulatory requirement, all Clinical Trials must adhere to the 'Principles of Informed Consent'. These requirements apply to Trial Volunteers, as well as Participants (Patients) (Reference: Section 4.8 of ICH GCP guidelines and Section 3.5 of SACT Guidelines).

Yours Faithfully

Digitally Signed by:
Dimakatso Mathibe
Senior Manager Medical Device Unit

Dr Dimakatso (Theresa) Mathibe, PhD, MBL

Senior Manager Medical Device Unit

Date: 31/01/2023 03:16:37 PM

APPENDIX 3:

University of Cape Town, Faculty of Health Sciences Animal Ethics Committee (FHS AEC) approval letters for animal trials conducted

a. AEC approval 013/021

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E53-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: Sumayah.ariefdien@uct.ac.za

10 September

AEC REF NO: 013/021

Dr J Scherman
Cardiovascular Research Unit
IIDMM
FHS

Dear Dr Scherman

PROJECT TITLE: PILOT STUDY FOR ACUTE EVALUATION OF TRANSAPICAL HEART VALVE REPAIR AND VALVE DEPLOYMENT DEVICES IN PIGS.

Thank you for submitting your study to the Faculty of Health Sciences Animal Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally authorised** the above mentioned study specifically for the use of **12 (+2 reserved) Landrace/White** pigs for one year.

Please note that the annual progress report is due in September 2014.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROF GRAHAM LOUW
CHAIR, HSF AEC

sariefdien

b. AEC approval 014/015

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E53-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: nosi.tsama@uct.ac.za

30 May 2014

AEC REF NO: 014/015

Dr J Scherman
Cardiothoracic Surgery
Chris Barnard Building

Dear Dr Scherman

PROJECT TITLE: STUDY FOR ACUTE EVALUATION OF TRANSPICAL AND TRANSAORTIC HEART VALVE REPAIR AND VALVE DEPLOYMENT DEVICES IN PIGS.

Thank you for submitting your study to the Faculty of Health Sciences Animal Ethics Committee for review.

It is a pleasure to inform you that the FHS AEC has authorised your study specifically for the use of 14 Landrace pigs for the period of one year.

Please note that the first annual progress report is due in May 2015.

Please quote the REC REF in all your correspondence

Yours sincerely

PROF PJ COMMERFORD
CHAIR, HSF AEC

lemjedi

c. AEC approval 015/008

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences Animal Ethics Committee
Room E53-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 404 7682 • **Facsimile** [021] 406 6411
e-mail: nosi.tsama@uct.ac.za
http://www.health.uct.ac.za/fhs/research/animalethics/

15 May 2015

Dr J Scherman
Cardiothoracic Surgery
Chris Barnard Building

Dear Dr Scherman

PROTOCOL TITLE: STUDY FOR ACUTE EVALUATION OF TRANSPICAL HEART VALVE REPAIR AND VALVE DEPLOYMENT DEVICE IN SHEEP.

FHS AEC REF NO: 015/008

Thank you for submitting your protocol to the Faculty of Health Sciences (FHS) Animal Ethics Committee (AEC) for review.

I am pleased to inform you that the FHS AEC has **authorised** your protocol, which will terminate on **15 May 2018**

Number of animals & species: 42 Sheep

Please quote the FHS AEC REF NO (above) in all future correspondence.

Please note that the authorisation of this protocol imposes the following obligations on the (PI) principal investigator:

1. To submit an annual mandatory progress report. The first annual report for this protocol is due on **15 May 2016**. The forms can be accessed from http://www.health.uct.ac.za/fhs/research/animalethics/forms
2. To submit a final mandatory report on the **15 May 2016**, please access the final report form from: http://www.health.uct.ac.za/fhs/research/animalethics/forms
3. Ensuring that all study participants perform within the confines of the procedures and experimental design of the protocol as authorised, or as amended.
4. Ensuring that all study participants comply with all applicable national legislation, UCT policies, FHS AEC policies and standard operating procedures (SOPs) and national standards (SANS 10386: 2008).

NTSAMA

5. Ensuring that you as the PI (principal investigator) immediately alert the FHS AEC to any event involving the welfare of the animals which has occurred during the course of the study, as well as the actions that were taken to respond to these events.
6. Ensuring that you as the PI (principal investigator) alert the FHS AEC to any new or unexpected ethical issues that arose during the course of the study, and how these issues were addressed.
7. Ensuring that all study participants are registered with or have been authorised by the South African Veterinary Council (SAVC) to perform the procedures on animals, or will be performing the procedures under the direct and continuous supervision of SAVC-registered veterinary professionals or SAVC-registered para-veterinary professionals.
8. If the principal investigator or any study participant is in any way uncertain how to respond to any of these obligations or deal with any of the issues referred to above, they must consult with FHS AEC.
9. All animals found dead must be reported to the RAF on the appropriate form: http://www.health.uct.ac.za/fhs/research/animalethics/forms
10. All animals found in distress must be reported to the RAF on the appropriate form.

My best wishes for a successful research and /or teaching endeavour.

Yours sincerely

PROF PJ COMMERFORD
CHAIR, FHS AEC

d. AEC approval 016/009

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Animal Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/animalethics/forms

01 July 2016

Dr J Scherman
Cardiothoracic Surgery
Chris Barnard Building

Dear Dr Scherman

PROTOCOL TITLE: COMPARISON AND ACUTE EVALUATION OF THE ANCHORING MECHANISMS OF A STENT WITH ARMS VERSUS A STENT WITHOUT ARMS VIA TRANS-APICAL DEPLOYMENT IN SHEEP

FHS AEC REF NO: 016/009

Thank you for submitting your protocol to the Faculty of Health Sciences (FHS) Animal Ethics Committee (AEC) for review.

I am pleased to inform you that the FHS AEC has **approved** your protocol, which will terminate on **30 July 2019**

Number of animals & species: 18 Sheep

Please quote the FHS AEC REF NO (above) in all future correspondence.

Please note that the approval of this protocol imposes the following obligations on the principal investigator (PI):

1. To submit an annual mandatory progress report. The first annual report for this protocol is due on **28 February 2017**. The forms can be accessed from http://www.health.uct.ac.za/fhs/research/animalethics/forms
2. To submit a final mandatory report on the **28 February 2019**, please access the final report form from: http://www.health.uct.ac.za/fhs/research/animalethics/forms
3. Ensuring that all study participants perform within the confines of the procedures and experimental design of the protocol as approved, or as amended.
4. Ensuring that all study participants comply with all applicable national legislation, UCT policies, FHS AEC policies and standard operating procedures (SOPs) and national standards (SANS 10386: 2008).

5. Ensuring that you as the PI immediately alert the FHS AEC to any event involving the welfare of the animals which has occurred during the course of the study, as well as the actions that were taken to respond to these events.
6. Ensuring that you as the PI alert the FHS AEC to any new or unexpected ethical issues that arose during the course of the study, and how these issues were addressed.
7. Ensuring that all study participants are registered with or have been authorised by the South African Veterinary Council (SAVC) to perform the procedures on animals, or will be performing the procedures under the direct and continuous supervision of SAVC-registered veterinary professionals or SAVC-registered para-veterinary professionals.
8. If the PI or any study participant is in any way uncertain how to respond to any of these obligations or deal with any of the issues referred to above, they must consult with FHS AEC.
9. All animals found dead must be reported to the RAF on the appropriate form: http://www.health.uct.ac.za/fhs/research/animalethics/forms
10. All animals found in distress must be reported to the RAF on the appropriate form.

My best wishes for a successful research and /or teaching endeavour.

Yours sincerely

PROF PJ COMMERFORD
CHAIR, FHS AEC

e. AEC approval 016/015

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Animal Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/animalethics/forms

14 December 2016

Dr J Scherman
Cardiothoracic Surgery
Chris Barnard Building

Dear Dr Scherman

PROTOCOL TITLE: LONG-TERM EVALUATION OF PROSTHETIC AORTIC VALVE IN A CHRONIC SHEEP

FHS AEC REF NO: 016/015

Thank you for submitting your protocol to the Faculty of Health Sciences (FHS) Animal Ethics Committee (AEC) for review.

I am pleased to inform you that the FHS AEC has **approved** your protocol, which will terminate on **30 December 2019**

Number of animals & species: 40 Sheep

Please quote the FHS AEC REF NO (above) in all future correspondence.

Please note that the approval of this protocol imposes the following obligations on the principal investigator (PI):

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My best wishes for a successful research and /or teaching endeavour.

Yours sincerely

PROF PJ COMMERFORD
CHAIR, FHS AEC

f. AEC approval 017/017

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Animal Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/animalethics/forms

20 September 2017

Dr J Scherman
Cardiothoracic Surgery
Ward D24
NGSH

Dear Dr Scherman

PROTOCOL TITLE: SURGICAL TECHNIQUE TRAINING FOR TRANS-APICAL AORTIC VALVE INSERTION IN A PIG MODEL

FHS AEC REF NO: 017/017

Thank you for submitting your protocol to the Faculty of Health Sciences (FHS) Animal Ethics Committee (AEC) for review.

I am pleased to inform you that the FHS AEC has **approved** your protocol, which will terminate on **30 September 2020.**

Number of animals & species: 10 Landrace Pigs

Please quote the FHS AEC REF NO (above) in all future correspondence.

Please note that the approval of this protocol imposes the following obligations on the principal investigator (PI):

1. To submit an annual mandatory progress report. The first annual report for this protocol is due on **28 February 2018**. The forms can be accessed from http://www.health.uct.ac.za/fhs/research/animalethics/forms
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My best wishes for a successful research and /or teaching endeavour.

Yours sincerely

PROF PJ COMMERFORD
CHAIR, FHS AEC

g. AEC approval 018/011

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Animal Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/animalethics/forms

02 August 2018

Dr J Scherman
Cardiothoracic Surgery
Ward 24
NGSH

Dear Dr Scherman

PROTOCOL TITLE: Pre-clinical safety and efficacy confirmation of a Trans-Apical Aortic Valve and Delivery Device for Aortic Valve Insertion in an acute Pig Model

FHS AEC REF NO: 018_011

Thank you for submitting your protocol to the Faculty of Health Sciences (FHS) Animal Ethics Committee (AEC) for review.

I am pleased to inform you that the FHS AEC has **approved** your protocol, which will terminate on **02 August 2021.**

Number of animals & species: 20 Pigs

Please quote the FHS AEC REF NO (above) in all future correspondence.

Please note that the approval of this protocol imposes the following obligations on the principal investigator (PI):

1. To submit an annual mandatory progress report. The first annual report for this protocol is due on **28 February 2019**. The forms can be accessed from http://www.health.uct.ac.za/fhs/research/animalethics/forms
2. To submit a final mandatory report on the **30 August 2021**, please access the final report form from: http://www.health.uct.ac.za/fhs/research/animalethics/forms
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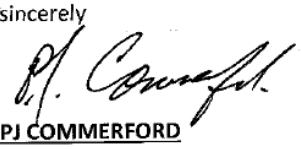
My best wishes for a successful research and /or teaching endeavour.

Yours sincerely



PROF PJ COMMERFORD
CHAIR, FHS AEC

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