

Summary

Chapter 1 is a general introduction to the subject matter of this thesis, outlining the development of transcatheter heart valve (THV) technology. The specific aims and outline of this thesis are presented.

Chapter 2 introduces the reader to the basic anatomy of the aortic valvar complex, its constituent components, and surrounding support structures. The anatomical description is greatly enhanced by high-quality images and is specifically focused on describing aortic anatomy for physicians performing transcatheter aortic valve implantation (TAVI).

Chapter 3 describes the processes of patient selection for TAVI from the perspective of an interventional cardiologist. This review stresses the importance of multimodal pre-procedural imaging and the role of the institutional Heart Team in patient selection. This chapter outlines the relevant investigations that should be performed prior to TAVI, focuses on the selection of the vascular access route, and summarises THV-sizing with multislice computed tomography (MSCT).

Chapter 4 is based on a textbook chapter that details pre-procedural planning and the performance of transfemoral TAVI. It describes the two most commonly used THV platforms: the CoreValve (Medtronic, Dublin, Ireland) and the Edwards SAPIEN (Edwards Lifesciences, Irvine, California, U.S.) valve. In each case, a step-by-step guide to vascular access, delivery catheter positioning, and prosthesis deployment is provided. The aetiology, incidence, and treatment of TAVI-related complications are outlined; (1) Cardiac: paravalvular aortic regurgitation; conduction abnormalities; atrial and ventricular arrhythmias; coronary obstruction; cardiac perforation; aortic root rupture; prosthetic valve dysfunction; embolization; thrombosis; infective endocarditis; and mitral regurgitation and mitral valve injury; and (2) Non-cardiac: stroke; vascular injury; acute kidney injury. Furthermore, the initial results of the major randomized trials of TAVI are described.

In **Chapter 5** we demonstrated the importance of MSCT-based valve sizing in TAVI recipients. We found that annulus dimensions were significantly greater when measured with MSCT compared to transoesophageal echocardiography (TOE), and this difference reduced the expected THV-oversizing by half (20 to 10%). Consequently, one in two patients in this cohort received the wrong CoreValve size. Furthermore, we showed that achieving the manufacturer recommended level of oversizing with TOE was not associated with a lower incidence of post-implantation paravalvular leak. In contrast, achieving the manufacturer recommendations using MSCT was associated with reduced paravalvular leak. Finally, we provided minimal MSCT oversizing recommendations for the 26 and 29 mm CoreValve prostheses using receiver-operating characteristic curves.

PART II. TAVI CANDIDATES AND TECHNOLOGY ADOPTION

In **Chapter 6**, the disease prevalence of aortic stenosis is evaluated and the number of potential TAVI candidates in Europe and North America is modelled. This systematic review and meta-analysis yielded a pooled prevalence of severe aortic stenosis in the general population ≥ 75 years of age of 3.4%. Using a clinical decision making algorithm derived from published TAVI studies, we estimated that some 290,000 patients in Europe (190,000) and North America (100,000) would meet current TAVI indications. This figure yields an estimated 27,000 potential TAVI candidates per annum.

In **Chapter 7**, the adoption of TAVI is described among 12 Western European Nations. The study demonstrates significant heterogeneity in the use of TAVI technology; the number of TAVI implants per million individuals ranged from 6.1 in Portugal to 88.7 in Germany (33 \pm 25). Using the estimated number of TAVI candidates described in Chapter 6, we described the penetration of TAVI in each nation: the weighted average TAVI penetration rate was low (17.9%), with significant variability between nations: Germany (36.2%) had the highest TAVI penetration while Portugal (3.4%) had the lowest. We correlated a variety of national financial and healthcare indices with TAVI utilization, and found that national economic indexes and reimbursement strategies were closely linked with TAVI use and largely explain the observed inequitable adoption of TAVI technology across Europe.

In **Chapter 8**, we review the processes of THV and surgical heart valve approval in Europe and in the U.S. We describe the potential for the introduction of objective performance criteria (OPC) for approval of new-generation THVs for use in high- and extreme-risk patient populations in the US. We recommend that the approval of THV devices for use in low- and intermediate-risk patients or for new indications should provisionally be considered only with data from RCTs. However, in the near future, data from specific RCTs (PARNTER II and SURTAVI) can form the basis for development of additional OPC for intermediate-risk patients. Development of these and future OPC should include considerations of technology maturity, short- and long-term data, specific events likely to be related to particular THV designs, patient risk profile, and statistical methods to produce OPC.

PART III. NOVEL APPLICATIONS OF TAVI TECHNOLOGY

Chapter 9 summarizes the initial evidence that was available for the innovative use of TAVI technology to treat failing surgical aortic bioprosthetic heart valves, the so-called TAV-in-SAV procedure. The basic construction of surgical bioprosthetic valves and their associated failure modes are described. The fluoroscopic identification of surgical bioprostheses and the salient procedural steps are outlined.

Chapter 10 builds on the early knowledge of TAV-in-SAV procedures described in Chapter 13. The discrepancy between the labelled valve size of surgical prostheses and the “real” internal stent diameter that is crucial for TAV-in-SAV procedural success is described. Clinical outcomes from large patient series undergoing these procedures are described. This review also describes the adaptation of TAVI technology to degenerative surgical mitral bioprosthetic valves.

Chapter 11 is derived from the Clinical Atlas of Transcatheter Aortic Valve Therapies. This unique interactive teaching tool aims to provide a highly visual aid for clinicians undertaking TAVI, and more specifically TAV-in-SAV procedures. High-quality images and videos of all current surgical bioprostheses are provided, along with a fluoroscopic identification guide, and sample TAV-in-SAV cases for reference.

In **Chapter 12** we perform the first propensity-matched comparison between TAV-in-SAV and redo surgery for patients with failing aortic bioprostheses. This analysis found that all-cause mortality was similar between groups at 30 days and 1 year (13.1% redo-SAVR vs. 12.3% TAV-in-SAV; $p = 0.80$). Similar incidences of stroke and pacemaker implantation were observed. The duration of ICU and hospital stay was reduced with TAV-in-SAV.

Chapter 13 describes the results of a large multinational registry detailing the procedural and clinical outcomes of patients with severe bicuspid aortic valve (BAV) disease treated with TAVI. The study includes 139 patients treated with the balloon-expandable ($n = 48$) or self-expandable ($n = 91$) TAVI systems. Most patients had BAV stenosis (66%) and BAV type 1 morphology (68%). The 30-day and 1-year mortality rates were 3.6% and 17.5%, respectively. We observed a high incidence of post-implantation aortic regurgitation grade ≥ 2 of 28.4%, though when patients with MSCT sizing were considered, aortic regurgitation \geq grade 2 was only prevalent in 17.4%. MSCT sizing was associated with reduced AR on multivariate analysis, and should be considered mandatory for patient with BAV disease undergoing TAVI. Further studies, evaluating the performance of novel TAVI systems in BAV morphology are required.

In **Chapter 14**, we report the technical specifications and first-in-human implant of a novel TAVI system. The CoreValve Evolut is deployed using the 14 Fr-equivalent EnVeo R delivery catheter that allows the valve to be recaptured and repositioned during deployment. The reduction in the diameter of the delivery catheter should increase the proportion of patients suitable for transfemoral TAVI, and the repositionability is intended to minimize the consequences of THV malposition. Large series with long-term follow-up are required to demonstrate the safety and efficacy of this device.

In **Chapter 15**, we performed a prospective multicentre observational study describing the feasibility and early safety of patients undergoing TAVI with transcarotid vascular access. This study includes 96 patients with unsuitable ilio-femoral vasculature that underwent transcarotid TAVI in French 3 sites between April 2009 and December 2013. Carotid access was achieved in all cases, without any significant vascular access complications. The 30-day

and 1-year mortality rates were 6.3% and 16.7%, respectively. In-hospital transient ischaemic attack occurred in 3.1%, increasing to 6.3% at 30-days. There were no cases of VARC-defined in-hospital stroke. These data provide the basis for larger studies to evaluate the safety and efficacy of this technique.

PART IV. TRANSCATHETER HEART VALVE FAILURE

Chapter 16 is a systematic review of all published cases of TAVI failure, including 87 individual cases of THV failure. Some TAVI failure modes were similar to surgical bioprosthetic heart valve failure: prosthetic valve endocarditis; structural valve failure; and THV thrombosis. Interestingly, the management of THV failure tended to differ to that historically described for surgical valve failure; most patients with THV thrombosis were treated with long-term anticoagulants rather than reoperation; and most cases of structural THV failure were treated with redo TAVI rather than proceeding to surgical valve replacement. Moreover, we identified two novel causes of TAVI failure: late embolization; and prosthesis compression. These failure modes have not been reported in the surgical literature. Our findings are expected to inform clinicians of the management of THV failure, and future iterations of consensus reporting guidelines.

PART V. TRANSCATHETER MITRAL VALVE IMPLANTATION

In **Chapter 17**, we provide an overview of emerging transcatheter mitral valve implantation (TMVI) devices. We outline the potential of these devices to treat a large number of patients with either primary or secondary mitral regurgitation that are very symptomatic and are refused surgical intervention due to excessive operative risk. Furthermore, we outline the importance of MSCT screening and the considerable hurdles associated with the development of this technology.

Chapters 18 and 19 we describe and present our experience with a systematic MSCT image analysis methodology for the assessment of candidates for transcatheter mitral valve implantation. We present results from 49 patients with heart failure and significant mitral regurgitation, in both systole and diastole, and for comparison we also report a metaanalysis of published works describing the mitral annular dimensions in patients without mitral regurgitation.