Screening, complications and outcome of aortic valve implantation
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Chapter 1

Introduction and outline
AORTIC VALVE STENOSIS

The aortic valve is located between the left ventricular outflow tract and the ascending aorta. It is a tricuspid valve consisting of semilunar cusps. For optimal functioning, the three cusps should be perfectly aligned allowing unobstructed, unidirectional flow from the left ventricle to the aorta. In patients with aortic valve stenosis, flow obstruction is observed. Although aortic stenosis can be congenital, it is mainly considered to be an age related disease; prevalence of severe aortic stenosis is estimated to increase from 0.4% in a general population, to 2% in people 65 years of age and 3-5% of those aged ≥ 75 years (1,2). The disease burden is expected to increase over the next decades owing to the ageing population with increasing life expectancies. Estimates based on current prevalence rates predict the number of patients to increase two- to threefold over the next 50 years (3,4).

DISEASE COURSE

The most prevalent form of aortic valve stenosis is calcific aortic valve disease (1,5). For years it was believed that this progressive disease was a consequence of a ‘degenerative’ process. However, nowadays calcific aortic valve stenosis is considered to be a result of a multifactorial process involving inflammation, lipid deposition, transition of valve cells and active leaflet calcification (6). The disease starts as aortic sclerosis. In the asymptomatic phase the valve becomes mildly calcified and thickened without causing outflow obstruction. If the obstruction progresses, at the early stage of disease, left ventricular output is maintained by an increase of the left ventricular wall thickness and contractility. Eventually, the left ventricle cannot maintain its output (6). Symptoms, including dyspnea, angina and syncope, arise in a late stage of the disease as a consequence of the chronic progressive left ventricular overload. Symptom onset marks an important point in the disease's course because their occurrence is associated with a very poor prognosis if the stenosis is left untreated. Reported mortality rates for symptomatic individuals are 25%-50% in the first year and even up to 90% at 5 years (7-9). Moreover, disease burden is high, as symptomatic patients suffer a decreased quality of life as a consequence of the symptoms which affect all daily activities (10).

TREATMENT

No pharmacotherapeutic measurements have proven to delay the progression of aortic valve stenosis (6). The only available treatment is implantation of an aortic valve prosthesis, either surgically or percutaneously (transcatheter). As symptom onset is associated with worse prognosis, intervention is inevitable (11,12). However, to determine the anticipated quality of life benefit of valve implantation, it is important to consider how much of the patient's symptoms are due to the (consequences
of aortic valve stenosis. This decision can sometimes be difficult and should be made by a dedicated heart-team. This heart-team also considers the preferred approach: surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI). This decision on treatment approach is based on multiple factors including the estimated surgical risk, comorbidities and frailty of the patient (13).

S U R G E R Y

Traditional SAVR requires a midline sternotomy and cardiopulmonary bypass. The first successful SAVR was performed in 1960, and over half a century it has been the standard treatment for severe symptomatic aortic valve stenosis (11,14). Over these years, major advances in technique, valve design and, most importantly, clinical outcome after SAVR have been made resulting in lower morbidity and mortality rates (15). Currently there are two main types of prosthetic valves available: mechanical and biological. Mechanical prostheses have a long durability and are therefore recommended in patients <60 years (12). However, a major disadvantage is the thrombogenicity of mechanical prostheses. Consequently patients with mechanical prostheses require lifelong use of anticoagulants (12). As some young patients refuse continuous anticoagulants and most elderly patients are at risk when receiving this medication, there has been a shift reported towards more bioprosthetic valve implantations (15). There are two main categories of surgical bioprosthetic valves: stented and stentless prostheses. The traditional valves have a stented framework, which facilitates easy and fast implantation. However, as the space-consuming stent may obstruct laminar blood flow, stentless prostheses have been introduced. Although stentless prostheses are considered to be generally more difficult to implant, experienced cardiac surgeons can reach implantation times comparable to stented prostheses (16). The debate on preferred prosthesis types is ongoing.

T A V I

In the past decade TAVI has become available as an alternative for SAVR. In TAVI a bioprosthetic valve is implanted within the orifice of the native aortic valve, using a catheter. Cribier and colleagues performed the first TAVI in 2002 (17). Initially TAVI was conceived as a last resort for patients who were inoperable or as an alternative for patients at high surgical risk due their complex comorbidities. Large randomized controlled trials showed superiority compared to conservative management in inoperable patients, and non-inferiority of TAVI compared to SAVR in high risk patients (8,18,19). After the success in this population, the number of TAVI procedures rapidly increased. Subsequent studies revealed similar outcome for TAVI and SAVR in intermediate-risk patients (20,21). The 2017 update of the American Heart Association/
American College of Cardiology guidelines now recommends TAVI for patients with a prohibitive risk for surgery (evidence class I level A), describes TAVI and SAVR as equal in high risk patients (class I level A), and TAVI as a reasonable alternative for SAVR in patients with intermediate surgical risk (class IIa level B-R) (13). Several different approaches for TAVI have emerged: the retrograde route (mainly transfemoral, but also -subclavian and -axillary), the directly aortic approach, via a ministernotomy and the antegrade transapical route, via a mini lateral thoracotomy. Transfemoral TAVI is considered the preferred access and can be performed under local anesthesia. Currently, only if small iliofemoral vessel diameters or vascular abnormalities preclude transfemoral access, patients receive a TAVI via a transaortic or transapical approach. To review the anatomy of the access routes, prior to TAVI a contrast enhanced Computed Tomography Angiography (CTA) is performed (22). CTA has become part of the preprocedural TAVI screening and is the current clinical standard to assess the cardiac, valvular and arterial anatomy. In addition a cardiac anesthesiologist reviews patients in this screening and if there is any uncertainty about denial for surgery, patients are reviewed separately by the cardiac surgeon. Following CTA, a dedicated multidisciplinary TAVI-team comes together, consisting of at least a cardiologist, cardiac-surgeon, radiologist and geriatrician. The TAVI-team once more considers the patients’ suitability for the procedure based on the (new) exams and determines the optimal access and prosthesis type and size based on a clinical review of the patient and CTA. Balloon expandable and self-expandable bioprostheses have so far been the most frequently used prostheses specifically the CoreValve (Medtronic, Dublin, Ireland) and different SAPIEN valves (Edwards Lifesciences, Irvine California, USA). Technical refinements have led to improvements in devices and already resulted in a third generation SAPIEN (SAPIEN 3), which is nowadays the most frequently used prosthesis type.

**OUTCOME**

The survival benefit of TAVI comes together with improvements in daily function and symptomatic relief in many patients (8). In a study of inoperable patients comparing TAVI with standard therapy, the rate of cardiac symptoms at 1 year was much lower for patients that underwent TAVI than in patients who had received standard therapy (25.2% versus 58.0%). But although TAVI has been successful, several complications remain an issue including vascular complications, strokes, paravalvular aortic leakage, and pacemaker implantations. The initial exploratory studies evaluated outcomes all in their own manner. After this first experience, postoperative complications, management and long-term outcomes became subject of debate. Initially the results of different studies were hardly comparable, all defining their own outcome. A major breakthrough was the consensus
criteria of the Valve Academic Research Consortium (VARC) in 2011 with a revision in 2012 (VARC-2) (23,24). In these documents the most important endpoints and complications are defined, making TAVI research and other comparisons of outcomes easier. More than 200,000 procedures have already been performed worldwide but as the field of TAVI evolves and indications shift, the number of procedures can only increase further.

AIMS AND OUTLINE OF THE THESIS
The aim of this thesis is to provide insight in the patient screening, periprocedural complications and clinical outcome after aortic valve implantation. The focus is on both the preprocedural work-up for TAVI as well as the effect of TAVI and conventional, surgical, aortic valve replacement.

SECTION I PATIENT SCREENING
Screening of the patients and their anatomy by CTA prior to TAVI has become standard practice in the work-up for the procedure. The iodinated contrast media used for CTA, may cause contrast-induced acute kidney injury. In Chapter 2 we analyze if short, 1-hour hydration with sodium bicarbonate is non-inferior to conventional 24-hour sodium chloride hydration to avoid renal function decline. After the CTA is conducted, analysis of the images frequently reveals pathology not directly relevant for the procedure, incidental findings. In Chapter 3 the influence of potentially malignant incidental findings on long-term survival after TAVI is discussed.

SECTION II PERIPROCEDURAL COMPLICATIONS
Two important periprocedural complications of aortic valve implantation are stroke, with an enormous clinical impact, and vascular complications that occur relatively frequently. In Chapter 4 we aim to elucidate the origin of thrombus causing stroke after TAVI and report the histopathologic analysis of thrombectomy material in three cases of thromboembolic complications. In Chapter 5 we analyze the current incidence, predictors and impact of vascular complications after TAVI with the latest generation balloon-expandable prosthesis, the SAPIEN 3.

SECTION III CLINICAL OUTCOME
Postprocedural outcome studies are necessary to evaluate the quality of current treatment. In Chapter 6, 4D flow magnetic resonance imaging (MRI) is used to evaluate the performance of surgical implanted stented and stentless bioprosthesis, 1 year after surgery. In Chapter 7 we compared the procedural outcome and mid-term survival after transfemoral TAVI of the SAPIEN XT and SAPIEN 3 prostheses in low to
intermediate surgical risk patients. Chapter 8 reports the trends in patient-, procedural characteristics and clinical outcome after TAVI over the last 8-years. In Chapter 9 we provide an overview of autopsy findings in patients with TAVI in their medical history and evaluate the added value of autopsy over a solely clinical determined cause of death.

In Chapter 10 the findings in this thesis are discussed and put in a future perspective. In Chapter 11 the content of this thesis is summarized. In Chapter 12 this content is summarized in Dutch.
REFERENCES