Percutaneous treatments of heart valve disease
van Dijk, Kirsten
INTRODUCTION
AND OUTLINE OF THE THESIS
INTRODUCTION

Mitral regurgitation (MR) and aortic valve stenosis (AS) are the two most frequently encountered cardiac valve diseases\(^1\), especially in the elderly patient population.\(^2\) The standard treatment for both valvular diseases is open heart valve surgery.\(^3\) At least one third of the patients are denied for surgical treatment due to comorbidities, such as advanced age, impaired left ventricular function and the presence of severe coexisting conditions.\(^1,4\) It is well known that by conservative treatment, these patients remain symptomatic and have a poor prognosis.\(^5-9\) In order to provide less invasive options to treat this mainly elderly high risk population, percutaneous devices for treatment of MR and AS were developed.

**MitraClip**

The MitraClip was developed based on the surgical edge-to-edge technique of Alfieri.\(^10\) This technique consists of leaflet apposition via a percutaneous transvenous and transseptal route. The procedure is performed in a cardiac catheterization laboratory under general anesthesia and the delivery and placement of the MitraClip is performed under transoesophageal echocardiographic guidance. A good evaluation of the mitral valve anatomy by an experienced center is very important, before the decision for MitraClip implantation can be taken. Mitral valve leaflets with severe calcifications, very short leaflets, no coaptation and rheumatic disease are all contra-indications for the MitraClip procedure. Appropriate evaluation requires specific transoesophageal echocardiography images.

The EVEREST I trial was designed to prove safety and feasibility of MitraClip implantation. A total of 107 patients with MR ≥ grade 3 were enrolled in this multicenter prospective study. The mid-term results of the study showed a reduced MR ≤ grade 2+ in 74% of the patients and very low rates of mortality and morbidity.\(^11\)

The EVEREST II trial is the only randomized clinical trial which compares the MitraClip procedure with conventional surgery. For the inclusion of this study all patients had to be eligible for both conventional surgery and MitraClip implantation. In both EVEREST I and II strict criteria had to be met for the mitral valve anatomy with the regurgitant jet originating from the A2-P2 leaflet position. All patients had MR ≥ grade 3+ (functional or degenerative) and were symptomatic or asymptomatic with new atrial fibrillation or pulmonary hypertension.\(^12\) A total of 279 patients were included in this trial, with a randomization ratio of 2:1 (MitraClip: conventional surgery). The results of this study showed that the primary efficacy endpoint (freedom from death, surgery for valve dysfunction and from MR > 3+ at 12 months) was obtained in 55% of the patients treated with a MitraClip and in 73% of the patients treated by conventional surgery. This difference was caused primarily by the higher rate of referrals for surgical treatment after MitraClip implantation. In a subgroup analyses for this primary end point, patients aged 70 or older and patients with functional MR scored significantly better when treated with a MitraClip. There was a better improvement of mitral regurgitation in the surgical
group than in the MitraClip group before hospital discharge and at 12 months follow up. After MitraClip implantation there were significantly less major adverse events, but this was mainly due to the need of more blood transfusions after surgical treatment.\textsuperscript{13} This trial shows that MR reduction with a MitraClip is safe and effective, but less effective in reducing MR than conventional surgery. MitraClip implantation seems to be more effective in functional rather than degenerative MR. Since surgery is less successful in functional MR most patients enrolled had degenerative MR.

In the EVEREST II High Risk Study patients with severe symptomatic MR and high surgical risk were enrolled for MitraClip implantation. There was also a concurrent comparator group enrolled in this study of patients with severe symptomatic MR and high surgical risk who were not eligible for MitraClip implantation. Fifty-nine percent of the patients in the MitraClip implantation group had a functional MR, which is a notable difference compared to the patients enrolled in the EVEREST II trial. MR reduction was achieved in 83\% of the patients, NYHA class improved and the MitraClip group had a better one-year survival than the comparator group.\textsuperscript{14}

In Europe, prospective studies and registries were performed with the MitraClip device, but all in patients who were considered inoperable or with a high surgical risk. Another notable difference between these European studies and the EVEREST trials is that most patients had functional MR. These studies showed that treatment with a MitraClip for severe symptomatic MR in patients with serious co-morbidity was safe and reduced MR in the majority of the treated patients. After implantation of one or more clips, patients showed improvement in functional status demonstrated by a decrease in NYHA functional class and Quality of life.\textsuperscript{15-20}

Research is ongoing in order to optimize success of this safe and promising technique.

Transcatheter aortic valve implantation

Since the first TAVI in 2002\textsuperscript{21}, there has been a rapid growth of the use of this technique worldwide. Currently there are several different types of devices developed for TAVI. The two most frequently used and studied devices are the balloon expandable Edwards Sapien prosthesis and the self-expanding CoreValve prosthesis. The Edward Sapien prosthesis can be placed by the transfemoral, transapical and transaortic approach. The CoreValve prosthesis can be placed by transfemoral and subclavian approach.

TAVI procedures can be performed in a cardiac catheterization laboratory or in an operating room equipped with fluoroscopy. The procedures are performed (depending on the type approach) under general anesthesia (all type of approaches) or local anesthesia with or without sedation (transfemoral approach). Before implantation a balloon aortic valvuloplasty is performed under rapid ventricular pacing (160-220 bmp). Thereafter the prosthesis can be placed under fluoroscopic guidance. The balloon expandable Edwards Sapien prosthesis is crimped on a ballooncatheter and deployed under rapid ventricular pacing with a balloon. The self-expanding CoreValve prosthesis is deployed by retracting the outer sheath from the delivery catheter with or without rapid ventricular pacing.
Many registry and prospective/retrospective studies were performed in the TAVI field world-wide. However, safety and feasibility are best represented in the three largest randomized clinical trials. The first randomized trial performed with TAVI was the PARTNER trial. In 2010 results were first reported about the PARTNER B cohort of patients with symptomatic severe AS who were considered inoperable. The 358 included patients were randomized to either TAVI treatment with an Edwards Sapien prosthesis by transfemoral approach or standard therapy (medical treatment and in the majority of the patients a balloon aortic valvuloplasty). This study showed that TAVI was superior to standard therapy by reducing the rate of all-cause mortality, cardiovascular mortality and repeat hospitalization. Furthermore, TAVI resolved the AS and resulted in improvement of cardiac symptoms. On the other hand, TAVI resulted in more frequent complications at 30-days (major vascular complications, major bleeding episodes and major strokes) compared to standard therapy.22 The results of the PARTNER A cohort, consisting of high surgical risk, but operable patients, were reported in 2011. These 699 included high surgical risk patients with symptomatic severe AS were randomized to either TAVI with an Edwards Sapien prosthesis (by transfemoral or transapical approach) or surgical aortic valve replacement (SAVR). TAVI and SAVR showed similar rates of survival. However, there were some differences in adverse events. In the TAVI group major vascular complications were more common, whereas major bleeding and new-onset atrial fibrillation were more frequently seen in the SAVR group. At 30 days significantly more patients in the TAVI group had symptomatic improvement and the patients in this group performed better in the 6-minute walk test than the SAVR group. At 1 year both groups had symptomatic improvement without a significant difference between groups. Also the days on the intensive care unit and index hospitalization were shorter in the TAVI group.23

More recently the results of the randomized trial with the CoreValve prosthesis were reported. In this trial 795 high-surgical risk patients with symptomatic severe AS were randomized to either TAVI with the self-expanding CoreValve prosthesis or to SAVR. Patients treated by TAVI had a significant higher rate of one-year survival than patients treated by SAVR, suggesting that TAVI may be superior to SAVR in high-surgical risk patients. The TAVI group in this trial had a lower rate of major adverse cardiovascular and cerebrovascular events compared to SAVR and no differences between groups were found in stroke rates. However, patients treated by TAVI had more major vascular complications, permanent pacemaker implantations, paravalvular regurgitation and cardiac perforation compared to SAVR. On the other hand the following conditions were more frequently seen in patients treated by SAVR compared to TAVI: bleeding, acute kidney injury, new-onset and worsening of atrial fibrillation.24

Ongoing research is performed to reduce the rate of the most common complications, such as permanent pacemaker implantation, paravalvular regurgitation, stroke and major vascular complications and to improve the devices and procedure. Also the Valve Academic Research Consortium has been developed to standardize endpoint definitions and to unify reporting to simplify comparing of clinical trials.25
OUTLINE OF THE THESIS

Both percutaneous therapies (MitraClip implantation and TAVI) have shown to be safe and feasible. Since both techniques are relatively new, many questions are raised about which patients will benefit the most from these new techniques and what complications are to be expected after treatment with one of these less invasive, percutaneous devices. The objective of this thesis is to evaluate the success of these two novel interventions by obtaining a better insight into appropriate patient selection by analyzing the success, failures and complications of these techniques.

Part I Percutaneous Mitral Valve Repair by MitraClip Implantation

Chapter 2 reviews the diagnostic work-up and treatment options for severe mitral regurgitation according to the most recent guidelines to clarify clinical decision making. Chapter 3 focuses on the predictors of survival and functional status after MitraClip implantation. Data to determine the benefit from MitraClip implantation for an individual patient are limited. We present clinical characteristics and their influence on survival and determine how these characteristics could play a role in selecting patients for this procedure. Other selection criteria for MitraClip implantation are evaluated in Chapter 4. Current available criteria for this procedure are those used in the EVEREST trial, developed to identify patients eligible for both surgery and MitraClip implantation, not to predict outcome of MitraClip implantation. We investigated the relation between mitral valve anatomy and outcome of patients referred for MitraClip implantation. In Chapter 5 hemodynamics during and after MitraClip implantation are studied, since MitraClip implantation will result in some degree of iatrogenic mitral stenosis. During the procedure mitral valve pressure gradient is measured to determine whether it is safe to place more clips. We investigated whether these intraprocedural measurements represent postprocedural measurements and whether the stenosis is affected by exercise. The effect of MitraClip implantation on the right ventricular function is described in Chapter 6.

Part II Transcatheter aortic valve implantation

Concomitant mitral regurgitation is common in patients with severe aortic valve stenosis. In Chapter 7 we analyzed the clinical course of mitral regurgitation and assessed its influence on survival and clinical status after TAVI. Chapter 8 discusses predictors for occurrence of left bundle branch block and permanent pacemaker implantation after TAVI with a CoreValve prosthesis. Furthermore, the necessity of pacing at follow-up is evaluated. In Chapter 9 the prevalence and prognostic relevance of chronic kidney disease prior to TAVI are evaluated. Furthermore the incidence and predictors for acute kidney injury after TAVI are assessed. TAVI by transfemoral approach is performed under general anesthesia in the majority of the centers. Chapter 10 reports the safety and feasibility of transfemoral TAVI procedures under local anesthesia.
In Chapter 11 the major findings presented in this thesis are summarized and future perspectives are discussed.

REFERENCES


