SUMMARY

Chapter I is the introduction to this thesis. It describes the most common prosthetic valves that are available for patients who require aortic valve replacement. This thesis focuses on the use of allografts and autografts for the replacement of the aortic valve or root. The allograft valve is also known as a human donor valve or homograft. The autograft valve is the patient's own pulmonary valve that is transplanted to the aortic position to replace the diseased aortic valve or root. By using the patient's own pulmonary valve it is necessary to also replace this valve, and this is done preferably using an allograft.

The goal of the thesis is defined as 'to develop an objective and valid methodology to support the choice for a particular aortic valve substitute in the individual patient, with a primary focus on autografts and allografts'. Eight research questions are formulated to reach this goal.

The numerous inter-related factors that play a role when the choice for a particular aortic valve substitute is made are outlined. It also becomes evident that there are no strict criteria available for the choice for a particular prosthesis in the individual patient, only general recommendations. Additionally, the experience with autografts and allografts is of limited size and duration, making it hard to reliably predict long-term outcome.

The guidelines for reporting morbidity and mortality after cardiac valvular operations are described. These will be used throughout the thesis.

Chapter II explains the microsimulation methodology that is proposed to overcome the problems that are associated with the clinical decision analysis for a particular aortic valve substitute. The aortic valve replacement microsimulation model is a computer application that allows simulation of random life histories of individual patients after aortic valve replacement. This is comparable to what a flight simulator does in the aviation industry: a flight simulator simulates flights of a particular airplane on a particular route, taking in account several conditions like the type of weather and possible chances of malfunction of parts of the plane. Microsimulation simulates the lives of particular patients after aortic valve replacement with a particular valve, taking into account several valve-related events that may occur. If microsimulation of a particular patient is repeated numerous times, a simulated patient population is created, consisting of patients with identical initial characteristics and with all possible outcomes after aortic valve replacement one can think of. From this population with identical patients the average prognosis of an individual patient with those characteristics can be calculated. Such predictions require estimates of the occurrence of valve-related events after aortic valve replacement and the effect they have on prognosis. In other words, the limited clinical evidence from real-life practice is used to feed the model with information on outcome after aortic valve replacement. The model uses this limited available mid-term information on groups of patients to make long-term predictions of outcome in an individual patient. It takes into account the most important factors that play a role when choosing a valve, and also overcomes the problems related to the limited clinical evidence that is yet available on prognosis after aortic valve replacement. On the downside, this requires several assumptions and is a potential disadvantage of the use of microsimulation.

Chapter III describes the clinical experience with the use of allografts for the replacement of the aortic valve and root in the Erasmus Medical Center Rotterdam, the Netherlands. Over a 13-year period 275 of these procedures took place in 267 patients. All patients were followed prospectively over time. The most important findings in this study were the relation between degeneration of the allograft valve and patient age, and the finding that surgical technique does not affect degeneration of the valve. Follow-up is limited, and long-term prognosis is unclear from these data.

Chapter IV describes the Dutch experience with the autograft procedure in 343 patients between 1988 and 2000. It confirms that after the autograft procedure there are 2 valve substitutes that are prone to degeneration. First of all, the autograft may dilate, causing regurgitation and eventually reoperation. In addition, the allograft that is usually implanted to replace the transplanted pulmonary valve is prone to degeneration that most often leads to stenosis of the valve substitute in the pulmonary position. Although information on a considerable number of patients was obtained, the duration of the follow-up was limited and does not provide sufficient insight into the long-term effects of these degeneration phenomena.

Chapter V concentrates on the surgical options in pediatric patients with aortic valve disease. It describes valvotomy (surgical enlargement of the stenotic aortic valve), the autograft procedure, and balloon dilatation (the interventional cardiology enlargement of the stenotic aortic valve). The study shows that valvotomy and balloon dilatation may be successful. However, residual stenosis will often necessitate aortic valve replacement at a later point in time. On the other hand, the autograft procedure effectively treats the aortic valve disease, but may result in aortic regurgitation and stenosis of the allograft in the right ventricular outflow tract. This is a bigger problem in children compared to adults, since children grow and the allograft in pulmonary position does not grow with the child. By postponing the autograft procedure (preferably until the child has stopped growing or a relatively large allograft can be implanted) with either valvotomy or balloon dilatation one can avoid the potential problems that are related to outgrowing of the valve implanted in pulmonary position that is often seen in young patients. This chapter illustrates that pediatric patients form a complex and diverse population that would be hard to capture in a microsimulation model.

Chapter VI describes the application of meta-analysis and microsimulation to predict the outcome after autograft aortic root replacement in adult patients. Autograft aortic root replacement is a well-established therapeutic option for young adults with aortic valve or root disease and has excellent mid-term results. Unfortunately, most series are small with a limited follow-up. In addition, there is little information on the durability of the autograft in aortic position and the allograft that is implanted in the pulmonary position. Meta-analysis and microsimulation modeling were used to predict long-term outcome of patients at different ages, based on currently available mid-term data. The reported results of 4 centers with autograft aortic root replacement in adults were combined with our own center's experience in a meta-analysis. The estimates of the occurrence of valve-related events after autograft aortic root replacement from the meta-analysis were entered into the microsimulation model. Next, the microsimulation model calculated for male patients of different ages (ranging from 25 to 65 years at the time of operation) life expectancy, event-free life expectancy, reoperation-free life expectancy, and life time risks of valve-related events. Most important findings were that autograft valve related events have little impact on survival, but do have a major impact on reoperation free survival and event free survival, evidenced by a actual life-time reoperation risk of 46% and a actual life-time event risk of 52%. Furthermore, it was found that the life expectancy of patients after autograft aortic root replacement is markedly reduced in comparison with the general population of the same age.

Chapter VII is a study on calculated prognosis after allograft aortic root replacement in adult patients that was done in cooperation with the section of Thoracic and Cardiovascular Surgery of the University of Oklahoma Health Sciences Center, in Oklahoma City, USA. Allografts, also known as homografts and donor valves, are valves obtained from other humans. They have been used since the 1960's for the replacement of the aortic valve or root. Aortic root replacement with cryopreserved allografts is an established therapeutic option for patients with aortic valve or root disease. It is associated with excellent hemodynamics, small endocarditis risk, low thrombo-embolic event rates and no need for anticoagulation. There is however concern regarding the long-term durability of this valve substitute, especially in younger patients. Since most reported series have a limited number of patients and/or follow-up, the combined use of meta-analysis and microsimulation was employed to calculate age-specific long-term prognosis after allograft aortic root replacement based on current mid-term evidence. The reported results of 3 centers with cryopreserved allograft aortic root replacement in adults were combined with our center's experience with cryopreserved allograft aortic root replacement in 165 adult patients and primary data from the Oklahoma center on 115 similar patients in a meta-analysis. The estimates of the occurrence of valve-related events after allograft aortic root replacement from the meta-analysis were entered into the microsimulation model. Next, the microsimulation model calculated for male patients of different ages (ranging from 25 to 65 years at the time of operation) life expectancy, event-free life expectancy, reoperation-free life expectancy, and life time risks of valve-related events and reoperations. Using the data from Rotterdam and Oklahoma on the relation between patient age and structural valve failure it was possible to construct a Weibull model that describes this relation, and implement it in the microsimulation model. Most important results of this study were the following. Structural valvular deterioration is the most important cause of reoperation. In a 25-year old patient it results in a huge lifetime reoperation risk of 84%, while in a 65-year old patient this is only 12%. The relation between patient age and structural valve deterioration is comparable to that of porcine stented bioprostheses, suggesting a similar underlying mechanism. Again, it was found that life expectancy of patients was markedly limited compared to the general population of the same age. An important limitation of this study was the fact that the estimates of the occurrence of valve related events, and in particular structural valve failure, were based on limited clinical information, causing a high degree of uncertainty with regard to outcome.

Chapter VIII compares outcome after autograft versus cryopreserved allograft aortic root replacement in adult patients, again in cooperation with the center in Oklahoma City, USA. Since limited information is available on outcome after autograft and allograft aortic root replacement, it may be difficult to make an objective choice between the 2 valve substitutes for patients who require aortic valve or root replacement. In this chapter the application of an evidence-based microsimulation model to calculate prognosis after autograft and allograft aortic root replacement, and compare the outcome between the 2 valve substitutes, is described. The meta-analyses from the previous chapters were used and, if possible, updated.

In addition, using additional information from the Rotterdam and Oklahoma datasets, a Weibull function was constructed to describe structural valve failure of the allograft in the pulmonary position after autograft aortic root replacement. This allowed us to take into account the structural valve failure pattern of both the autograft in the aortic position and the allograft in the pulmonary position after autograft aortic root replacement versus the structural valve failure of the cryopreserved allograft after allograft aortic root replacement. For male patients at different ages (25-65 years) total life expectancy, event-free life expectancy and actual lifetime risks of experiencing valve-related events were calculated after autograft versus allograft aortic root replacement. The impact of valve-related events on outcome was calculated, and relative life expectancy compared to healthy age-matched individuals was assessed. The results showed that in young patients the autograft compared to the allograft might be a better option for replacement of the aortic root, even when taking into account that after autograft aortic root replacement the allograft in the pulmonary position may also require reintervention for structural valve failure. However, again the clinical evidence on which these calculations are based is limited, and considerable uncertainty exists with regard to the calculated outcomes.

Chapter IX describes the application of microsimulation to predict the outcome after aortic valve or root replacement with autograft roots, allograft roots, stented bioprostheses and bileaflet mechanical valves. It illustrates the capability of the model to take into account the multiple interrelated factors that affect the prognosis after aortic valve replacement. In addition, it shows the ability of the model to give a detailed insight into the factors that determine outcome, allowing improved insight into the prognosis of patients after aortic valve replacement with different valve substitutes. For young patients calculated life expectancy is better with autografts, allografts or mechanical prostheses compared to porcine stented bioprostheses. However, with older age this difference disappears. Event-free life expectancy of young patients is better with mechanical valves or autografts, compared to allografts and bioprostheses. Autografts have a relatively good durability and in young patients with mechanical valves the risks of bleeding associated with the use of anticoagulant drugs is relatively low. Therefore, the outcome with these valve types is superior compared to allografts and bioprostheses. However, patients over the age of 65 have a better event-free life expectancy with autografts, allografts or bioprostheses compared to mechanical valves. This is related to the increased risk of bleeding and the increased mortality associated with bleeding in patients with mechanical valves over the age of 65 years, while patients over the age of 65 years with a bioprosthesis will most likely be outlived by there bioprosthesis and not require reoperation. An important figure in chapter IX is Figure 3. It shows that life expectancy after aortic valve replacement is markedly reduced compared to the general population, especially in the young age groups. Valve-related events play only a minor role in this reduction of life expectancy.

Chapter X contains the discussion and conclusions to this thesis and proposes future research emerging from this thesis. It answers the question whether patient-specific recommendations can be made with regard to the preferred valve substitute for patients requiring aortic valve replacement based on the methodology described in this thesis. This is done by commenting on the clinical experience with autografts and allografts, by the discussion on the methodology of meta-analysis and microsimulation, and by evaluating the outcome of the evidence-based calculations from the microsimulation model.

Furthermore, the necessary requirements for the general acceptance of this methodology by clinicians are discussed, and in particular the necessity to get the microsimulation model out of its ‘black box’ and to make it understandable for potential users.

Also, the finding in this thesis that the life expectancy after aortic valve replacement is markedly reduced compared to the general age- and gender-matched population regardless of the occurrence of valve-related events, is discussed in detail.

Finally, new research questions that emerged from this thesis are discussed, and an overall conclusion is formulated.