CHAPTER X

GENERAL DISCUSSION

The goal of this thesis was 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. This includes the important question:

Can patient-specific recommendations be made with regard to the preferred valve substitute for patients requiring aortic valve replacement, based on the methodology described in this thesis?

This question will be discussed by:

(1) Commenting on the current clinical evidence on outcome after aortic root replacement with autografts and allografts,
(2) Critically evaluating the methods of meta-analysis and microsimulation with regard to their ability to predict outcome after aortic valve replacement,
(3) Comparing calculated outcome after autograft versus allograft aortic root replacement, and versus other valve substitutes, and finally to actual situations.

Furthermore, basic requirements for the general acceptance of the microsimulation methodology by clinicians will be proposed. Also, the important new insights into the life expectancy of patients after aortic valve replacement that were obtained through these studies will be a separate point of discussion. Finally, new research questions that emerged from this thesis will be mentioned.

Clinical experience with autografts and allografts for aortic valve and root replacement

As is outlined in chapters III and IV, current clinical evidence on outcome after aortic valve and root replacement with autografts and allografts is limited in several ways.

Chapter III describes our own center's results of a prospective study with a considerable amount of 275 allograft aortic valve and root replacements over a period of 13 years[1]. Although this series is one of the largest and longest in Europe, numbers are relatively small and duration of follow-up is limited. The mid-term results of our center with allograft aortic valve or root replacement are adequate. Initially the subcoronary implantation technique was used a total of 95 times, while in more recent years root placement with reimplantation of the coronary arteries became the preferred surgical technique. Up to January 2001 180 root replacements have taken place. With the shift of surgical technique from subcoronary implantation to root replacement, the patient profile also changed. Patients operated with the subcoronary technique had mainly isolated valve disease, no aneurysm or dissection, had a better preoperative NYHA-class, and none required circulatory arrest. On the other hand, patients operated with the root replacement technique more often presented with complex aortic root disease, active endocarditis, required urgent surgery more often, and in 18% it was necessary to employ circulatory arrest. With regard to structural valve deterioration no difference was seen between the 2 surgical techniques. Younger patient age was the most important predictor of structural valve deterioration. Until recently, several reports showed a potential advantage of the root replacement technique over the subcoronary implantation technique with regard to allograft valve function and valve-related reoperation[2,3]. However, the latest study emerging from the extensive Brisbane experience shows that on the long term freedom from valve-related reoperation does not differ between the two surgical techniques[4]. Therefore, it would be conceivable to add the clinical evidence of allografts implanted with the subcoronary technique to the meta-analysis that feeds the microsimulation model. Since the subcoronary technique has been used since 1962 for allograft replacement of the aortic valve, this would provide important additional long-term information to the model. However, one should also keep in mind that patients who are eligible for allograft aortic root replacement are not always eligible for allograft aortic valve replacement using the subcoronary implantation technique. For example, a patient with an ascending aorta aneurysm and aortic regurgitation may benefit from an allograft aortic root replacement but is probably not a candidate for allograft aortic valve replacement using subcoronary implantation. Also, patients operated in the 1960's and 1970's probably represent a different patient population when compared to patients who are nowadays eligible for allograft aortic valve or root replacement.

Chapter IV describes a retrospective analysis of the Dutch national clinical experience with the autograft procedure. This national project was initiated because of the growing concern regarding the reported progressive dilatation[5-7] of the pulmonary autograft root in aortic position and the uncertainty related to the durability of the allograft in pulmonary position[8-10]. Since the reported clinical experience with autograft aortic valve and root replacement is even more limited than that of allografts, a national effort seemed appropriate, to at least increase the number of patients. Although it was accomplished to collect reliable information of 343 patients who underwent autograft aortic valve or root replacement (99% of all Dutch autograft patients), mean follow-up was limited to a mean of 4 years. It was evident from this limited experience that both the autograft in the aortic position and the allograft in the right ventricular outflow tract have a limited durability. The clinical long-term consequences of the limited durability of the 2 valves remain yet unclear. The study also includes children, which adds an important risk factor for early degeneration of the allograft in the right ventricular outflow tract caused by somatic growth of the individual. The results may therefore not be directly applied to the adult population that is eligible for autograft aortic valve or root replacement. This is also illustrated by the findings in Chapter V, where the surgical options are discussed for children with aortic valve disease. Children with aortic valve disease represent a different and complicated patient population in comparison to adults. Their heart valve disease is usually of a congenital nature and is often accompanied by other (cardiac) anomalies that may affect outcome[8]. Due to this heterogeneity among children no attempts have yet been made to extend the use of the microsimulation model to the pediatric patient population.

In summary, the clinical experience with autograft and allograft aortic valve and root replacement is still limited both in number of patients and duration of follow-up. However, current limited experience shows that both the autograft and allograft have a limited durability at mid-term follow-up. The use of the autograft is associated with an additional potential problem, namely degeneration of the allograft implanted in the right ventricular outflow tract. It is hard to make a straightforward comparison between autograft and allograft aortic valve or root replacement based on these clinical studies for a number of reasons. First, the mean age of the patients differs considerably between the two valve types (36 years for autografts versus 51 years for allografts). Also, the large proportion of children in the autograft series makes a comparison difficult. Next, the limited duration of follow-up does not allow for direct predictions of long-term outcome. Finally, the complexity and uncertainty of the potential problems related to both the valve in aortic position and pulmonary position after autograft aortic valve or root replacement form an important barrier for making comparisons between outcome after autograft and allograft aortic valve or root replacement.

Meta-analysis and microsimulation:
Objective and valid tools for prediction of outcome after aortic valve replacement?

Meta-analysis is a powerful tool for pooling data from different sources in a objective, systematic and quantitative manner. By using meta-analysis, numbers are increased and confidence limits become smaller, i.e. the estimates become more precise. However, there are several potential pitfalls to meta-analysis that also apply to the subject of this thesis. Selection bias is one example of a potential pitfall using meta-analysis[11], but also applies to individual series. Since it is well known that unfavorable results are less likely to be published, published results will most likely represent only the best experience with autograft and allograft aortic root replacement. Ideally, it would be best to also include clinical experiences that are not published. Unfortunately we were unable to track down such unpublished experiences, and our meta-analyses probably give an optimistic view of outcome after autograft and allograft aortic root replacement. Using meta-analysis it may sometimes be possible to show selection bias by comparing for each study in the meta-analysis the outcome measures to relevant quality criteria of the study. For example, a prospective study will most likely have higher complication rates compared to a retrospective study. Heterogeneity between studies is another potential source of bias when using meta-analysis. By pooling data from different centers, different surgeons, different patients and different countries and continents, substantial heterogeneity is encountered. It is important in a meta-analysis to have a well-balanced trade-off between heterogeneity (more uncertainty of estimated outcomes but better applicability) and homogeneity (more precise estimates of outcome with limited applicability). By applying clearly predefined selection criteria it was attempted to reduce heterogeneity. Also, homogeneity testing was done to identify potential heterogeneity[12]. One important source of heterogeneity is the type of valve disease that requires treatment. As evidenced from the clinical experience with allograft aortic valve and root replacement in Chapter III, the patient profile has changed considerably with the shift from allograft aortic valve replacement using the subcoronary technique to allograft aortic root replacement. This change resulted in a significantly higher overall mortality in the latter group, which is probably related to the type of valve and root disease that these patients presented with. We were yet unable to make a distinction between the type of valve disease that necessitated operation, but it will be a topic of research in the near future. Finally, the quality of the study design in the meta-analysis is of great importance. For example, one can imagine that a retrospective study will provide underestimates of valve-related events in comparison to a prospective study[13]. The meta-analyses are a combination of our center's prospective experience and mostly retrospective published reports. Therefore the estimates of the occurrence of valve-related events are probably an underestimate of the true occurrence of these events.

Microsimulation and associated simulation methodologies emerged from the field of operational research and industrial engineering. The best known application of a simulation program is the flight simulator used in the aviation industry to train pilots in simulated flights.

To date, microsimulation techniques have been used sporadically in clinical studies. A PubMed search for the term "microsimulation" dated 12 November 2001 results in 59 publications that are mainly related to health economics, for example the cost-effectiveness of screening programs. Chapter II of this thesis describes in detail the principles of microsimulation and its application to study prognosis after aortic valve replacement.

The main power of microsimulation is that it actually simulates random individual life histories of numerous (for example 10,000) patients with the same characteristics, allowing insight into the distribution of possible outcomes after aortic valve replacement for that particular patient and the importance of the individual valve-related events. It generates a hypothetical 'superdataset' of patients with identical characteristics who are all followed until death. Therefore it overcomes the 2 main problems that are associated with the current clinical evidence related to autograft and allograft aortic root replacement, namely the small number of patients and the limited follow-up. However, in order to do so a considerable number of assumptions are necessary. These assumptions can be categorized into simplifications and extrapolations.

An example of simplification in the microsimulation model is that currently only patient age and patient gender are considered when calculating prognosis, while a number of other factors are important determinants of outcome. For example, the need for concomitant coronary artery bypass grafting is a well-known risk factor for both operative and long-term mortality[3, 14-17]. Currently, the model does not take this factor into account, but assumes an average patient profile with regard to this factor based on the occurrence of concomitant coronary artery bypass grafting in the meta-analysis. In the near future we intend to implement this factor into the model. Other factors that are known to affect prognosis after aortic valve replacement, like type of aortic valve disease, left ventricular function, active endocarditis and cardiac rhythm will hopefully be added on with time[17, 18].

Another simplification of the model concerns the choice of the aortic valve substitute in those patients who require a reoperation with replacement of their aortic valve substitute. For example, in the microsimulation model when an allograft needs to be replaced for structural valve deterioration it will automatically be replaced by a mechanical prosthesis while actually an allograft, bioprosthesis or autograft could also replace this valve. Further research is necessary to investigate the effect of the choice of a particular valve substitute on prognosis of the patient in those who requires an aortic valve re-replacement.

A final example of a simplification in the microsimulation model is the assumption that the hazard for thrombo-embolism is constant with time and patient age, while in fact there is evidence that this hazard increases with age. However, this hazard also increases in the general population and is therefore implemented in the background mortality of the model that is based on the general Dutch population. Further studies are necessary to study the true relation between thrombo-embolism, time and patient age.

An example of extrapolation in the microsimulation model is the Weibull function that describes the progression of autograft and allograft structural valve deterioration with time. This Weibull function is based on the limited clinical information that is yet available on the durability of autograft aortic roots, cryopreserved allograft aortic roots, and allografts implanted in the right ventricular outflow tract. For autografts, the Weibull function is currently based on only 10 observed autograft failures from studies with a mean follow-up of 4 years or less. Based on this very limited experience the model generates predictions for long-term outcome. It is not hard to imagine that these estimates have a lot of random uncertainty, and with time may undergo considerable changes. This example shows that although the microsimulation model is capable of calculating long-term prognosis based on current clinical evidence, it is also limited by the clinical evidence. It is therefore essential to perform sensitivity analyses on the input parameters of the model, in order to study the magnitude of the uncertainty that is associated with the parameters and to put the calculated output into a perspective.

How to answer the question that is raised in the heading of this section: Are meta-analysis and microsimulation objective and valid tools for prediction of outcome after aortic valve replacement? The combined methodology is as objective as can be, given current reported evidence. It is not yet precise (this will come with growing evidence), but most likely it is valid, again given current evidence. If the current evidence that the model is based on is severely biased, for instance by selection bias, there may be a problem with validity. To date, the output of the model is not ‘a golden rule’, but merely ‘an informed guess’ based on evidence that is currently available. This brings us to another potential advantage of the model, namely that it is easy to adapt the input of the model to the growing evidence on outcome after autograft and allograft aortic root replacement. It may eventually even be fine-tuned to the individual patient that is sitting across the table in the doctor’s office deciding what the most appropriate valve substitute is in his or her unique clinical situation.

Is there an age- and gender-specific preference for a particular aortic valve prosthesis using meta-analysis and microsimulation based calculated outcome?

In young patients, overall prognosis is on average slightly better after autograft than after allograft aortic root replacement (see Figures 5-8, Chapter VIII). It is however important to realize that these predictions carry a considerable uncertainty, as evidenced from the sensitivity analyses in Chapter VIII. Especially the uncertainty concerning the durability of the autograft plus pulmonary allograft versus cryopreserved aortic allograft has an important effect on outcome. An interesting finding in Chapter IX is that prognosis of young adult patients after autograft aortic root replacement versus aortic valve replacement with a mechanical bileaflet valve is similar with regard to total life expectancy. It is even better with a mechanical bileaflet valve when considering event-free life expectancy (see figure 3, Chapter IX). The type of valve-related events that patients with an autograft encounter during their remaining life expectancy are very different from the events that patients with a mechanical prosthesis encounter. Autograft patients will probably require at least one reoperation for degeneration of their valves, while patients with mechanical valves encounter problems related to anticoagulation and endocarditis. The finding that young patients are surprisingly well off with a mechanical valve is related to the relatively short life expectancy they have: they will in general not reach an age (65 years and older) where anticoagulation related events become a major determinant of morbidity and mortality[19-21]. The relatively short life expectancy after aortic valve replacement compared to the general age- and gender-matched population will be discussed later on.

Older patients benefit more from a tissue valve than a mechanical prosthesis, as evidenced by Figure 3 in Chapter IX. Because of their limited life expectancy the older patient will generally not live long enough to face a reoperation of a degenerated bioprosthesis, while in older patients with mechanical prostheses the hazard for anticoagulant-related bleeding increases exponentially with increasing patient age, as does the mortality related to bleeding. Over the age of 65 a tissue valve is preferred over a mechanical prosthesis.

From virtual reality towards the patient: How can calculated outcome after aortic valve replacement become useful for the clinician?

Besides objections related to potential limitations of the input and the structural assumptions of the microsimulation model, the use of microsimulation in clinical practice may also encounter problems with general acceptance because of its ‘black box’ status. Although the output of the model is comprehensible and useful for the clinician, the methodology of the model often remains unclear to its potential users. It is well known that for a methodology to become accepted, one has to be able to clearly outline the concept of the methodology to its users[22]. In order to become used in clinical practice, a model should be simple, robust, easy to control, adaptive, complete on important issues, and easy to communicate with. In the 1960’s this problem was already recognized with the use of operations research models in the daily practice of managers. Mathes[23] stated the following in Science in 1966 on the subject of managers and management scientists working together to apply models:

“ The difference (managerial) people know only two degrees of probability, zero and one, and the similarity (scientific) people recognize every degree of probability, except zero and one. The difference people tend to act before they think, if they ever think; whereas the similarity people think before they act, if they ever act.”

Therefore it is essential that microsimulation as a method for clinical decision analysis is further developed in a close cooperation between health scientists and clinical experts in the field of heart valve replacement. Without this joint effort, it is most likely to end up unused on a shelf. On the one hand, the health scientists should aim at refining the model in order to obtain calculated outcome estimates that are not only precise, but also valid for the individual patient. On the other hand, clinicians should also be closely involved, and continuously test the outcomes of the model to reality. One can argue whether the microsimulation model should be refined to include all possible patient risk factors. This would result in a good applicability to the individual patient, at the cost of the transparence of the model since it will become very complex. Another option would be to keep the microsimulation model relatively simple and transparent, allowing the treating physician to work out the fine-tuning for the individual patient.

The application of the microsimulation methodology to calculate prognosis after aortic valve replacement should be published in clinical cardiology and cardio-thoracic surgery journals and presented at national and international meetings in order to reach the clinician and to elucidate the microsimulation methodology to those who may benefit and learn from it. The microsimulation model will also become available on the internet on a short notice for easy access use by third parties. The internet version of the model should be accompanied by clearly formulated directions for use, and a manual that describes the underlying structure of the model and the assumptions that are made.

Microsimulation as a method for clinical decision analysis should reach a bigger audience, raise concerns and be mocked, become an open book to clinicians, should continuously improve through these influences, and hopefully become an established but dynamic support tool for obtaining new insights into prognosis after valve replacement.

Life expectancy after aortic valve replacement: What are the areas for improvement?

An unforeseen but very important finding resulting from the studies in this thesis was the fact that life expectancy of patients after aortic valve replacement was considerably reduced compared to healthy age- and gender-matched individuals. The calculated reduction in life expectancy using microsimulation was confirmed by actual observations in the Portland dataset[24]. In the microsimulation model a calculated age and gender specific excess mortality hazard was applied to the Dutch population life tables, based on previous work[25, 26]. This reduction in life expectancy is most pronounced in young patients: it is approximately halved compared to the life expectancy of a healthy individual. Interestingly, events that are related to the valve substitute can only for a small part explain this 50% reduction in life expectancy (see Figure 3 Chapter IX). Therefore, through the improvement of the currently available aortic valve substitutes only a minor gain in life expectancy can be obtained for young patients. Focus should thus <u>not</u> be on improving aortic valve substitutes but on gaining knowledge with regard to the unexplained part of excess mortality.

One can currently only speculate about the other possible causes of excess mortality after aortic valve replacement, that in the microsimulation model are currently ‘hidden’ in the calculated excess mortality hazard that was applied to the Dutch population life tables. It could be that young patients have a relatively aggressive form of aortic valve disease that, by the time of operation, already has caused irreversible damage to the left ventricle and results in an increased cardiac mortality or sudden death in this group of patients. If this is true, then operation of these patients should take place at an earlier point in time to prevent damage to the left ventricle. Further studies are therefore needed to investigate the causes of death of patients after aortic valve replacement, and the effect of the timing of operation in relation to the severity of aortic valve disease. Another explanation for the substantial reduction in life expectancy could be that young patients mainly have congenital heart valve disease that may be associated with congenital abnormalities of the cardiac muscle that in turn could cause increased cardiac death. Thus far, no studies have investigated this possible relation, and it may be worthwhile to contemplate collecting left ventricular cardiac muscle biopsies of all patients who undergo aortic valve replacement to investigate this hypothesis.

It appears that the difference in life expectancy between patients after aortic valve replacement and healthy age- and gender-matched individuals decreases with age. At age 75, life expectancy after aortic valve replacement almost equals that of healthy 75-year-old individuals. However, one should take into account that the 75-year-old patient who undergoes aortic valve replacement is not the average 75-year-old patient who needs aortic valve replacement. He or she represents a strict selection of relatively "healthy" patients without important comorbidity and with a relatively good life expectancy. Taking this into account, these 75-year-old patients also may have a relatively short life expectancy compared to the average healthy 75-year-old individual. For these older patients, the minimization of valve-related events does result in a substantial increase in life expectancy. Therefore, carefully choosing the preferred valve substitute is also very important in the older age group.

Future research emerging from this thesis

Numerous new research questions have emerged from this thesis. The most intriguing ones are displayed below in random order and are meant to stimulate new research efforts:

1. What is the effect of the choice of the aortic valve substitute in aortic valve **re-**replacement on prognosis?
2. What is the effect of type of valve disease, left ventricular function, coronary artery disease, other cardiac disease, and cardiac rhythm on outcome after aortic valve replacement?
3. What are the main causes of excess mortality after aortic valve replacement besides valve-related events? Is there a pathophysiological or morphological explanation? Is there a difference in overall mortality in those operated 20 years ago versus 10 years ago versus those operated in the 21st century? How does hemodynamic performance of aortic valve prostheses affect prognosis?

4. What is the quality of life of patients after aortic valve replacement with different aortic valve substitutes?

In conclusion, this thesis shows that clinical experience with autograft and allograft aortic root replacement is limited, both with regard to number of patients and duration of follow-up. Meta-analysis and microsimulation provide an objective and flexible tool to overcome these limitations and allow calculations of long-term prognosis after autograft and allograft aortic root replacement based on current limited evidence. Using this methodology, detailed information can be obtained on the determinants of prognosis, providing improved insight into outcome after autograft and allograft aortic root replacement. However, both meta-analysis and microsimulation have their limitations and the output of the microsimulation model strongly depends on the quality of the input and the assumptions of the model. Continuous refinement and updating of the microsimulation model are therefore necessary to provide objective and valid estimates of outcome after aortic valve replacement in the future. Furthermore, education of clinicians on the methodology of microsimulation is essential for successful application in clinical practice. An internet application of the model should become available in the near future for easy access use by clinicians.

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