CHAPTER II

STRUCTURING THE PROBLEM: INTRODUCTION TO MICROSIMULATION MODELING

It became clear in the previous chapter that it is complicated to predict prognosis after implantation of a certain aortic valve substitute in the individual patient who requires aortic valve replacement. Multiple interrelated factors (patient-, physician-, and prosthesis-related) affect outcome after aortic valve replacement. In addition uncertainty exists with regard to long-term durability of certain valve substitutes.

Published clinical experiences provide information on outcome after aortic valve replacement on a group level. By applying standard statistical techniques for risk factor assessment (for example Kaplan-Meier curves and the Cox proportional hazard model), it is possible to identify factors that may influence long-term outcome in that particular patient group. However, it is not possible to deduct this directly to the individual patient. In addition, in reported series on human tissue valves follow-up time is limited. This results in a considerable degree of uncertainty regarding long-term outcome.

Clinical decision analysis is the science that deals with structuring and analyzing complicated clinical problems like the one addressed in this thesis. It allows for systematic assessment of clinical strategies in individual patients and is particularly useful when uncertainty exists concerning the optimal therapeutic strategy. In decision analysis, a clinical problem is represented by a decision tree. The tree describes the sequence of chance events and decisions over time. In this chapter the application of clinical decision analysis techniques to the prosthetic aortic valve choice dilemma is described, starting with the decision tree. It will soon become clear that this problem cannot easily be solved with a simple decision tree but that more advanced models are necessary. First the use of a Markov state-transition model, that allows events to be repeated over time, will be discussed. Next the application of microsimulation modeling will be explained. This technique not only allows events to be repeated over time but also allows for a memory, in that hazards depend on the occurrence of previous events. The basic assumptions of the aortic valve replacement microsimulation model will be discussed in detail. Finally, the advantages and disadvantages of modeling techniques compared to standard methods of outcomes research will be discussed.

II-1. Decision trees

A decision tree represents potential clinical strategies, and the consequences of these strategies. The basic decision tree underlying the prosthetic aortic valve choice dilemma is displayed in Figure II-1. It starts with a decision node (square), indicating the choice for a particular aortic valve substitute. After implantation of a valve substitute the patient has a

chance of dying as a result of the procedure or staying alive (the circles in the decision tree represent chance nodes). If the patient stays alive, he or she will be at risk for developing valve-related events for the remainder of life. In case the patient develops a valve-related event, he or she can either die as a result of the event or stay alive (with or without reoperation).

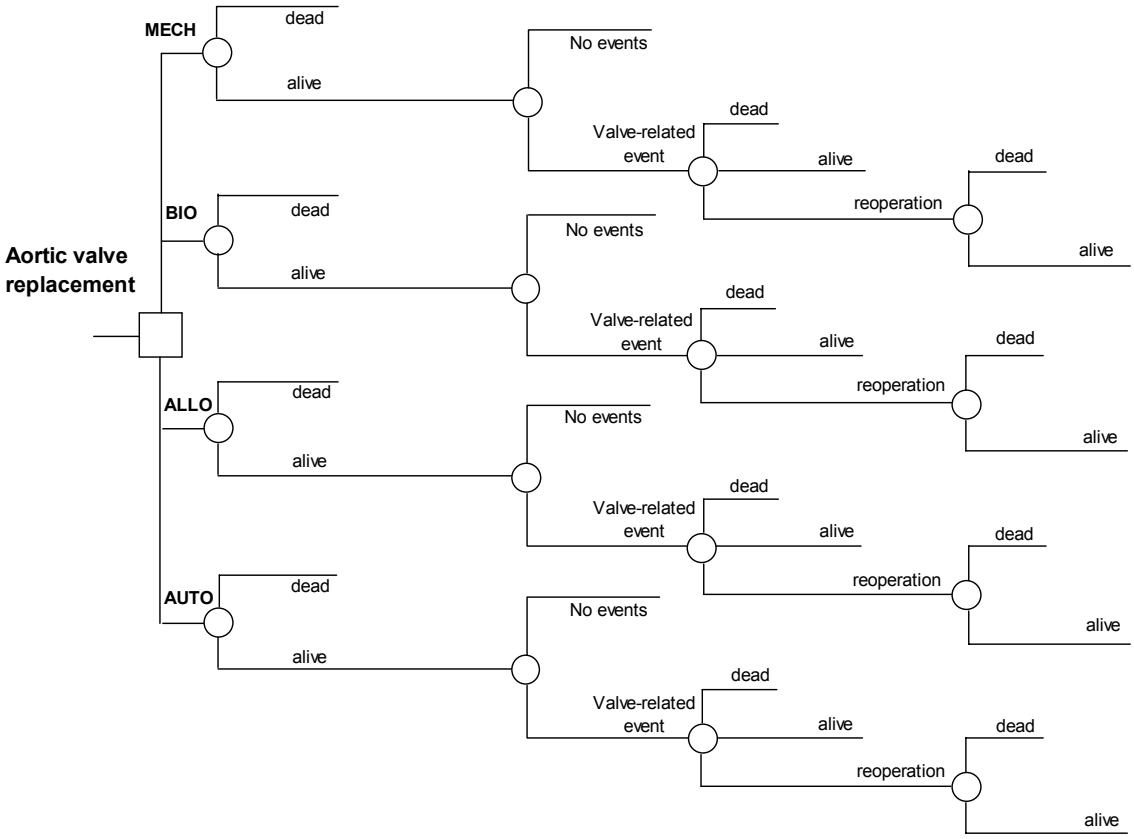


Figure II-1. A decision tree describing the possible outcomes after implantation of 4 different aortic valve substitutes (MECH = mechanical valve, BIO = bioprosthesis, ALLO = allograft, AUTO = autograft).

The overall chances of operative mortality and valve-related events vary considerably between the different types of aortic valve substitutes. If these chances could be defined in percentages it would be possible to calculate outcome (for example mortality risk or event risk) using this relatively simple decision tree. However, this is not the case. Usually the occurrence of valve-related events after aortic valve replacement is expressed as a linearized annual occurrence rate, implying that events may occur more often in patients with a relatively long life expectancy. In addition, the occurrence of bleeding, thrombo-embolism, and the occurrence of structural valve failure in bioprostheses and allografts are dependent on patient age. To complicate matters even more, it is possible to experience several and different valve-related events after aortic valve replacement. For these reasons it is not possible to use a

simple decision tree to solve the prosthetic aortic valve choice dilemma. It does however provide a solid structure to systematically organize the problem.

II-2. Markov state-transition modeling

Since valve-related events may occur repeatedly over time and their risk may change over time, and because simultaneously the patient is at risk of dying from non-valve related causes, prognosis after aortic valve replacement can more accurately be represented by a state-transition model. State-transition models allocate members of a population into one of several health states. Transitions occur from one state to another at predefined time intervals according to transition probabilities. In Figure II-2 the basic assumption of a state-transition model is applied to the aortic valve replacement problem: patients who undergo aortic valve replacement can enter a number of discrete health states over time.

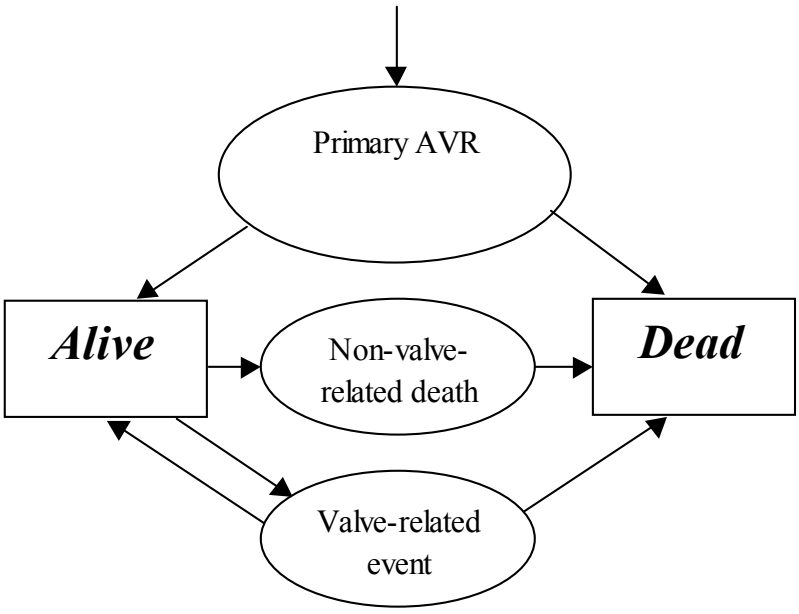


Figure II-2. Schematic representation of different health states of a patient after aortic valve replacement.

First of all, a patient can die as a result of the operation. If the patient survives the operation he or she enters the state "Alive" and is at risk for developing valve-related events for the remainder of life. If the patient experiences a valve-related event, he or she may die due to the event (immediate or as a result of reoperation) or stay alive (with or without reoperation). Eventually, the patient will either die of valve-related or non-valve-related causes.

A Markov state-transition model creates an infinite large virtual population of patients that is followed over time. In figure II-3 an example of a Markov state-transition model applied to the aortic valve replacement patient group is displayed.

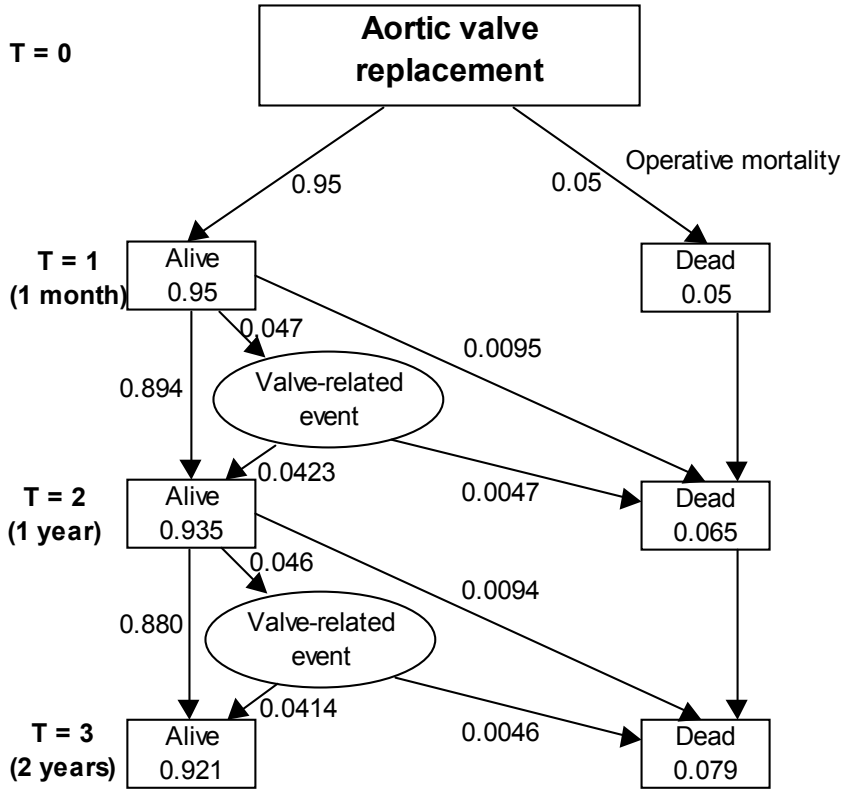


Figure II-3. Example of a Markov state-transition model applied to a patient population after aortic valve replacement. The numbers represent the fractions of the population in the different health states and in the transitions between health states. T = 0: time of operation, T = 1: 30 days postoperative, T = 2: 1 year postoperative, T = 3: 2 years postoperative.

At predefined time intervals transitions may occur from one health state to another, depending on (1) operative mortality rates, (2) the probability of dying from non-valve-related causes and (3) the probability of dying due to a valve related event during that time interval. If one assumes that operative mortality is 5%, then 5% of the population will die due to the operation. Next, suppose that during the interval T1-T2 (from 1 month until 1 year postop) the probability of death due to natural causes is 1%, and the chance of having a valve related event is 5% and the lethality of this event is 10%. During this time there is competition between death due to natural causes and death due to valve-related events. Competing risks are taken into account with the Markov model by using hazards instead of risks. Of the patients 89.4% will stay alive without experiencing an event, 4.7% will experience the valve-related event (4.2% will survive, and 0.47% will die as a result), and 0.99% will die of natural

causes. In summary, during the time intervals T0-T2 (the first year after operation), 5% of the population has died as a result from the operation, 0.99% due to natural causes, and 0.47% due to valve related events. At T=2 93.6% of the original population is still alive, while 6.4% has died. Suppose the same hazards apply to the next time period (T2-T3). This will result in a survival rate of 92.2% and a death rate of 7.8% at T=3. It is possible to change the hazards of valve related events and of death due to natural causes with each time period.

This example shows that this Markov state-transition model:

1. Takes in account the life expectancy of the patient. By varying the hazard of death due to natural causes, it is possible to vary life expectancy.
2. Allows for hazards to change with each time interval, enabling for example the hazard for structural valve failure to increase with time.
3. Allows for valve related events to occur repeatedly over time.

A shortcoming of this Markov state-transition model example is that the probability of an event is independent from the previous state, in other words there is no memory. For example, if a patient has had an aortic valve replacement in the past, in real life the chance of dying as a result of a repeat aortic valve operation is increased[1, 2]. It is possible to add memory to this Markov model example, for example to increase the risk of death with each reoperation. This will however result in a very complex structure of the model ("curse of dimensionality") and defeat the purpose of the model: to provide a simple and transparent scheme of the clinical problem.

II-3. Microsimulation modeling

Microsimulation is based on the same principle as Markov state-transition modeling (Figure II-2): after aortic valve replacement a patient can enter several health states. Transition from one health state to another does take place according to the transition probabilities, but the most important difference with Markov state-transition modeling is that Markov modeling is deterministic or probabilistic, while microsimulation is stochastic. In Markov state-transition modeling a virtual population is followed over time, while using microsimulation life histories of virtual individuals in a population are generated. Markov modeling uses average numbers of events in the population and assumes that the probability of an event is independent from the previous state. On the other hand, microsimulation actually simulates life histories of individuals in a population repeatedly many times, and allows the probability of events in an arbitrary complex way to depend on the occurrence of previous events. After gathering a sufficiently large number of life histories, the average

estimates of occurrence of events in the simulated microsimulation population will approach those of the deterministic Markov model.

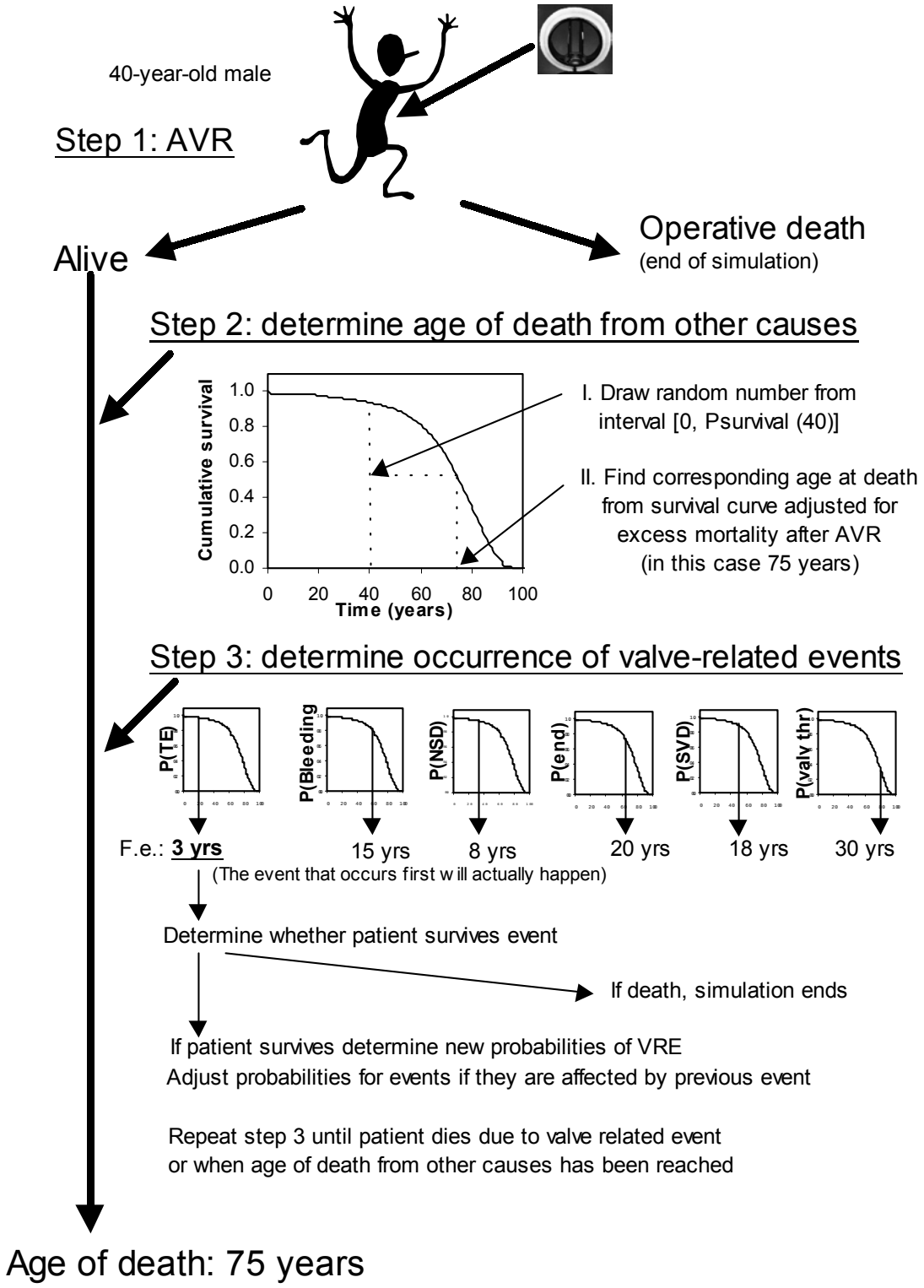
Figure II-4 represents the microsimulation of one life history of a virtual 40-year-old male individual in a population of 40-year-old males requiring aortic valve replacement. A number of steps can be discerned:

Step 1. First, it is randomly determined whether a patient will survive the operation. Operative mortality is dependent on the age of the patient and of the valve type that is implanted. Let's assume that the patient survives the operation. Next, the real microsimulation process can start.

Step 2. From the general population life table for 40-year-old males the age of death is randomly drawn. In this case the Dutch general population life table adjusted for excess mortality after aortic valve replacement is used (see paragraph II-4-1)) The random draw in the example results in death at the age of 75, if no valve related events interfere.

Step 3. Next, for all valve-related events the simulated age at which they will take place is simulated by randomly drawing the age at which each valve related event would take place from the distribution of the duration until each valve related event starting at the time of primary valve surgery. The distribution of the occurrence of the different valve related events will be discussed in the next paragraph. The valve related event with the earliest age of occurrence is taken to be the first event that really happens. The probability of immediate mortality (directly or due to reoperation) is used to randomly determine whether the patient will die of the event or not. In the first case the simulation of this patient is finished, in the latter case the simulation goes on. The time of the next event is determined. If the distributions of time until events are affected by the event that just occurred, new random times until event are drawn from the adapted distributions. Again the event with the earliest simulated time of occurrence will be the one that really occurs. This process continues until the patient has died from a valve-related event, or because the simulated time of death has been reached.

Step 4. This simulation is repeated for a large number of random 40-year-old male patients (for example 10,000 or 100,000), and thus a virtual population is created. From this population average estimates of outcome can be calculated, for example event-free life expectancy, total life expectancy, and lifetime event risk. The more patients are simulated, the more precise these estimates become since random noise disappears.



Step 4: repeat Step 1-3 many times to create simulated population

Figure II-4. Example of the microsimulation of a life history of a virtual 40 year old male individual in a population of 40 year old males requiring aortic valve replacement.

This example shows that microsimulation is not only capable of (1) taking in account life expectancy of the patient, (2) changing hazards over time and (3) allowing events to occur repeatedly over time, but also of (4) adjusting hazards depending on events that occurred in the past. In addition, it allows detailed insight into the life history of each virtual patient, including the duration of the event-free period, the total number of years lived and the numbers of each of the events per patient.

In order to apply microsimulation to the aortic valve substitute choice dilemma, a number of basic assumptions are necessary. These will be discussed in the following paragraphs.

II-4. Basic assumptions of the microsimulation model

A microsimulation model aims to provide an objective, reliable and valid structure to estimate prognosis after aortic valve replacement. In order to do so it is essential that the underlying structural assumptions of the model, i.e. (1) operative mortality estimates, (2) the evidence-based estimates of mortality due to non-valve related causes (background mortality) and (3) the evidence-based estimates of the occurrence and lethality of valve related events are valid, i.e. unbiased and precise. In the next 3 paragraphs these issues will be discussed.

II-4-1. Operative mortality

Every aortic valve replacement is associated with a risk of death due to the surgical procedure. This risk may vary with the type of prosthesis that is implanted, and obviously increases with patient age and with each reoperation. In addition, the etiology of the valve lesion, concomitant procedures and other well-known risk factors may also affect operative mortality.

Implanting a mechanical valve or a bioprosthesis is relatively easy, because only the aortic valve itself is replaced and the implantation of these devices is straightforward. However, replacing the aortic root as is done using autografts and allografts, is far more complicated. The patient's aortic root is excised, and the coronary arteries are mobilized and re-implanted in the new aortic root. In addition, the autograft procedure also requires replacement of the pulmonary valve. Using the microsimulation model it is possible to vary operative mortality for each aortic valve substitute separately.

Operative mortality increases with patient age. Figure II-5 shows the distribution of operative mortality by age group according to the 1997 U.S. data on aortic valve replacement from the STS database (http://www.sts.org).

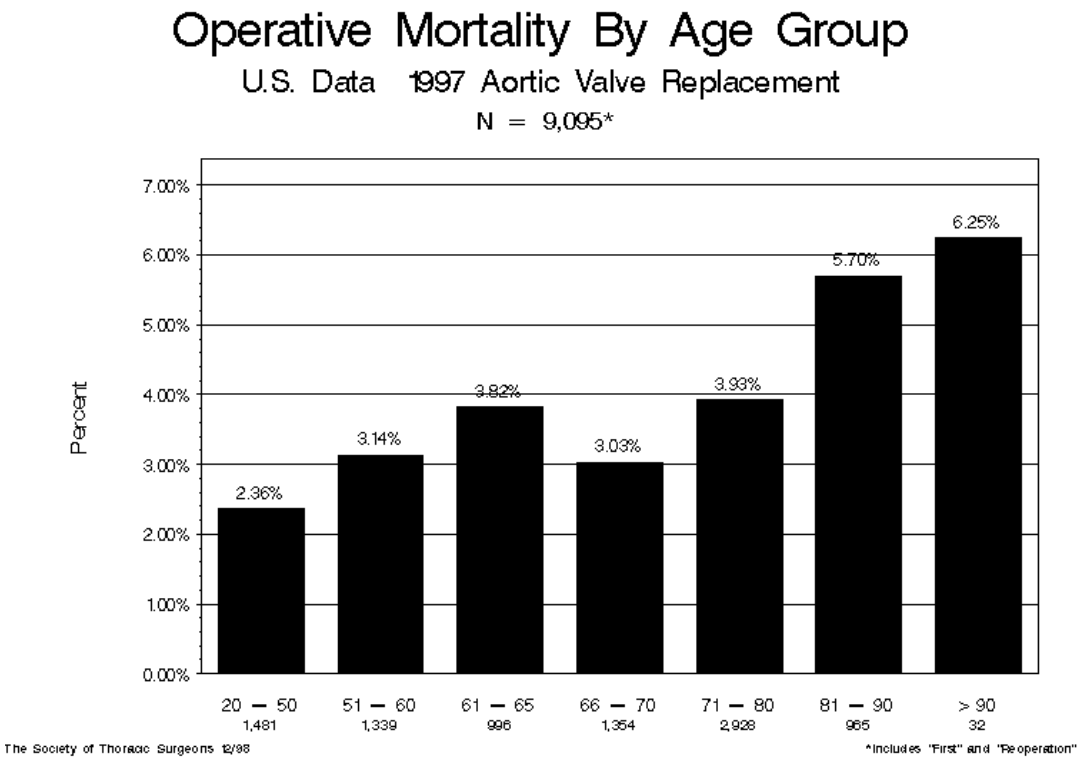


Figure II-5. Distribution of operative mortality rates by age group according to the 1997 U.S. data on aortic valve replacement from the national Society of Thoracic Surgeons database.

Operative mortality increases from an average of 2.4% in patients younger than 50 years at the time of operation to 6.3% in patients over 90 years of age. According to the UK Heart Valve Registry 30-day mortality of patients aged 80 years or older is 6.6% [3], while overall 30-day mortality after isolated aortic valve replacement is 4.7% (source: The United Kingdom Heart Valve Registry Report 1997). The microsimulation model allows operative mortality to increase with age by multiplying an age-specific odds ratio with the estimated risk of operative mortality.

Operative mortality also increases with each reoperation, with reported overall estimates varying from 5.6 to 18% [1, 2] (http://www.sts.org). Figure II-6 shows the 1997 U.S. data from the STS database on operative mortality at first versus reoperation, illustrating that compared to the first elective operation the operative risk of the elective reoperation more than doubles. Using the microsimulation model the risk of operative mortality is increased with each reoperation, by multiplying an odds ratio with the estimated risk of operative mortality with each reoperation. For example, when operative mortality of the initial operation

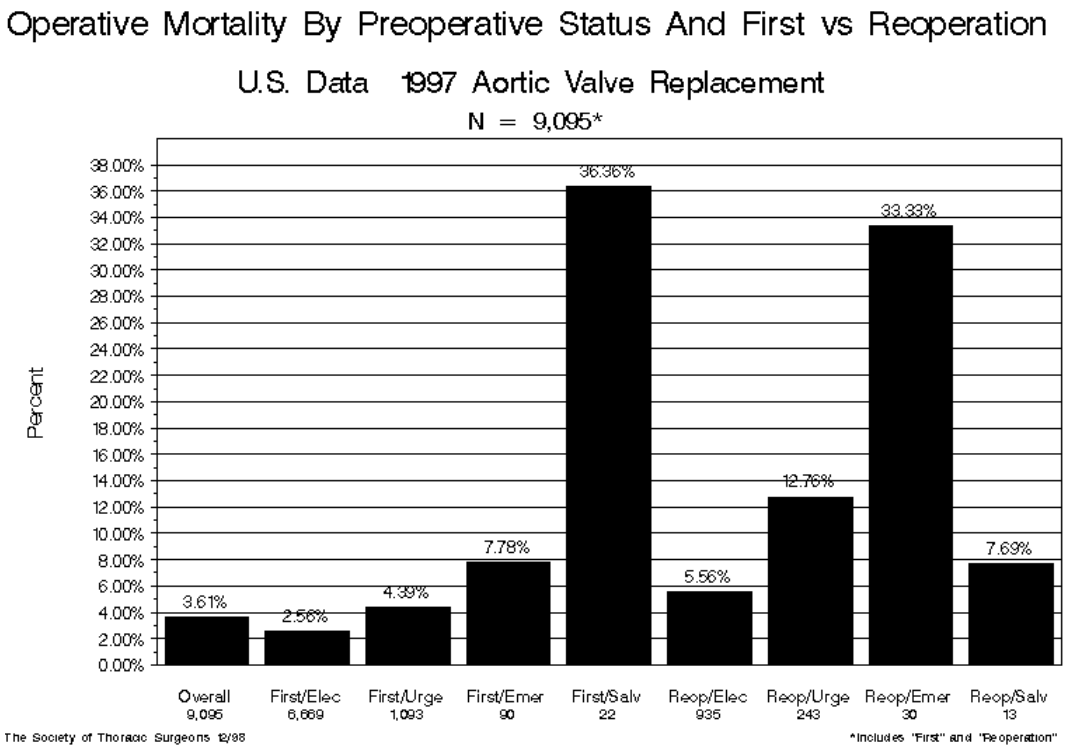


Figure II-6. Operative mortality rates in primary versus reoperative aortic valve replacement according to the 1997 U.S. data on aortic valve replacement from the national Society of Thoracic Surgeons database.

is 5%, and the operative mortality odds ratio for each subsequent reoperation is 1.7, then operative mortality of the first reoperation is 5%*1.7=8.5% and the second reoperation 8.5%*1.7=14.5%.

II-4-2. Background mortality

Survival of a 40-year old male patient after aortic valve replacement differs considerably from survival of a healthy 40-year old male. Figure II-7 shows that 20-year survival of a 40-year old male patient (from the Portland dataset, estimated using a Gompertz model) after aortic valve replacement is 44%, while that of a healthy 40-year old male is 89%[4, 5]. Operative mortality and the occurrence of valve-related events cannot solely explain this difference in survival.

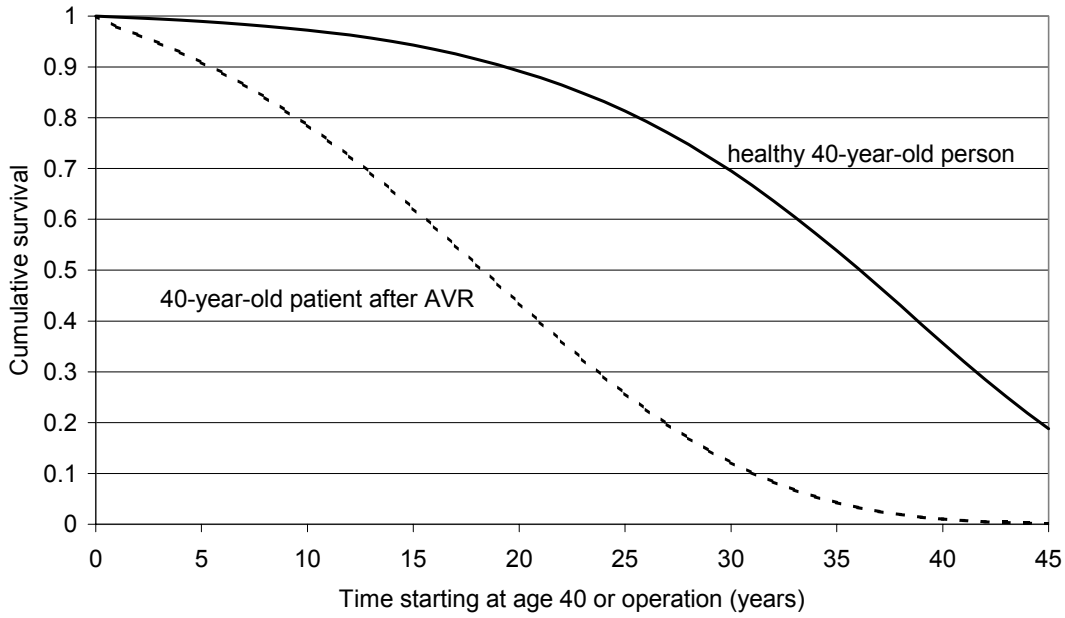


Figure II-7. Cumulative survival of a 40-year-old male patient after aortic valve replacement with a mechanical valve or bioprosthesis (dotted line) compared to a 40-year-old healthy male (solid line).

Aortic valve disease is not limited to the aortic valve itself: it also affects the heart. One can imagine that the strain posed on the myocardium by aortic valve disease will result in damage of the myocardium. Therefore, cardiac death will probably be more common in patients with heart valve disease compared to the general population. Also, sudden unexplained unexpected death is probably more common in the former group. These may partly explain the observed differences in mortality.

Several groups have investigated the causes of excess mortality in patients after aortic valve replacement [6-9]. Risk factors for late mortality after aortic valve replacement include pure aortic regurgitation, pre-operative atrial fibrillation, advanced New York Heart Association class, and coronary artery disease.

How can excess mortality in patients after aortic valve replacement best be implemented in the background mortality of the microsimulation model? Previous studies found that excess mortality is of a multiplicative nature, and decreases from a hazard ratio of 6 at age 35 to a hazard ratio of 1 at age 75 [8, 10]. A 75-year old patient has a similar life expectancy compared to a healthy 75-year old, largely caused by patient selection before operation. In a recent publication on the application of Markov state-transition modeling to the aortic valve substitute choice dilemma it was stated that excess mortality after aortic valve

replacement is merely determined by coronary artery disease [11]. This excess mortality of 1.2% yearly was added to the life table estimates of the US general population. Although the presence of coronary artery disease is often referred to in relation to excess mortality after aortic valve replacement [6, 7], a recent study found that this relationship is only a weak one and mainly associated with patient age [8]. Therefore we employed a multiplicative excess mortality throughout the studies in this thesis. Compared to the additive model, the multiplicative model results in a shorter life expectancy of younger patients (-16% at age 50) while the life expectancy of older patients is slightly better (+6% in patients aged 80)[12].

The aortic valve replacement microsimulation model allows both the use of an additive excess mortality [11] and multiplicative excess mortality [10, 13].

II-4-3. Modeling the occurrence of valve-related events

Valve-related events that occur after aortic valve replacement can be implemented in the microsimulation model in different ways:

1. Zero-risk; there is no risk of an event.
2. Constant hazard; the probability of the event is constant over time.
3. Two-period; there is a discrete period of increased hazard of a predefined duration, followed by a period of 'baseline' constant hazard.
4. Weibull function; this distribution describes a risk that increases with time [14-16].

In addition, the microsimulation model allows these hazards to vary with age, with the occurrence of each valve-related event and with each reoperation.

The results of valve-related events (death or reoperation) are implemented in the microsimulation model as risks. Death can be a direct result of the event or can occur indirectly through mortality risk related to reoperation.

In the following paragraphs the models used to describe the occurrence of the individual valve related events will be discussed.

Structural valvular deterioration (SVD)

SVD is restricted to tissue valves. Mechanical valves are designed to last a lifetime and therefore in theory have a zero risk of SVD. An example of an exception is the Bjork Shiley valve that showed an increased risk of strut fracture and is no longer in use [17]. Tissue valves on the other hand have a limited life span. The hazard of SVD increases with time since implantation in bioprostheses, in allografts and is also likely in autografts [18-21], and is therefore best described using a Weibull function. In addition, for bioprostheses and allografts

the hazard of SVD is increased in younger patients [18, 20, 22], necessitating the addition of the factor patient age to the Weibull function.

In the microsimulation model SVD is modeled as described above. The consequences of SVD are either death or reoperation. The chances of death and reoperation due to SVD can be entered into the model. In case of reoperation, a new aortic valve device needs to be specified.

Non-structural dysfunction (NSVD)

NSVD occurs in all types of aortic valve substitutes and no evident changes in hazard take place over time [18]. Therefore, NSVD is described using an exponential distribution. The consequences of NSVD are either death or reoperation. The chances of death and reoperation due to NSVD can be entered into the model. In case of reoperation, a new aortic valve device needs to be specified.

Valve thrombosis

Valve thrombosis is a very rare complication that is mainly reported in mechanical valves and to a minor extent in bioprosthetic prostheses [23, 24]. The hazard function for valve thrombosis peaks in the first year after operation and declines thereafter [25]. Since it is a very rare complication and has not been described after allograft or autograft implantation, it is described throughout this thesis using an exponential distribution or a zero risk. The consequences of valve thrombosis are either death or reoperation. The chances of death and reoperation can be entered into the model. In case of reoperation, a new aortic valve device needs to be specified.

Embolism

Embolism or thrombo-embolism is most common in patients with mechanical prostheses, but may also occur after implantation with the other types of aortic valve substitutes. There is a period of increased hazard of embolism immediately after aortic valve replacement with a mechanical prosthesis [25]. This is caused by the fact that it takes some time to determine the optimal dose of anticoagulants to obtain the optimal anticoagulation level. Furthermore, during the initial period after aortic valve replacement, there is not yet endothelisation of the sewing ring of the mechanical valve causing additional thrombogenicity. This period of increased hazard is reported to last 3-6 months [25]. Thereafter, the risk is constant over time. It does however vary with the level of anticoagulation [26, 27].

Also, the hazard increases with the aging of the patient. However, this hazard also increases with the aging of the entire population [25, 28]. Additionally, the hazard of embolism increases with each embolic event [25].

Since embolism is not common after implantation with allografts or autografts, we used constant hazard estimates of embolism in the model throughout this thesis. It is however possible using the microsimulation model to define a two-period hazard or use a Gompertz distribution, to increase embolism hazard with patient age and also to increase hazard with the occurrence of each embolic event. The chance of death due to the occurrence of a thrombo-embolic event can be entered into the model.

Bleeding

Bleeding may occur after implantation with any of the aortic valve substitutes, but is most important after aortic valve replacement with a mechanical prosthesis and related to the anticoagulation level [26, 27]. In the first period after operation there may be an increased hazard caused by greater initial variation in the level of anticoagulation. Thereafter the hazard is constant over time, although variation with the level of anticoagulation remains. In addition, the bleeding hazard increases with patient age, as does the bleeding hazard in the general population.

Since bleeding is not common after implantation with allografts or autografts, we used constant hazard estimates of bleeding in the model throughout this thesis. It is however possible using the microsimulation model to define a two-period hazard or apply a Gompertz distribution, that increases bleeding hazard with patient age and also to increase hazard with the occurrence of each bleeding event. The chance of death due to a bleeding event can be entered into the model.

Endocarditis

Endocarditis may occur after implantation with any of the aortic valve substitutes, but is most common in patients with a mechanical prosthesis or a bioprosthesis. Also, patients who underwent aortic valve replacement because of endocarditis are more prone to develop operated valvular endocarditis. After an early period of increased hazard after implantation with a mechanical prosthesis or a bioprosthesis, the hazard remains constant over time [29].

After implantation with an allograft or an autograft no early increased hazard is observed, and the hazard can well be described using an exponential distribution. The consequences of

endocarditis are either death or reoperation. The chances of death and reoperation can be entered into the model. In case of reoperation, a new aortic valve device needs to be specified.

II-5. The advantages and disadvantages of microsimulation

In this chapter it was illustrated that the use of a microsimulation model allows for simulation of the life histories of patients with particular characteristics. By simulating a large number of life histories a large population of patients with these particular characteristics is built. A major advantage of microsimulation compared to standard techniques of outcome research is that a detailed insight into the events that may occur in the individual patient is obtained. For example, using Cox regression analysis one can identify that patient age is a risk factor for late mortality. When using microsimulation one can actually calculate late mortality for a patient with a certain age, given the fact that age is a risk factor. An additional advantage of microsimulation is the fact that it allows predictions of long-term outcome based on current clinical evidence by systematically extrapolating evidence on the occurrence of valve-related events, while taking in account competing risks between valve-related events and mortality due to natural causes.

Two major disadvantages of the microsimulation model are (1) that it is a simplification of real life and (2) that it is limited by the quality of the input.

By structuring the clinical problem, simplification of reality can not be avoided. As long as the model remains an adequate representation of reality for the purposes of the study this is no problem. One can test whether this is the case. For example, mortality as calculated with the microsimulation model should correspond to mortality in a large real life data set of similar patients.

The quality of the input of the model is the second potential limitation to a microsimulation model. The basic assumptions of the aortic valve replacement microsimulation model all carry some uncertainty. For example, the structural valve failure hazard for allografts varies with patient age. The empirical data on this subject are scarce and have a limited time span. This results in a considerable degree of uncertainty regarding this parameter. By means of sensitivity analysis one can investigate the magnitude of the effect that this uncertainty may have on the outcome of the model. For instance, by halving and doubling the hazard for structural valve failure one can investigate whether the uncertainty related to this parameter has a substantial effect on the outcome of the model.

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