Joint Modelling of Longitudinal and Survival Data

with Applications in Heart Valve Data

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Joint Modelling of Longitudinal and Survival Data with Applications in Heart Valve Data

Gemengde modellen voor longitudinale- en overlevingsdata met toepassingen in hartklep data

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In memory of my grandmother

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Chapter 1

General Introduction

1.1 Motivating Case Studies

1.1.1 Background of Aortic Valve Disease

The heart is one of the most important organs in the entire human body. Specifically, it is a pump composed of muscle which pumps blood throughout the blood vessels to various parts of the body by repeated rhythmic contractions. The four heart valves determine the pathway of blood flow through the heart and they normally allow blood flow in only one direction through the heart. Moreover, they open or close incumbent upon differential blood pressure on each side. Specifically, the four valves are: the tricuspid valve, the pulmonary valve, the mitral valve and the aortic valve. Figure 1.1, represents graphically the heart anatomy. The blood flows from the right atrium to the right ventricle through the tricuspid valve. Thereafter, the blood flows through the pulmonary valve to the lungs, where oxygenation takes place. Next, the blood re-enters the heart into the left atrium, through the mitral valve into the left ventricle. Finally, it enters the aorta through the aortic valve. Another important part of the heart is the aortic root which connects the heart to the systemic circulation.

Heart valve disease occurs when one or more valves are not functioning properly due to stenosis and/or regurgitation. Valve stenosis is the disease in which the opening of the valve is narrowed, while valve regurgitation or insufficiency is the leaking of the valve that causes blood to flow in the reverse direction during ventricular diastole. Echocardiography is an excellent tool to evaluate patients with suspected heart valve disease. All four valves can develop the diseases mentioned above, however, in this thesis we focus on the aortic valve which lies between the left ventricle and the aorta.

The treatment for severe aortic valve disease is to replace or repair the diseased valve. Only a minority of the heart valves can be repaired, the majority requires replacement. There are two types of prosthetic heart valves, namely biological heart valves (homograft/allograft, bioprosthetic) and mechanical heart valves. Homograft or allograft valves are donated human aortic valves. Bioprosthetic valves are generated from animals (porcine, bovine). The advantage of a biological valve replacement is that patients typically do not need lifelong use of blood-thinning medications (anticoagulant). However, the duration of the valves is 10-15 years and patients, especially younger patients, may need follow-up surgeries. Mechanical valves are more durable than biological valves and usually do not have to be replaced. However, blood-thinning medication is required in order to prevent blood clots from forming on or around the new valve.

As mentioned before, aortic allograft implantation has been used for a variety of aortic valve or aortic root diseases mainly in non-elderly patients. Initial reports on the use of either fresh or cryopreserved allografts date from the early years of heart valve surgery (Ross, 1962; Barrat-Boyes, 1964; O'Brien, 1995). Major advantages ascribed to the use of an allograft are the excellent hemodynamic characteristics as a valve substitute; the low rate of thrombo-embolic complications and, therefore, absence of the need for anticoagulant

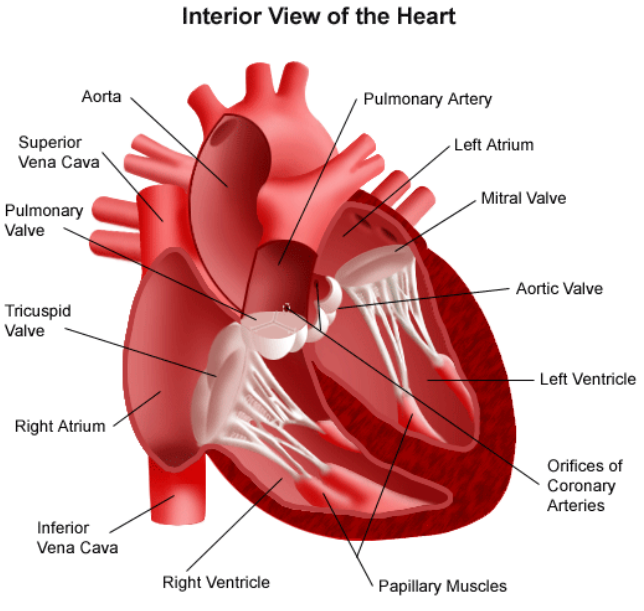

Figure 1.1: Heart

treatment; and the resistance to endocarditis. Furthermore, the aortic allograft has proven its value in complex aortic root pathology such as endocarditis with aortic annulus destruction. In particular, the aortic annulus is a ring of tough fibrous tissue which is attached to and supports the leaflets of the heart valve. An aortic allograft can be used as a simple valve substitute, using a subcoronary implantation technique, in which only the valve is being replaced or as a full root replacement with coronary artery reimplantation. A major disadvantage of using human tissue valves, as with all biological valve substitutes, is susceptibility to (tissue) degeneration and the potential need for reinterventions. The durability of a cryopreserved aortic allograft is age dependent, leading to a high life-time risk for reoperation, especially for young patients (Lund et al., 1999; O'Brien et al., 2001; Smedira et al., 2006; Takkenberg et al., 2003). Thus, reoperation after aortic allograft root implantation will be required in a substantial number of patients, especially in the second decade after initial operation. Patient monitoring is therefore essential in detecting allograft dysfunction in an early stage. Echocardiography plays an important role in early detection, allowing for careful monitoring of aortic stenosis (AS) and regurgitation in a non-invasive manner. Reoperation can then be performed before the onset of severe symptoms or before heart failure develops.

Although the current ESC and ACC/AHA guidelines state that aortic valve replacement

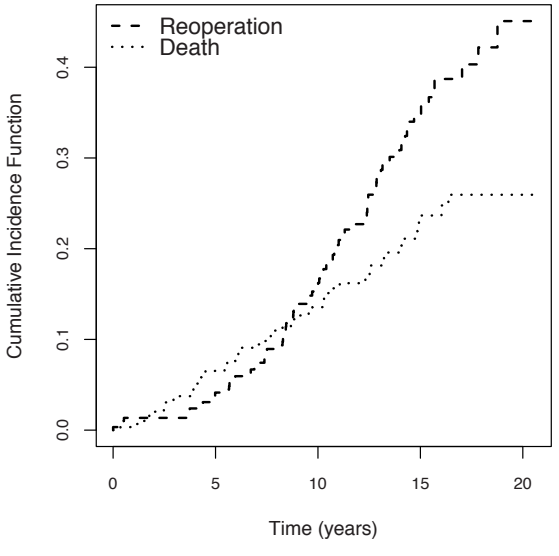

Figure 1.2: Cumulative Incidence function for reoperation and death

is indicated in patients with severe symptomatic AS (Nishimura et al., 2014; Vahanian et al., 2007), not all patients undergo aortic valve replacement. In particular, elderly patients with multiple comorbidities are often treated medically instead of surgically. Advanced cancer and permanent neurological defects, as a result of stroke or dementia, may make cardiac surgery inappropriate. Furthermore, patients with a downslide of overall physical strength and endurance often do not return to an active life, and the presence of other comorbid disorders could have a major impact on outcome. Valve replacement is technically possible at any age, but the decision to proceed with such surgery depends on many factors, including the patient's wishes and expectations. The biomarker brain natriuretic peptide (BNP) is helpful in determining disease severity and progression of severe AS and may be helpful in therapeutic decision making, especially when repeatedly measured.

1.1.2 Datasets

The first study was conducted in the Erasmus Medical Centre in The Netherlands and includes all patients who received a human tissue valve allograft in the aortic position in the Department of Cardio-Thoracic Surgery in a period of 21 years. Specifically, patients were

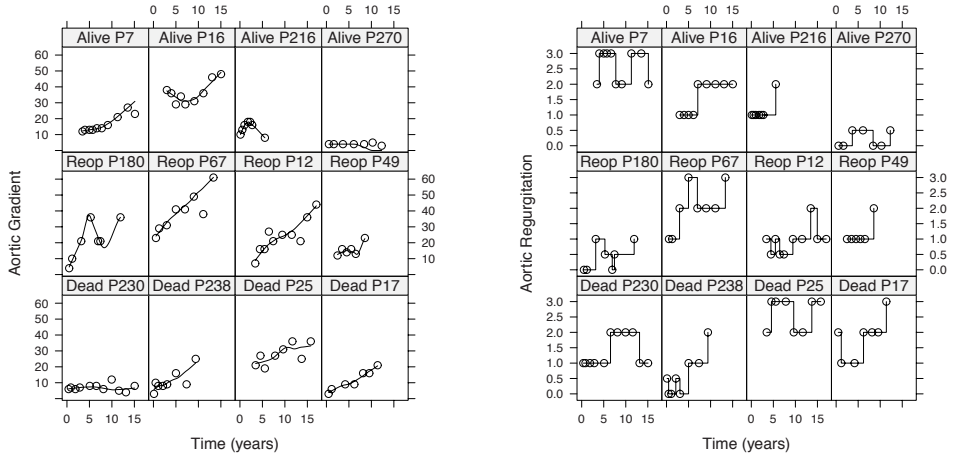

Figure 1.3: Smooth longitudinal profiles for aortic gradient and aortic regurgitation for 12 randomly selected patients

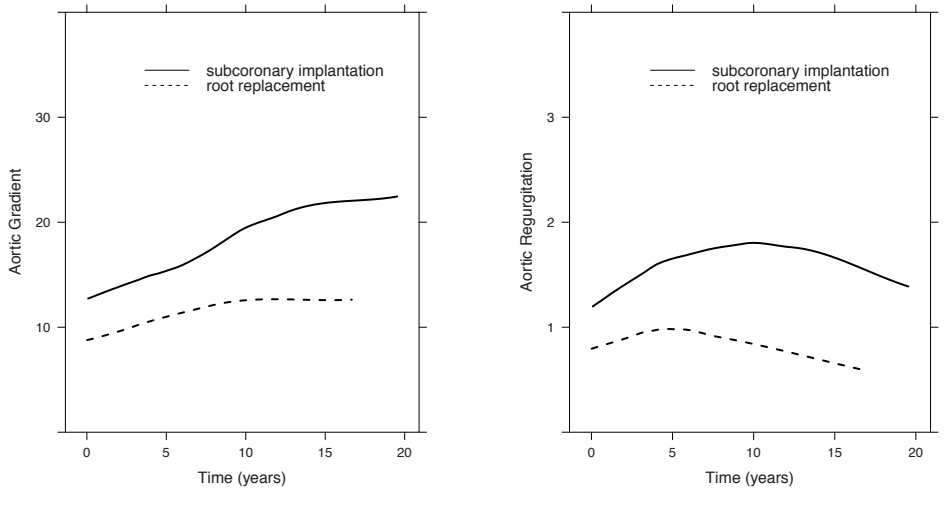

Figure 1.4: Smooth average longitudinal profiles for aortic gradient and aortic regurgitation

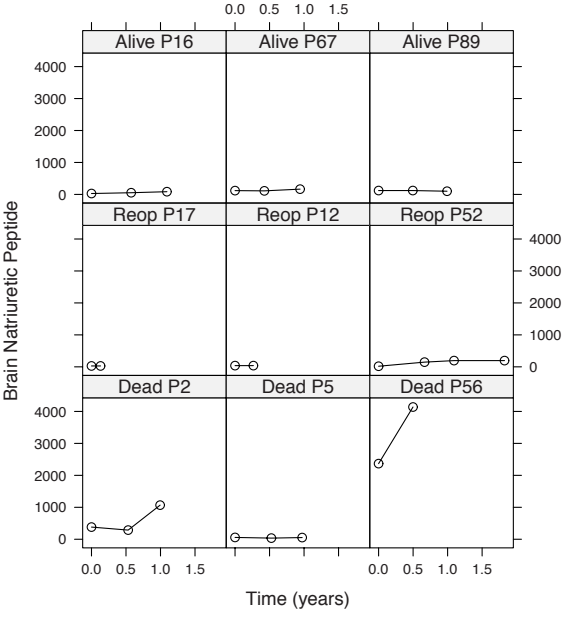

Figure 1.5: Longitudinal profiles for brain natriuretic peptide for 9 randomly selected patients

followed prospectively over time by annual telephone interviews and biennial standardized echocardiographic assessment of the valve function, Bekkers et al. (2011). Particularly, echocardiographic examinations were scheduled at 6 months and 1 year postoperatively and biennially thereafter. From 1987 until 2008, 286 patients who survived aortic valve or root replacement with an allograft valve were followed until 08-Jul-2010. During follow-up 57 (20%) patients died and 74 (26%) patients required a reoperation on the allograft. Figure 1.2 illustrates the cumulative incidence functions for the two events. We observed that patients showed a higher hazard of death the first nine years and a higher hazard of reoperation afterwards. A total of 1,252 echocardiographic measurements of aortic gradient and aortic regurgitation were performed. Specifically, aortic gradient is a quantification of AS severity and aortic regurgitation of aortic regurgitation severity. Each subject was monitored at different time points and had a different number of visits (median number = 4, range = 1 to 11) and median years of follow-up equal to 6.7 (range from 0 to 19.5 years). Aortic gradient (mmHg) is a continuous variable, while aortic regurgitation has an ordinal scale (grade: 0 (none), 0.5 (trace), 1+, 2+, 3+, and 4+). In Figure 1.3, the subject-specific evolutions for aortic gradient and aortic regurgitation are presented of 12 randomly selected patients, while in Figure 1.4, the smooth average longitudinal profiles of all patients for the two types of

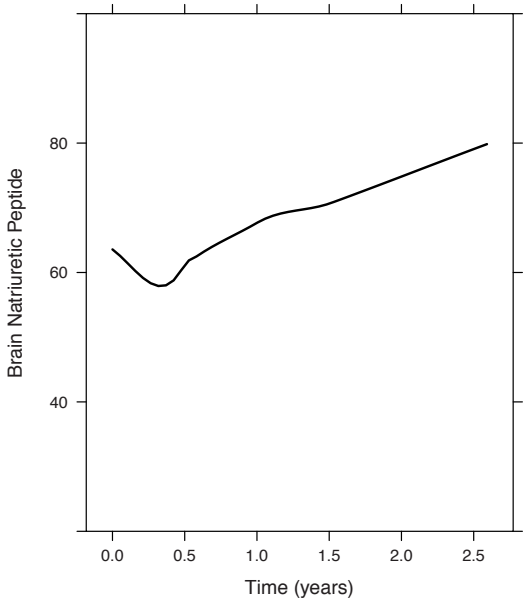

Figure 1.6: Smooth average profiles for BNP. BNP = brain natriuretic peptide

operation are shown.

The second study was also conducted in the Cardio-Thoracic Surgery department of the Erasmus Medical Centre in The Netherland and consists of patients from a dataset of a previously reported prospective cohort study of 191 adult patients with severe AS. These mostly elderly patients were diagnosed with severe aortic valve disease in seven cardiology clinics, in the wider Rotterdam area, between 2006 and 2009 and were prospectively followed for 2 years, Heuvelman et al. (2012). Inclusion criteria were aortic valve area $\leq$ 1 cm^2, peak transaortic jet velocity $\geq$ 4 m/s, or aortic valve / left ventricular outflow tract velocity time integral ratio $\geq$ 4. The patients were followed clinically, including BNP measurements and echocardiographically at baseline and then after at 6, 12 and 24 months. Particularly, BNP is a 32-amino acid polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells (cardiomyocytes) and thus, is a biomarker reflecting the severity of stenotic aortic valve disease. During the follow-up period, 15% of the patients (N=28) died and 48% (N=91) received a transcatheter aortic valve implantation. In total 561 BNP measurements were collected over a 2-year period (with mean follow-up duration equal to 0.9 years and range from 0 until 2.5 years). In Figure 1.5 we illustrate the subject-specific evolution for BNP of 9 randomly selected patients, while in Figure 1.6, the smooth average

longitudinal BNP profile of all patients is shown.

High values of aortic gradient, aortic regurgitation and BNP indicate a worsening of the patient's condition, with an increased risk of death or reoperation. Moreover, they are all measurements of the valve function, and hence, it is expected that they are biologically interrelated. Finally, the occurrence of death or reintervention (reoperation) induces missing of longitudinal measurements. Statistical methods, such as simple regressions (linear regression and Cox regression), are not always appropriate when dealing with datasets as described above (Akins et al., 2008). Specifically, these methods do not account for the correlation between the measurements within the same patients. Moreover, the analysis of the progression of the disease with survival is not applicable using such approaches. Mostly, the last available follow-up measurement is assumed, however, this may lead to invalid results.

1.1.3 Clinical Question

Standard regression models contain several limitations in describing valve function over time and coupling valve function with outcome measures like death and reoperation. This thesis aims to appropriately analyze longitudinal and survival data and thereafter derive accurate risk predictions for future patients. Physicians decide for a reintervention based on their clinical experiences and on general guidelines. For a patient with a biological prosthetic valve, such as an allograft, a prediction tool that helps to assess valve function over time and couples this information with reoperation and/or survival probabilities would be valuable in everyday medical practice. That is, medical experience combined with the appropriate statistical model would enable physicians to make better informed decisions regarding their actions and thus improve clinical output.

1.2 Introduction to Joint Models of Longitudinal and Survival Data

In medical studies, often longitudinal data are collected together with time-to-event outcomes. Examples of such studies are the valve datasets described in Section 1.1.2, where high risk patients with heart valve abnormalities are followed-up echocardiographically. Other examples can be found in HIV clinical trials, where for each subject biomarkers, such as CD4 cell counts are measured over time together with time-to-AIDS or death (DeGruttola and Tu, 1994; Tsiatis et al., 1995; Faucett and Thomas, 1996). Yet another example is the prostate cancer study, where patients are followed-up over time and during that period death or metastasis can occur (Yu et al., 2004; Proust-Lima and Taylor, 2009). The two types of outcomes are generally analyzed separately. However, in some settings a joint modelling approach is required. Specifically, in (1) longitudinal studies, when we wish to account for possible outcome dependent dropout and in (2) survival analysis when we wish to investigate the effect of a time-dependent covariate measured with error, and also (3) when the association

between longitudinal and survival outcomes is of interest. In the following Sections we describe in more detail the motivation of the joint modelling approach.

1.2.1 Mixed-Effects Models for Longitudinal Data

A standard modelling framework for the analysis of longitudinal data is the mixed-effects model. These models are based on the idea that each subject in the population has his own evolution over time. To introduce these models, we let $y_i(t)$ denote the follow-up measurements for the i-th individual ($i = 1,\ldots,n$) at time t. Furthermore, these measurements could be obtained at specific time points t_{ij}, $j = 1,\ldots,n_i$. The mixed-effect model can be written as

$$\begin{cases} y_i(t) &= x_i(t)^\top \beta + z_i(t)^\top b_i + \varepsilon_i(t), \\ b_i &\sim N(0,D), \\ \varepsilon_i &\sim N(0,\sigma^2), \end{cases}$$

where β denotes the vector with the regression coefficients of the design matrix for the fixed effects $x_i^\top$ and $z_i^\top$ denotes row vectors of the design matrix for the random effects b_i. In particular, the fixed and the random effects refer to the population-average and subject-specific effects, respectively. Furthermore, D is the covariance-variance matrix of the random effects, $\varepsilon_{ij}(t)$ are the error terms and σ is the variance of the error. The nice feature of these models is that they explicitly account for the correlation within the measurements obtained from the same patients and can handle unequally spaced visit times.

A major challenge for the analysis of longitudinal outcomes is the fact that these outcomes are often incomplete. Although patients are assigned to visit the physician at specific time points, in practice, they often miss some visits for a variety of reasons. Missing values in longitudinal studies occur in basically two different ways. The first type is when patients are missing at intermittent times, meaning that other measurements are observed following missing values. The second type of missing data occurs when data is not available for a subject after some time point, and the patient is said to have dropped-out of the study. The main concern in longitudinal analysis with missing data arises when there is an association between the longitudinal profile and the missing process. The appropriateness of different methods of analysis of incomplete longitudinal data is determined by the missing data mechanism. Specifically, there are three types of mechanisms (Little and Rubin, 2002), namely,

- Missing Completely at Random (MCAR): when the probability that the responses are missing, is unrelated to the longitudinal outcome. For example, when a patient forgets to attend an appointment or moves to another city.
- Missing at Random (MAR): when the probability of missingness depends on the set of observed longitudinal responses, but is unrelated to the outcomes that should have been obtained. For example, the patient leaves the study on doctor's advice based on previously observed longitudinal measurements.

- Missing Not at Random (MNAR): when the probability that the longitudinal responses are missing depends on observed and unobserved data. For example, a patient leaves the study due to an event (death/reoperation), and the event is related with his aortic gradient and aortic regurgitation measurements, including those that would have been observed if they would have kept on going to the appointments.

So in the case of MCAR, the incomplete observed data could be considered as a random sample of the complete data. Therefore, under this assumption, we could proceed with the analysis by using only the observed data. In the case of MAR mechanism, the missing observations are no longer random samples that are generated from the same sampling distribution as the observed values. Hence, the missing process must be modeled together with the longitudinal process. However, in the context of likelihood inference, and when the parameters describing the measurement process are functionally independent of the parameters describing the missingness process, data under the MAR assumption could be ignorable, while deriving valid inferences. MNAR is more general and represents the most complex missing data scenario. In this case, a joint distribution of the longitudinal and the missing processes is required in order to obtain valid inferences. In the literature different types of modelling frameworks for handling missing data in the longitudinal setting have been considered. Namely, selection models, pattern mixture models and shared-parameter models (Little, 1995; Molenberghs and Kenward, 2007). Selection and pattern mixture models are applied for discrete times, however, in reality, often patients do not adhere to the posited study schedule and may skip visits and dropout from the study at random time points (such as in the heart valve data). Thus, in this context, we need a joint distribution for the longitudinal and the missing processes that is applicable for continuous time.

1.2.2 Cox Models for Survival Data

When interest is on an event outcome, survival models such as Cox regressions are routinely used. To formally introduce this type of models, we let the T_i^* denote the true failure time for the i-th individual and C_i the censoring time, then $T_i = \min(T_i^*, C_i)$ represents the observed failure time for the i-th patient. In the Cox model the hazard function is assumed to satisfy the following relationship

$$h_i(t) = \lim_{dt \to 0} \frac{Pr(t \leq T^* < t + dt \mid T^* \geq t)}{dt} = h_0(t) \exp(\gamma^\top w_i), \quad t > 0,$$

where w_i are covariates that are associated with the hazard, γ is the corresponding vector of regression coefficients and $h_0(t)$ is the baseline hazard. In its basic form, we assume that the hazard ratio $(h_i(t)/h_0(t))$ depends only on covariates, whose value is fixed during follow-up, such as age, sex and randomized treatment (baseline covariates). However, when interest is also in investigating whether time-varying covariates are associated with the risk for an event, the extended Cox model could be employed (Therneau and Grambsch, 2000). Further

extensions allow the Cox model to handle multiple baseline hazard strata and clustered data where the failure times of interest are clustered into groups (such as patients in the same centre).

The use of time-dependent covariates is much more complicated in practice than the fixed ones. Thus, their inclusion in a survival model significantly complicates the analysis. There are two types of time-dependent covariates, namely, external or exogenous covariates and internal or endogenous covariates. Specifically, endogenous covariates require special treatment compared to exogenous ones. A time-varying covariate is exogenous if its value at any time point t is not affected by an event occurring at an earlier time point $s < t$. Standard examples are the period of the year (e.g., winter, summer) and environmental factors (e.g., temperature, humidity, pollution levels). Another example of exogenous covariates are those whose complete path is predetermined from the beginning of the study, such as a treatment dose. On the other hand, all covariates measured on the patient (e.g., biomarkers), are endogenous. Suppose there are two time-varying covariates, namely aortic gradient values that have been measured during follow-up and the air pollution levels. In addition it is known that a reoperation is required for a particular patient after 5 years since the initial valve replacement. It is evident that at a future time point (5.2 years) the level of aortic gradient will be affected from the fact that this patient underwent reoperation, whereas the air pollution levels at the same future time point would not be affected by this reoperation.

Unfortunately, the time-dependent Cox model is only theoretically valid for exogenous time-varying covariates, meaning that it is not appropriate when it comes to studying biomarkers or other patient parameters. The reasons behind the inadequacy of the Cox model is that it assumes that from one visit to the next, the marker's level remains constant and a sudden change in the levels occurs when the patients comes for a visit. It is obvious that such an assumption is reasonable for covariates such as treatment dose, but leads to a crude approximation of the path of biomarkers such as aortic gradient and BNP. In particular, we expect that aortic gradient and patient parameters in general, would continuously change over time. Ignoring these special characteristics and fitting the extended Cox model, would result in bias for the estimated effect of a biomarker.

1.2.3 Basic Joint Models

To analyze the heart valve datasets while addressing all issues mentioned in Sections 1.2.1 and 1.2.2 in this thesis, we utilize the framework of joint models for longitudinal and time-to-event data. The idea behind these models is to couple a survival model for the continuous time-to-dropout process with a mixed-effects model for the longitudinal outcome. The basic joint model is written as

$$\begin{cases} y_i(t) &= x_i(t)^\top \beta + z_i(t)^\top b_i + \varepsilon_i(t), \\ h_i(t) &= h_0(t)\exp\left[\gamma^\top w_i + \alpha\{x_i(t)^\top \beta + z_i(t)^\top b_i\}\right], \quad t > 0, \end{cases}$$

where α quantifies the effect of the underlying longitudinal outcome to the risk for an event. Moreover, it is assumed that the risk for an outcome dependent dropout is associated with the true and unobserved value of the longitudinal outcome. Following on the previous discussion, such a model is more realistic from a biological point of view compared to the time-dependent Cox models due to the fact that they explicitly assume that biomarkers evolve smoothly over time and do not remain constant between visits.

The key assumption of a joint model is that the random effects underlie both the longitudinal and survival processes. This means that these random effects account for both the association between the longitudinal and event outcomes, and the correlation between the repeated measurements in the longitudinal process (conditional independence assumption). When approached from the missing data point of view, the joint model implicitly makes assumptions for the complete longitudinal outcomes including measurements that would have been observed after the event or censoring. Formally we have that,

$$\begin{aligned} P(T_i \mid y_i^o, y_i^m) &= \int p(T_i, b_i \mid y_i^o, y_i^m) db_i \\ &= \int p(T_i \mid b_i, y_i^o, y_i^m) p(b_i | y_i^o, y_i^m) db_i, \end{aligned}$$

where y_i^o and y_i^m are the observed and the missing longitudinal measurements, respectively. Under the conditional independence assumption we observe

$$\begin{aligned} P(T_i \mid y_i^o, y_i^m) &= \int p(T_i \mid b_i, y_i^o, y_i^m) p(b_i | y_i^o, y_i^m) db_i \\ &= \int p(T_i \mid b_i) p(b_i | y_i^o, y_i^m) db_i. \end{aligned}$$

We obtain that the dropout process depends on the missing observations through the posterior distribution of the random effects $p(b_i|y_i^o, y_i^m)$. This implies that the joint models correspond to a MNAR missing data mechanism. Since under the joint model the longitudinal and the survival submodels share the same random effects, the joint models belong to the shared-parameter models.

1.3 Joint Modelling of Longitudinal and Survival Data in the Literature

Excellent overviews of the joint modelling literature are given by Tsiatis and Davidian (2004), Yu et al. (2004) and Rizopoulos (2012). The basic joint model which consists of one longitudinal and one survival outcome was introduced by Self and Pawitan (1992), DeGruttola and Tu (1994), Tsiatis et al. (1995), Faucett and Thomas (1996) and Wulfsohn and Tsiatis (1997).

Specifically, Self and Pawitan (1992) proposed a two-step method for parameter estimation where they condition on the survival information when computing expected

values of the covariates. They also used partial likelihood to obtain estimates of the risk parameters, but they derived corresponding variances, to account for the uncertainty in the expected covariate values. To obtain these variances, they assumed that the variance of the covariate random effects is fixed and known. DeGruttola and Tu (1994) considered a joint model in which the time-to-event is modelled parametrically, which facilitates straightforward likelihood inference. Tsiatis et al. (1995) proposed also a two-step procedure (different from Self and Pawitan) for fitting their model. First, they assumed a growth curve random components model with normal errors for the biomarker and they used the modified expectation maximization (EM) algorithm for estimation. Then, they substituted these estimates into the proportional hazards model and used Cox regression to obtain estimates of the survival parameters. Faucett and Thomas (1996) assumed the Markov Chain Monte Carlo (MCMC) method of Gibbs sampling, to generate the joint posterior distribution of all unknown parameters of the comprehensive model given only the observed data. Wulfsohn and Tsiatis (1997) considered a full likelihood approach for the joint model based on a linear mixed model for the longitudinal process and a proportional hazards model. Thereafter, numerous extensions of the standard joint model have been published.

Henderson et al. (2000) proposed a more general model by postulating two stationary Gaussian processes, including both random effects and serial correlation for the longitudinal measurements and survival times, respectively. The serial correlation processes allow the trend to vary with time and induce a within subject autocorrelation structure that may be thought of as arising from evolving biological fluctuations in the process about smooth trend (Wang and Taylor, 2001; Henderson et al., 2000). Tsiatis and Davidian (2004) provided an interesting contradiction between the random effects and serial correlation assumption.

Tsiatis and Davidian (2001) and Song et al. (2002) focused on minimizing the impact that erroneous distributional assumptions for the random effects could have on the derived inferences. Specifically, Tsiatis and Davidian proposed a conditional score approach and developed a set of unbiased estimating equations. Song, Davidian and Tsiatis considered the model of Wulfsohn and Tsiatis (1997) by relaxing the assumption of normality of the random effects to a distribution with a smooth density.

Brown and Ibrahim (2003) considered a flexible specification of the subject-specific profiles and Brown et al. (2005) and Rizopoulos and Ghosh (2011) presented joint models considering multiple longitudinal outcomes. In addition, Brown (2009), Rizopoulos and Ghosh (2011) and Rizopoulos (2012) assumed different association structures of the longitudinal and survival outcomes. In many clinical studies, patients may experience multiple events during the follow-up period. Elashoff et al. (2008), Williamson et al. (2008), Hu et al. (2009) and Huang et al. (2011) focused on the competing risks and multiple failure types problems. Moreover, joint models that combine recurrent and terminating events with longitudinal endogenous covariates, are proposed by Liu et al. (2008) and Liu and Huang (2009). Li et al. (2010) proposed a joint model with longitudinal ordinal measurements and competing risks, in which a partial proportional odds model for the longitudinal ordinal outcome is linked to the event times by latent random variables.

When it comes to using these models in practice, a prerequisite step is to validate the model's assumptions. A standard tool to assess these assumptions, are the residual plots. Dobson and Henderson (2003) used the conditional residuals and Rizopoulos et al. (2010) the multiple imputation residuals. Finally, Taylor et al. (2005), Garre et al. (2008), Yu et al. (2008), Proust-Lima and Taylor (2009) and Rizopoulos (2011) considered the joint modelling framework to derive individualized predictions for a longitudinal and a survival outcome that are updated at each new visit.

1.4 Joint Models Described in the Thesis

1.4.1 Multiple Longitudinal and Survival Outcomes

Case studies, such as the ones presented in Section 1.1.2, may consist of multiple longitudinal and survival outcomes. From the definitions of these markers it is clear that they measure different aspects of the heart valves' functioning, and it is strongly expected that they are biologically interrelated. Therefore, it is medically relevant to measure the association of each biomarker with the risk events, after having adjusted for the effects of the others. Specifically, in the first case study aortic gradient, which is a continuous outcome, is collected together with aortic regurgitation which is an ordinal outcome. Furthermore, in both case studies an individual is at risk of failing in multiple ways. In particular, the patients could die or require a new heart valve. Thus, in Chapters 3 and 5 we extended the basic joint model to handle a continuous and an ordinal longitudinal outcome together with a competing risks setting.

1.4.2 Investigation of Association Structure

An important assumption for the joint models is the functional form of the time-dependent covariates. Misspecification in any part of the model could affect the accuracy of the derived estimates. Thus, after appropriately postulating the evolution of the biomarkers and the confounders, the focus lies on the association structure of the longitudinal and survival outcomes (Brown, 2009; Rizopoulos and Ghosh, 2011; Rizopoulos, 2012). The basic joint model includes the standard parameterization, which connects the underlying value of the markers with the time-to-events at a specific time point. Particularly, this functional form is followed in Chapters 2, 4 and 5. Additional time-dependent parameterizations are presented in Chapter 5, where we allow the risk of the events to depend on both the current value and the slope of the trajectories of aortic gradient and aortic regurgitation at a time point. Furthermore, we assume the survival outcomes to depend on the entire history of the biomarkers by including the integral of the longitudinal profile in the linear predictor of the survival submodels (cumulative effect). A more frequently used approach, is to postulate a time-independent parameterization, where the survival submodels are connected with the

random effects of the longitudinal submodels. This parameterization is presented in Chapter 3.

1.4.3 Dynamic Risk Prediction

1.4.3.1 Prediction from a Single Model

To more accurately guide clinical decision making, physicians require prognostic tools that can incorporate the complete biomarker information. The motivation behind this, is that an inherent characteristic of many medical conditions is their dynamic nature. That is, the rate of progression is not only different from patient to patient but also dynamically changes with time for the same patient. Hence, it is medically relevant to investigate whether repeated measurements of a biomarker could provide a better understanding of disease progression and a better prediction of the risk for death or reintervention than a single biomarker measurement. Joint models have recently gained increasing interest for subject-specific predictions (Taylor et al., 2005; Garre et al., 2008; Yu et al., 2008; Proust-Lima and Taylor, 2009; Rizopoulos, 2011). Subject-specific risks predictions based on the joint model, would clearly be a useful tool in everyday clinical practice and therefore would guide more accurately clinical decision making regarding the prevention of valve diseases. Thus, in Chapter 5, we extend the concept of predictions, in the setting where we have multiple longitudinal outcomes and competing risk survival outcomes and derive dynamically updated cumulative incidence functions.

1.4.3.2 Predictions using Bayesian Model Averaging

As motivated in Section 1.4.2, there are several ways to link the longitudinal and the survival outcomes. Moreover, we could even perform additional joint models with different structures for each submodel. For instance, in a mixed-effect model the average and the subject-specific evolutions over time may be nonlinear, while an alternative model would be to use a nonlinear structure only for the average evolution over time. In practice, one usually chooses the final model from a list of candidate models. The selection of the best prognostic model is an important task and is most often obtained using standard algorithms, such as, backward, forward and stepwise methods or likelihood-bases information criteria, such as Akaike information criterion (AIC), Bayesian information criterion (BIC) and deviance information criterion (DIC). However, these approaches do not account for model uncertainty. For instance, if two or more models are correct, the selection on a single model is not certain to be the true model. In addition, when interest lies in predictions for a new patient, there could be several models that offer accurate predictions. More important, each patient is unique, thus assuming a single prediction model for all future patients may not be appropriate. To overcome this problem, we propose, in Chapter 5, to suitably combine predictions from different models using the Bayesian model averaging (BMA) approach (Hoeting et al., 1999).

The advantage of using BMA in our application is that predictions are tailored to each individual patient, because the model weights are both subject- and time-dependent. Hence for different future patients from the study population but also for the same patient but at different time points, the models may differ in weight.

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CHAPTER 2

Clinical Applications of Joint Models and Mixed models

CHAPTER 2A

An Introduction to Mixed Models and Joint Modelling: Analysis of Valve Function Over Time

This Chapter is based on: Andrinopoulou, E.R., Rizopoulos, D., Jin, R., Bogers, A.J., Lesaffre, E. and Takkenberg, J.J. (2012). An introduction to mixed models and joint modeling: analysis of valve function over time. *The Annals of Thoracic Surgery*, 93:1765 – 1772.

Abstract

An important target of many clinical studies is to identify biomarkers, including risk scores, with strong prognostic capabilities. While biomarker evaluations are commonly utilized to predict the progress of the disease at single time points, appropriate statistical tools to assess the prognostic value of serial biomarker evaluation are rarely used. The goal of this Chapter is to demonstrate flexible and appropriate statistical methodology to assess the predictive capability of serial echocardiographic measurements of allograft aortic valve function. Moreover, the concept of joint modelling of longitudinal and survival data to optimally utilize the relationship between repeated valve function measurements and time-to-death or time-to-reoperation, is introduced and illustrated. Optimal and suboptimal methods are illustrated using a prospective cohort of patients who survived aortic valve or root replacement with an allograft valve and who were followed clinically and echocardiographically over time.

2A.1 Introduction

Presently, biomarkers, including risk scores, play a prominent role in medical decision making. It is recognized that compared with the use of only a baseline biomarker measurement, serial biomarker evaluations may carry important additional information regarding the progression of the disease under study, Wolbers et al. (2010). During the course of a disease, clinicians use both baseline and accumulated serial biomarker information for a patient to gain a better understanding of the disease dynamics. Thus, when using only single-moment biomarker values, potentially important information is not utilized to guide medical actions. This is an important issue after heart valve surgery. After heart valve surgery, valve function is monitored periodically over time. Not only initial or current valve function, but also the rate at which valve function deteriorates, provide important prognostic information regarding, for example, the hazard of a reoperation or death. Because clinicians use this serial information on valve function intuitively in clinical practice, it seems logical that this is also done when we statistically analyze outcome of patients after cardiac valve interventions.

The 2008 guidelines for reporting mortality and morbidity after cardiac valve interventions recommend the use of longitudinal data analysis to assess valve function over time, Akins et al. (2008). The guidelines state the following: “Longitudinal data analysis of a series of assessments is superior to analyzing only condition at last follow-up. This methodology is also superior to dichotomizing outcomes and analyzing them with actuarial methods as if they were events, such as freedom from grade 3+ mitral regurgitation after repair.” Nevertheless, many authors still use “condition at last follow-up” or actuarial methods to describe valve function.

This Chapter aims to demonstrate how longitudinal data can be analyzed according to the

recommendations stated above. Moreover, it shows how longitudinal data may be combined with time-to-event analysis. This is done using the example of a prospective cohort of patients who survived aortic valve or root replacement with an allograft valve and were followed clinically and echocardiographically over time. To emphasize the benefits of the methods that are going to be proposed, simplistic approaches ignoring the special structure of the data will also be applied for comparison.

Table 2A.1: Descriptive statistics for the baseline characteristics

Characteristics	Descriptive Statistics
Age, years; median (IQR)	47 (34–56)
Male gender, n (%)	212 (72%)
Marfan syndrome, n (%)	15 (5%)
LV function, n (%)	
Good	219 (75%)
Impaired	51 (18%)
Moderate	6 (2%)
Bad	14 (5%)
Type of operation, n (%)	
Subcoronary implantation	78 (26%)
Root replacement	218 (74%)
Donor age, years; median (IQR)	59 (42–69)
Allograft diameter, mm; median (IQR)	23 (21–24)

IQR = interquartile range; LV = left ventricular

2A.2 Patients and Methods

2A.2.1 Patients

All patients who receive a human tissue valve in the aortic position in Erasmus University Medical Centre (Department of Cardio-Thoracic Surgery) are followed prospectively over time by annual telephone interviews and biennial standardized echocardiographic assessment of valve function in patients 16 years and older (Bekkers et al., 2011). Approval from the Institutional Review Board was obtained for this prospective follow-up study (MEC 00-813); the Institutional Review Board waived informed consent.

From 1987 until 2008, 275 patients who survived aortic valve or root replacement with an allograft valve were followed until July 8, 2010. The total number of follow-up years is 3,292 and the completeness of follow-up is 98%. Table 2A.1 displays patient and operative characteristics. During follow-up 61 patients died and 78 patients required a reoperation on the allograft. Cumulative survival at 18 years was 69% (95% confidence interval 62% to 77%)

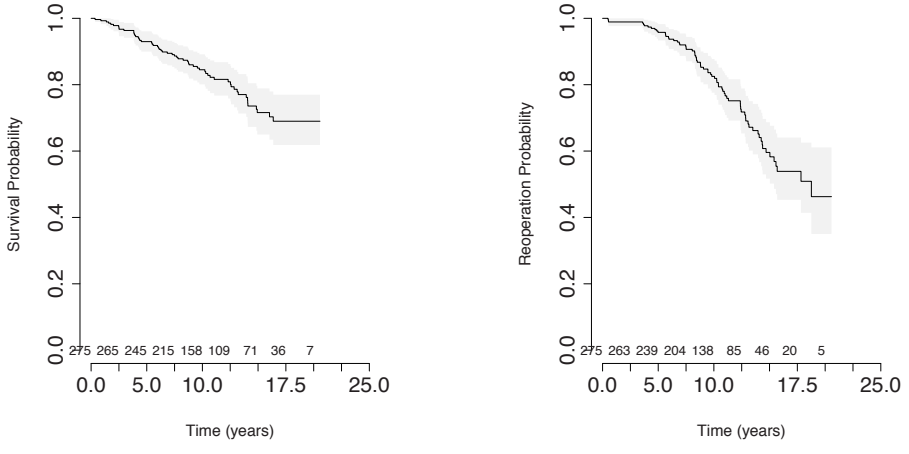

Figure 2A.1: Kaplan-Meier curves for survival and reoperation

and freedom from reoperation on the allograft was 53% (95% confidence interval 45% to 63%). Figure 2A.1 provides the Kaplan-Meier estimates of survival and allograft reoperation, including the number of patients at risk at each year of follow-up.

In the 275 patients, a total of 1,228 echocardiographic measures of aortic gradient and aortic regurgitation were performed for each patient at different time points (median number of measurements 4, range 1 to 11; median echocardiographic follow-up 6.7 years, range 0 to 19.5 years). Aortic gradient (mm Hg) was collected as a continuous variable while aortic regurgitation was collected using an ordinal scale (grade: 0 [none], 0.5 [trace], 1+, 2+, 3+, and 4+).

Using this dataset we performed the following analyses: (1) Longitudinal analysis of aortic gradient over time; (2) longitudinal analysis of aortic regurgitation over time; and (3) joint modelling for patient survival and aortic gradient over time. All approaches were compared with more simple methods that are typically used in everyday clinical papers.

2A.2.2 Methodology for Analysis of Serial Data Over Time

To account for the special features of serial evaluations of clinical parameters over time, a class of statistical models (known as mixed-effects models) has been developed (Verbeke and Molenberghs, 2000). The nice feature of these models is that they can work with unbalanced datasets (ie, datasets with an unequal number of follow-up measurements between subjects

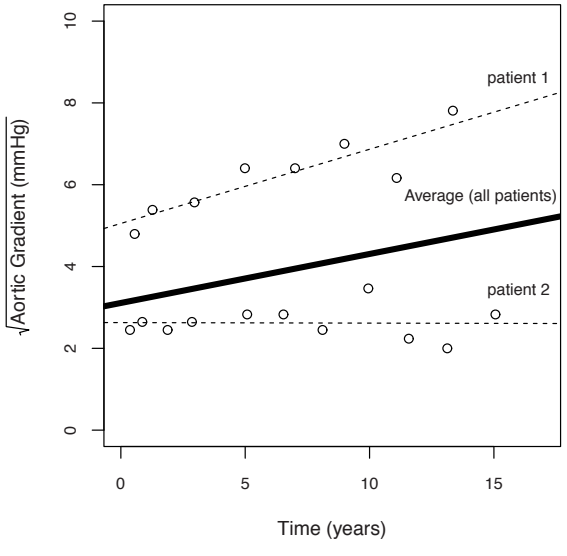

Figure 2A.2: Graphical representation of mixed-effects models. The solid line shows the fixed effects, which describe the average evolution in time of the aortic gradient; the dashed-lines show the random effects (patient-specific), which describe the evolution in time for each patient

and varying times between repeated measurements of each subject), and that they explicitly take into account that measurements from the same patient may be more correlated than measurements from different patients. The intuitive idea behind these models is described by Figure 2A.2. It shows that mixed-effects models have 2 parts; namely, a fixed effects and a random effects part. The fixed effects part (solid line in Figure 2A.2) describes the average evolution in time of a specific clinical parameter under study (in this example aortic gradient), where this average is taken overall from the subjects in the sample at hand and is an estimate of the evolution of the clinical parameter in the target population. The random effects (patient-specific) part (dashed lines in Figure 2A.2) describes the evolution in time for each of the patients under study, and it is in fact this part that accounts for the correlation in the data within patients. An alternative approach to account for the dependencies in the response of each patient is to directly include a serial correlation term in the residual errors. Even though a combination of the two approaches (random effects and serial correlation terms) is mathematically possible, in the applications of real data it often leads to estimation problems. Therefore, it is advisable to rely and expand on either of the two approaches but not both.

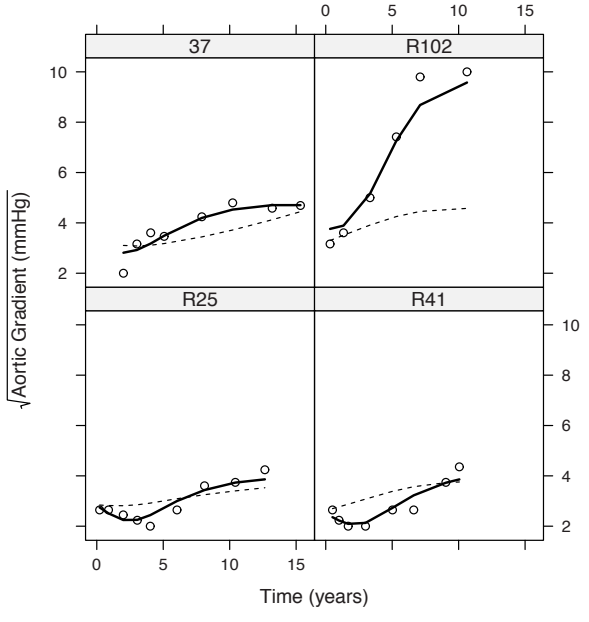

Figure 2A.3: Fitted longitudinal profiles for four patients in the study. The solid line is based on the mixed-effects model analyses for aortic gradient and the dashed line is based on the regression model analyses for aortic gradient

In Figure 2A.2 and all of the following analyses, the square root of the aortic gradient was used because the assumption that the variance of the error terms is constant (homoscedasticity) was not satisfied in the original scale. One important aspect when applying this methodology is to carefully study the shapes of the patient-specific evolutions in time. For example, for the two patients depicted in Figure 2A.2 the square root of the aortic gradient seems to follow a linear profile in time. However, as will be shown later (Fig 2A.3), this may not hold for all patients. In order to obtain valid results, it is important to postulate a mixed model that is capable of appropriately capturing such nonlinear evolutions.

Depending on the nature of the clinical parameters of interest, there are different versions of mixed-effects models that can be used. Namely, linear mixed-effects models for continuous data and generalized linear mixed models for categoric data (Verbeke and Molenberghs, 2000).

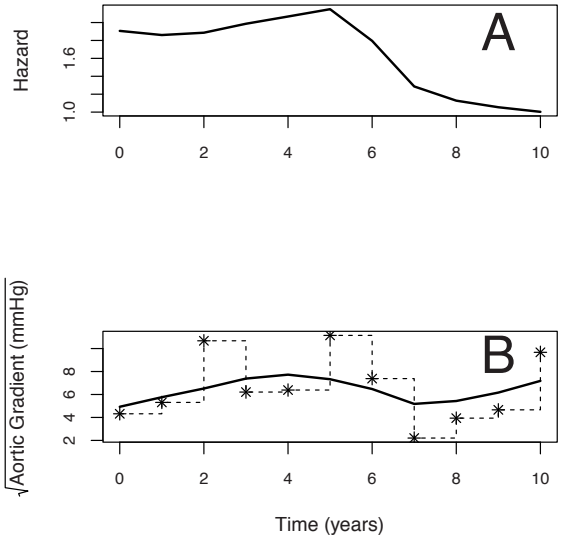

Figure 2A.4: Graphical representation of joint models. (A) Contains the hazard function for an event. In (B), the dashed line describes a time-dependent covariate as used in the time-dependent Cox model, and the solid line the mixed-effects model reconstruction of the covariate path

2A.2.3 Methodology for Longitudinal Data Analysis Combined With Survival Analysis

In addition to analyzing the trend over time in valve function, it may also be of interest to investigate the predictive capability of serial valve function measurements in relation to patient survival. Figure 2A.4 illustrates the challenge of combining time-to-event measures (in this case patient risk for an event, panel A) and longitudinal data (in this case aortic gradient, panel B). To estimate the association between a single echocardiographic valve function measure and the risk for death, standard statistical tools such as Cox regression are applicable. However, when it comes to the analysis of serial valve function measurements in relation to event occurrence (eg, patient survival), the time-dependent Cox model is not appropriate (Tsiatis and Davidian, 2004; Ibrahim et al., 2010; Kalbfleisch and Prentice, 2002). Problems arise from the fact that the aortic valve measurements contain biological variation; that is, aortic valve function does not remain constant in between two successive measurements of the patient, which is what the Cox model assumes (Figure 2A.4(B), dashed line). The problem

with ignoring this biologic variation and using the time-dependent Cox model is that derived results may be substantially biased (Sweeting and Thompson, 2011; Prentice, 1982).

A relevant modelling framework capable of resolving these issues is the joint model for longitudinal and survival data described by Tsiatis and Davidian (2004). This is a relatively new and powerful method that takes into account special features. The basic idea behind these models is to construct a suitable mixed-effects model to describe the evolution in time for the marker, and then to use these estimated evolutions as a time-dependent covariate in a Cox model instead of the observed marker. This idea is depicted graphically in Figure 2A.4, where at each time point we associate the level of the marker as estimated from the mixed-effects models (panel B, solid line) with the risk for an event (panel A). In Section 2A.5 we present the mathematical formulation of this model in more detail.

2A.2.4 Statistical Software

Suitable software is available for applying mixed-effects models and joint modelling in R (see Section 2A.5 for R codes). Appropriate software can be found for the mixed-effects models also in SAS (SAS Institute, Cary, NC).

All analyses have been performed with the statistical software package R (free download from www.rproject.org) version 2.13.0, using the following packages.

- Fitting linear and generalized linear mixed-effects models; Package: lme4 (version: 0.999375-39).
- Regression modelling strategies. We used this package to transform the data in a specific format in order to fit the continuation ratio (CR) model; Package: rms (version: 3.3-1).
- Data analysis using regression and multilevel/hierarchical models; Package: arm (version: 1.4-11).
- Joint modelling of longitudinal and survival data; Package: JM (version: 0.8-3).

2A.3 Results

2A.3.1 Longitudinal Analysis of Aortic Gradient Over Time

To illustrate the advantages of the mixed-effects analyses we contrast it with a simplistic regression analysis that ignores the correlation between the measurements of each patient. All results are summarized in Table 2A.2.

First, a suitable mixed-effects model was constructed for the aortic gradient data. The patient-specific profiles of aortic gradient (see examples in Figure 2A.3) were allowed to be nonlinear in time using natural cubic splines with two internal knots (placed at the quartiles of the distribution of the observed follow-up times) in both the fixed effects (likelihood ratio

Table 2A.2: Wald test from the mixed-effects and the regression models

	Mixed-Effects Model		Regression	
Variable	DF Numerator/Denominator	p-value	DF	p-value
Aortic gradient				
intercept	1/952	< 0.0001	1	< 0.0001
Effect of time	3/952	< 0.0001	3	< 0.0001
Type of operation	1/266	0.0007	1	0.003
Sex	1/266	0.654	1	0.097
Age	1/266	0.028	1	0.149
Marfan	1/266	0.109	1	0.0005
LV function	3/266	0.761	3	0.172
Donor age	1/266	0.0001	1	< 0.0001
Diameter (mm)	1/266	< 0.0001	1	< 0.0001
Effect of time: type of operation	3/952	0.393	3	0.725
Effect of time:age	3/952	< 0.0001	3	< 0.0001
	Generalized Linear Mixed-Effects Model		Generalized Linear Model	
Aortic regurgitation				
Effect of time	5	< 0.0001	5	0.0006
Age	1	0.0004	1	< 0.0001
Type of operation	1	< 0.0001	1	< 0.0001
Sex	1	0.091	1	0.005

DF = degrees of freedom; LV = left ventricular

test for nonlinearity: p-value < 0.001) and random effects part of the model (likelihood ratio test for nonlinearity: p-value < 0.001). The splines approach has the advantage that it allows for nonlinear evolutions in time but can also accommodate simple linear relationships. In addition, we allowed in our analyses for separate average evolutions of aortic gradient for the two operation types (root replacement and subcoronary implantation) and for patient age. Moreover we also controlled at baseline for gender, Marfan syndrome, left ventricular function, donor age, and allograft valve diameter.

To communicate the results from the nonlinear plot more easily we used effect plots that illustrate the average evolution of the aortic gradient in time for various combinations of the other covariates. Figure 2A.5 presents the effects plot for the two types of operation, for males with median age (47 years), median donor age (59 years), and median valve diameter (23 mm), with no Marfan syndrome and a good left ventricular function. From this plot we observe that the square root of aortic gradient increases steadily in time and with an almost similar rate for the two types of operation. Moreover, it is shown that the subcoronary implantation technique is associated with an overall greater aortic gradient, but that an increase in aortic gradient over time does not differ statistically between the subcoronary implantation technique versus root replacement (Table 2A.2, mixed-effects model). Additionally, older patient age is associated

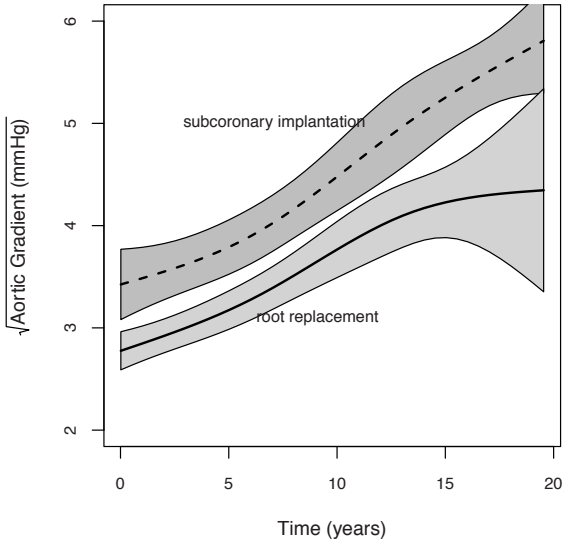

Figure 2A.5: Effect plot based on the mixed-effects model analyses. The 47-year-old male patients without Marfan syndrome, median allograft diameter (23 mm), and donor age (59 years), and good left ventricular function are presented

with a lower overall aortic gradient and this decrease is statistically significant over time. Furthermore, older donor age and smaller allograft diameter are associated with higher aortic gradients.

To illustrate the added value of the mixed-effects model, we repeated the analysis using a simplistic regression analysis that ignores the correlation between the repeated measurements of the patients. In order to compare the two approaches, in the regression model we used exactly the same formulation as for the fixed effects part of our mixed model. Particularly, we used the transformed aortic gradient (into the square root) and the nonlinearity spline function for time.

Table 2A.2 presents the Wald tests for each variable in our analysis under both approaches. As can be seen, we obtain different p-values and therefore different conclusions for some covariates, although all repeated measurements are used (and not only the last measurement) but the correlation within patients is ignored. Furthermore, from Figure 2A.3 we can observe that the fit of the simple linear regression is inferior to the fit of the mixed-effects model.

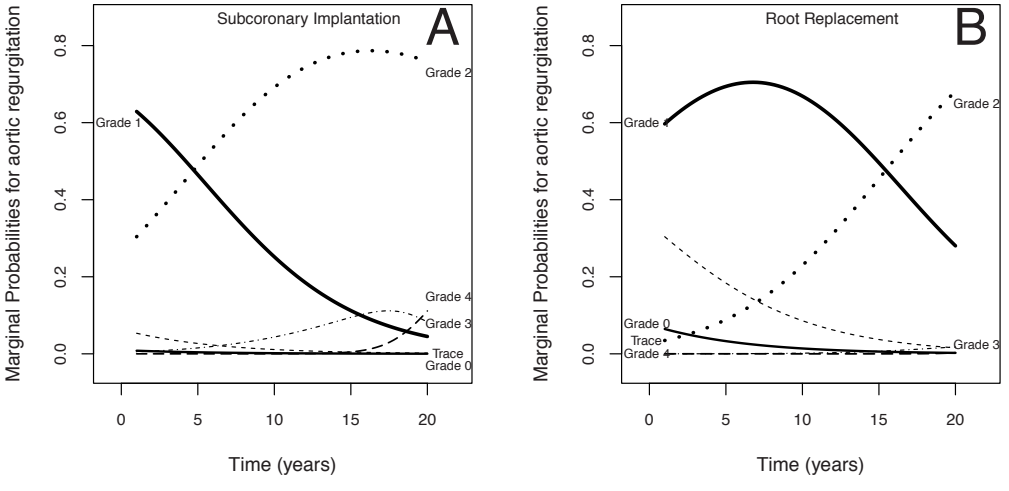

Figure 2A.6: (A) Marginal probabilities from the mixed-effects continuation ratio model for aortic regurgitation. Profiles represent male patients who underwent subcoronary implantation at a median age of 47 years. (B) Marginal probabilities from the mixed-effects continuation ratio model for aortic regurgitation. Profiles represent male patients who underwent root replacement at a median age of 47 years

2A.3.2 Longitudinal Analysis of Aortic Regurgitation Over Time

We continued the mixed-effects analyses in a similar manner for the aortic regurgitation measurements. The longitudinal information for each patient was summarized, while accounting for the correlation in the aortic regurgitation serial measurements, by a mixed-effects CR model (Harrell, 2001; Agresti, 2002). This model accommodates the conditional probability that a patient does not move beyond a stage once a particular stage is reached (see Section 2A.5). For aortic regurgitation, the data did not support nonlinear evolutions over time. Therefore, linearity was assumed for both the fixed effects and random-effects part. The covariates type of operation, baseline patient age, and gender were included in the model.

In Figure 2A.6 we illustrate for male patients with a median age of 47 the probability of a particular aortic regurgitation grade at a particular time after operation according to the subcoronary implantation technique and the root replacement technique. For example, the

probability of having grade 2 aortic regurgitation at 10 years postoperative is approximately 70% with the subcoronary implantation technique and approximately 20% with the root replacement technique. Moreover, Figure 2A.6 underlines that the transition from grade 1 to grade 2 after operation is taking place earlier when using the subcoronary implantation technique. Furthermore, longer time since operation, younger patient age, and subcoronary implantation technique are significantly associated with aortic regurgitation (Table 2A.2, mixed-effects model). Specifically, with increasing time since operation, aortic regurgitation increases. In addition, aortic regurgitation is greater in patients who underwent subcoronary implantation.

Similar to the previous Section, we illustrated the added value of the mixed-effects model by comparing it with a simplistic model (a standard CR model without random effects) including the same covariates. Here we again used all repeated measurements but ignore the correlation within patients.

The Wald tests for each variable and under both approaches are presented in Table 2A.2. As in the previous analysis, it can be seen that ignoring the correlation between the measurements of the patients yields different results. For instance, gender is found statistically significant from the simplistic analysis (male gender is statistically significant associated with aortic regurgitation), whereas the mixed models approach does not corroborate this result (Fitzmaurice et al., 2004).

Table 2A.3: Comparison of the estimates between Cox model and joint modelling for reoperation and death

	Cox Model		Joint Modelling	
Variable	Hazard ratio	p-value	Hazard ratio	p-value
Reoperation				
Type of operation (root replacement)	1.66	0.062	1.35	0.254
Age	0.97	0.0001	0.97	0.002
Aortic gradient	1.02	< 0.0001	1.75	< 0.0001
Death				
Type of operation (root replacement)	1.11	0.732	1.38	0.281
Age	1.06	< 0.0001	1.07	< 0.0001
Aortic gradient	0.97	0.024	0.94	0.607

2A.3.3 Joint Modelling for Patient Survival and Aortic Gradient Over Time

Now that we have shown that through mixed models it is possible to optimally utilize serial data on valve function, we will illustrate how joint models use serial valve function data to predict discrete outcomes such as death and reoperation. To illustrate the virtues of the

joint modelling approach, first a simple analysis was performed, in which a Cox model is fitted including only the last measurement of aortic gradient, baseline age, and type of operation as potential predictors of reoperation and death. We then specified a joint model that explicitly postulates a linear mixed-effects model for aortic gradient. This mixed model controls for time, type of operation, and age. Moreover, separate average evolutions of aortic gradient for the two operation types were assumed. The survival component of the joint model consists of a Cox model adjusting for type of operation and age. The same type of joint model was assumed for both death and reoperation.

We should mention that different baseline covariates could be included in the Cox and the mixed-effects models depending on the interest of the analysis.

Table 2A.3 represents the parameter estimates and the p-values for both methods. In the Cox model for reoperation a higher aortic gradient and younger patient age are associated with an increased reoperation hazard. However, under the joint modelling approach the strength of the association between the aortic gradient and the risk of reoperation is much greater. In the Cox model for mortality, older patient age and lower aortic gradient are associated with an increased death hazard. Using the joint model for mortality older patient age is the only factor that remains significantly associated with an increased death hazard. Again, by using serial echo data instead of only the last echo measurement the model outcome changes and different conclusions are drawn.

2A.4 Comment

This Chapter aimed to illustrate how serial measurements over time, in this case echocardiographic valve function after allograft aortic valve surgery, can be adequately analyzed using longitudinal data analysis. We have shown that valuable extra information can be obtained by using longitudinal data analysis for prognostication in comparison with using "condition at last follow-up" or actuarial methods. It is obvious that the models required for this type of analysis are more advanced compared with simple counts and actuarial methods, but they are comprehensible, reproducible, and require only standard available software. In addition, we have shown that it is feasible to effectively incorporate longitudinal responses in time-to-event models, allowing for more adequate prognostication of time-related event occurrence by utilizing serial measurements instead of single measures.

2A.4.1 Why Should We Use Longitudinal Data Analysis?

The hazard of death or reoperation is the focus of many papers on outcome after cardiac valve interventions. However, many important variables that are utilized to prognosticate are measured more than once over time. For instance, measures of valve dysfunction after implantation of a biologic valve substitute (like aortic gradient and aortic regurgitation) are collected repeatedly at several time points. The statistical analysis of these repeated measures

poses several important challenges. Measures may not always be obtained at the same time for all patients and, in addition, different patients may have a different number of follow-up visits. Thus, if serial biomarkers change rapidly then little information is recorded and therefore the analysis may lead to bias. Furthermore, the fact that measurements obtained for the same patient will be more correlated than measurements between individuals may be an important factor for predicting the endpoint. It is evident that such serial evaluations of clinical parameters may carry important information regarding the progression of the disease.

The goal of a longitudinal data analysis is to investigate the rate of progression using all provided information. The example given in this Chapter illustrates that proper longitudinal data analysis accounts for the correlation of repeated measurements within patients, unbalanced follow-up, and biologic variation. Ignoring all these special features (as the simplistic models described in this Chapter do) may typically result in bias and loss of the predictive capability of the covariates (Verbeke and Molenberghs, 2000; Fitzmaurice et al., 2004).

More simplistic methods mentioned and applied for the dataset described in this Chapter could be appropriate in a different setting. For example, if the mode of valve failure is not gradual over time as it is with the degenerating allograft, but quite sudden as in the case of prosthetic valve endocarditis, then a more simplistic methodological approach that does not take into account serial measurements may be more appropriate.

2A.4.2 Why Combine Longitudinal Data With Time-To-Event Data?

An additional challenge is not only to adequately use longitudinal data analysis to assess valve function over time, but also to take into account that valve function cannot be seen independent from death or reoperation. Often, longitudinal and time-to-event data are collected together. Thus, it may be of interest to investigate the relationship between serial biomarkers and time-to an event. For instance, a higher aortic gradient may indicate a higher or lower risk of reoperation or death. To resolve this issue joint models for longitudinal and survival data are increasingly used in clinical studies (Henderson et al., 2000; Wulfsohn and Tsiatis, 1997). Joint models are the appropriate statistical tool for assessing the progression of serial biomarker accounting for the dropout of patients due to reasons that are related with the repeated endpoint. This is a new and fast developing field in biostatistics that shows promising results in the analyses of serial biomarker measurements (Fitzmaurice et al., 2008). Of note, we have not presented the joint modelling of the analysis of aortic regurgitation with death and reoperation due to the lack of freely available software to perform joint modelling of an ordinal longitudinal outcome in conjunction with a time-to-event.

In conclusion, using inappropriate methods and ignoring special characteristics of longitudinal data lead to underuse of potential variable information, and may bias the results and conclusions. Particularly, this has been shown with theoretical work and simulations in the statistical literature (Tsiatis and Davidian, 2004; Prentice, 1982; Agresti, 2002). Therefore,

serial biomarker data such as valve function are preferably analyzed using the mixed models, as illustrated in this Chapter. This allows for proper description of serial measurements over time and provides a foundation for joint modelling of mixed-effects models and time-to-event analysis.

2A.5 Appendix

A data frame "Age, Sex, Marfan, LVfunction, Diameter..mm, DonorAge, TypeoOperation, AoGradient, AoI, Time, Death., LastFUP, Reoperation., FUPreop," with the following variables was used in the following code:
Age: Age when received the aortic valve
Male: Male gender
Marfan: Marfan syndrome
LVfunction: Left ventricular function before operation
Diameter: Diameter of the aortic valve in mm before operation
DonorAge: Age of the donor
TypeoOperation: Type of operation
AoGradient: Aortic gradient
AoI: Aortic Regurgitation
Time: Time of the echo test in years after implant
Death
Reoperation
LastFUP: The longest follow-up year about the status of survival
FUPreop: The longest follow-up year about the status of reoperation

Mathematical formulations

- *Cox model*: $h_i(t) = h_0(t)\exp\{\gamma^\top W_i\}$,
  where $h_0(t)$ is the baseline hazard, W_i denotes the baseline covariates for the Cox model, and $\gamma^\top$ is a vector including the coefficients.
- *Linear mixed-effects model*: $Y_i = X_i\beta + Z_i b_i + \varepsilon_i$,
  where β is the vector of fixed effects coefficients, X is the design matrix for the fixed effects for observations in groups, Z is the design matrix for the random effects for observations in groups, b is the vector of random-effect coefficients for groups and ε is the vector of errors for observations in groups.
- In *Joint Modelling*, the hazard function of the survival submodel is:

$$h_i(t) = h_0(t)\exp\{u^\top H_i + \alpha m_i(t)\},$$

  where $m_i(t) = x_i^\top(t)\beta + z_i^\top(t)b_i$ denotes the value of the time-dependent covariate at time t, α quantifies the effect of this covariate at time t to the hazard for an event at

the same time point, H_i denotes the baseline covariates from the Cox model, and u the coefficients.
The likelihood of the joint modelling is:

$$\mathrm{P}(y_i, T_i, \delta_i \mid b_i; \theta) = \mathrm{P}(y_i \mid b_i; \theta)\mathrm{P}(T_i, \delta_i \mid b_i; \theta)db_i,$$

where y_i denotes the longitudinal outcome for the i-th subject, T_i denotes the observed failure time ($T_i = min(T_i^*, C_i)$, where C_i is the censoring time), δ_i is the event indicator, and b_i is a vector including the random effects.

The idea behind the joint models is that the random effects b_i account for both correlation between the same patients and the association between the longitudinal and survival outcomes. Thus the longitudinal and the survival submodels share the same random effects.

The method described above is one of the possible approaches to model longitudinal and survival data. Different joint models have been illustrated in the statistical literature but are beyond of the scope of this manuscript.

- *Continuation Ratio Model*

  As described by Harrell (2001), the CR model is based on conditional probabilities. The forward continuation ratio model is formulated as follows for $Y = 1, \ldots, k$ (k categories of the outcome)

$$\mathrm{P}(Y_i = j \mid Y_i \geq j, X) = \frac{1}{1 + \exp[-(\alpha + \theta_j + X_i\tau + Z_i u_i)]},$$

  where again τ is the vector of fixed effects coefficients, X is the design matrix for the fixed effects for observations in groups, Z is the design matrix for the random effects for observations in groups, u is the vector of random-effect coefficients for groups, α is an overall intercept, and θ_j are increments from α.

  We continue with the presentation of part of the syntax that has been used to apply the analyses described in this Chapter.

1. R code for mixed-effects models:
   ## With the library() function we load the package needed each time.
   library(nlme)
   ## To fit a mixed-effects model we use the function lme(). We use the "random"
   ## argument to specify the random effects and the "na.action" argument to specify if
   ## missing values will be excluded or not. In the following code we assume that the
   ## covariance matrix for the random effects is diagonal and the missing values should
   ## be excluded. Moreover, we use the function ns() from the package "splines" to
   ## include natural cubic splines.
   fm <- lme(sqrt(AoGradient) ∼ ns(Time, 3)TypeoOperation + TypeoOperation + . . . ,

data = mergeData22, na.action = na.exclude, random = list(IDnr = pdDiag(form = ∼ ns(Time, 3))))
With the function summary(), R prints the results.
summary(fm)

2. R code for the CR model (generalized linear mixed-effects model):
library(lme4)
library("rms")
library("arm")
First we transform the dataset to the specific format using the formula cr.setup()
from "rms" package (as described by Harrell (2001)).
u <- cr.setup(data2$AoI)
cohort <- u$cohort
y <- u$y
data <- attach(data2[u$subs,])
data <- data.frame(y, cohort, data$Time, data$IDnr, data$Age,. . .)
Following, we fit a generalized linear mixed model using the function glmer()
from "lme4" package. The "family" argument is used to specify the distribution of
the response variable.
glmer(y ∼ cohort Time + Age + . . . + (Time | IDnr), data = data, family = binomial)

3. R code for joint modelling:
library(JM)
To fit a joint model we first fit a mixed-effects model.
lmeFit.av <- lme(sqrt(AoGradient) ∼ TimeTypeoOperation + Age, data + data1, random = ∼ Time | IDnr)

Following, a Cox model is fitted.

   a. *For Death*
   coxFit.avD <- coxph(Surv(LastFUP, Death.) ∼ Type.of.operation + Age, data = data1.id, x = TRUE)

   a. *For Reoperation*
   coxFit.avR <- coxph(Surv(FUPreop, Reoperation.) ∼ Type.of.operation + Age, data = data1.id, x = TRUE)

For the joint modelling approach the formula jointModel() is used from "JM"
package.
jointFit.avD <- jointModel(lmeFit.av, coxFit.avD, timeVar = "Time", method = "piecewise-PH-aGH", iter.EM = 80)

```
summary(jointFit.avD)

jointFit.avR <- jointModel(lmeFit.av, coxFit.avR, timeVar = "Time", method =
"piecewise-PH-aGH", iter.EM = 80)
summary(jointFit.avR)
```

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CHAPTER 2B

Congenital Valvular Aortic Stenosis in Young Adults: Predictors for Rate of Progression of Stenosis and Aortic Dilatation

This Chapter is based on: van der Linde, D., Andrinopoulou, E.R., Oechslin, E.N., Budts, W., van Dijk, A.P., Pieper, P.G., Wajon, E.M., Post, M.C., Witsenburg, M., Silversides, C.K., Oxenius, A., Bogers, A.J., Takkenberg, J.J. and Roos-Hesselink JW. (2013). Congenital valvular aortic stenosis in young adults: predictors for rate of progression of stenosis and aortic dilatation. *International Journal of Cardiology*, 168:863 – 870.

Abstract

Background: Congenital aortic stenosis (AS) is the most common obstructive left-sided cardiac lesion in young adults, however little is known about the progression in adults. Therefore, we aimed to evaluate the progression rate of AS and aortic dilatation in a large multicenter retrospective cohort of asymptomatic young adults with congenital valvular AS.

Methods: Data were obtained from chart abstraction. Linear mixed-effects models were used to evaluate the progression of AS and aortic dilatation over time. A joint model combining longitudinal echocardiographic and survival data was used for survival analysis.

Results: A total of 414 patients (age 29±10 years, 68% male) were included. Median follow-up duration was 4.1 (2.5–5.1) years (1,587 patient-years). Peak aortic velocity was 3.4±0.7 m/s at baseline and did not change over time in the total patient population (-0.01±0.03 m/s/year). Increased left ventricular (LV) mass was significantly associated with faster AS progression (p-value<0.001). Aortic dilatation was present in 34% at baseline and 48% at follow-up (p-value<0.001). The aortic diameter linearly increased over time with a rate of 0.7±0.2 mm/year. Rate of aortic dissection was 0.06% per patient-year. Seventy patients required an aortic valve intervention (4.4% per patient-year), with AS progression rate as most powerful predictor (HR 5.11 (95% CI 3.47–7.53)).

Conclusions: In the majority of patients with mild-to-moderate congenital AS, AS severity does not progress over time. However patients with LV hypertrophy are at risk for faster progression and should be monitored carefully. Although aortic dissections rarely occur, aortic dilatation is common and steadily progresses over time, warranting serial aortic imaging.

2B.1 Introduction

Congenital valvular aortic stenosis (AS) represents 4% of all congenital heart defects (CHD) (van der Linde et al., 2011a). It is the most frequent indication for aortic valve replacement (AVR) in adults under the age of 60 years, with subsequently a restraint life expectancy (Puvimanasinghe et al., 2001). Clinical outcome of congenital AS considerably varies, and includes a wide spectrum ranging from a lifelong asymptomatic course to progressive disease in childhood requiring repeated interventions. So far, research on evolution of AS and predictors of progression mainly focused on calcified AS, or congenital AS in childhood (Otto et al., 1997; Rosenhek et al., 2000; Ten Harkel et al., 2009). Only limited serial echocardiographic data are available describing the natural course of AS and identifying predictors of progression and outcome of AS in young adults (Yap et al., 2007; Beppu et al., 1993).

The underlying cause for congenital AS is often a bicuspid aortic valve (BAV), which is strongly associated with aortic dilatation (Siu and Silversides, 2010; Yap et al., 2005). Several studies report about the progression rate of aortic dilatation and associated predictors

in mixed-groups of BAV patients (normally functioning, regurgitant and stenosed valves), but none of these studies specifically focus on patients presenting with AS (Ferencik and Pape, 2003; Novaro and Griffin, 2004; La Canna et al., 2006; Thanassoulis et al., 2008; Davies et al., 2007). Continuing controversy still exists as to whether BAV-associated proximal ascending aortic dilatation is caused by intrinsic aortic wall pathology or haemodynamic factors, or perhaps a combination of both (Fedak et al., 2002; Hope et al., 2010).

The aim of the present study was to determine the stenosis and aortic dilatation progression rate and identify risk factors for fast disease progression in a large cohort of asymptomatic young adult patients with congenital valvular AS.

2B.2 Methods

All adult patients with congenital valvular AS, who attended the outpatient clinic for adult CHD of a participating centre, between January 2005 and October 2011, were identified. Eligible patients were selected from prospective databases: the CONCOR database (the Dutch registry for adult patients with CHD), Van de Velde et al. (2005), and the Leuven and Toronto database for adults with CHD. Inclusion criteria were: age 18–55 years old and a baseline peak aortic velocity >2.5 m/s. Patients had to have serial echocardiographic examinations at least 1 year apart. Exclusion criteria included subvalvular or supravalvular AS, previous AVR, history of acute rheumatic fever, or mitral valve condition (mitral insufficiency >2+ or mitral valve area <1.5 cm^2). Demographic, clinical and surgical data were obtained from chart abstraction. All available transthoracic echocardiograms, electrocardiograms and exercise tests were collected. The collected information was registered in a dedicated research database. Indications for surgery included severe AS with any valve-related symptoms, symptoms during exercise testing and left ventricular (LV) ejection faction <50%, or an ascending aortic diameter >50 mm.

The study protocol was approved by the Medical Ethical Committee of the participating centres, and conducted according to the Helsinki Declaration. Informed consent was waived.

2B.2.1 Echocardiographic Data

AS severity was objectified by measurements of peak aortic velocity, mean gradient and continuity equation aortic valve area (Baumgartner et al., 2009). The degree of aortic regurgitation was graded by experienced sonographers and cardiologists as mild, moderate, or severe (Zoghbi et al., 2003). LV mass was calculated using the modified Devereux formula (Devereux et al., 1986). Left ventricular hypertrophy (LVH) was defined by a body surface area (BSA)-indexed threshold of >115 g/m2 for men and >95 g/m2 for women (Lang et al., 2006). BSA was calculated with the Mosteller formula (Mosteller, 1987). We defined the aortic valve as calcified if there was calcified thickening and increased echogenicity of the cusps in the parasternal long or short axis views. The ascending aorta diameter was measured

at end-diastole from leading edge to leading edge at four levels: annulus, sinus of Valsalva, sinotubular junction (STJ) and proximal ascending aorta. If the aortic diameter was more than two standard deviations (SD) above normal values by gender, the aorta was considered dilated (Hiratzka et al., 2010).

2B.2.2 Statistical Analysis

The Statistical Package for Social Sciences, version 19.0 (SPSS, Inc., Chicago, Illinois) was used for descriptive data analysis. Normally distributed continuous variables were summarized using the mean±SD. Non-normally distributed continuous variables were summarized using the median and interquantile range (IQR). Categorical variables were summarized using the frequency and percentage. The McNemar test was used to compare the frequency of aortic dilatation at baseline and follow-up. p-value <0.05 were considered statistically significant.

For advanced statistical analyses, R (version 2.14.1, available at: www.r-project.org) was used. Linear mixed-effects models were used to assess changes in peak aortic velocity and proximal ascending aortic diameter over time while accounting for the correlation between repeated follow-up measurements in each patient. Annual progression rates were calculated while taking into account all echocardiograms for each patient. The following covariates were included in the models: baseline peak aortic velocity, age, gender, prior aortic valve intervention (balloon valvuloplasty or open valvulotomy), smoking, aortic valve calcification, LV mass, total LV load (peak aortic valve gradient + systolic blood pressure), aortic regurgitation and baseline aortic diameter. Residual plots were used to validate the models' assumption. Wald tests were used to assess which parameters were most associated with the progression over time.

Probabilities of intervention-free survival from baseline were obtained by the Kaplan-Meier method. Survival of the congenital AS patients was compared to the expected survival of the age-matched general Dutch population (Survival data for the Dutch population, 2012). An event was defined as AVR or death. The linear mixed-effects model predicting peak aortic velocity progression was inserted into a Cox regression survival model as a time-varying covariate. The purpose of this joint modelling approach is to account for any biological variation in aortic valve function and repeated measurements within patients. Benefits of joint modelling include reduction of bias and improvement of efficiency, and resulting in more precise estimates (Tsiatis and Davidian, 2004).

2B.3 Results

A total of 1,318 patients were assessed for eligibility to participate in this study. Nine hundred and four patients were excluded, mainly due to previous AVR (n=484), peak aortic velocity <2.5 m/s (n=374), or lack of serial echocardiographic examinations (n=31). A total

Table 2B.1: Baseline characteristics

	Total group (n=414)	Men (n=281)	Women (n=133)
Age at baseline, years	29.3±10.0	29.5±10.2	28.9±9.8
Body surface area, m^2	1.9±0.2	2.0±0.2	1.7±0.2
Body mass index, kg/m^2	25.0±4.4	25.0±4.2	24.8±4.9
Blood pressure, mm Hg			
Systolic	124.3±15.8	126.8±15.4	119.1±15.4
Diastolic	74.8±10.3	75.7±10.3	72.8±10.0
Prior intervention	124 (30.0)	91 (32.4)	33 (24.8)
Balloon aortic valvuloplasty[a]	87 (21.0)	61 (21.7)	26 (19.5)
Open aortic valvulotomy[a]	55 (13.3)	43 (15.3)	12 (9.0)
Aortic stenosis severity			
Peak aortic velocity, m/s	3.4±0.7	3.4±0.7	3.4±0.7
Mean aortic gradient	25.5±10.8	26.0±11.2	26.1±11.5
Aortic valve area, cm^2	1.3±0.4	1.3±0.4	1.2±0.4
Bicuspid aortic valve	391 (94.4)	269 (95.7)	122 (91.7)
Aortic diameters, mm (indexed for BSA) → % dilated			
Annulus	22.9±3.5 (12.2±2.0)→ 8 (1.9)	23.8±3.5 (12.1±2.1)→ 5 (1.8)	21.1±2.8 (12.2±1.9)→ 3 (2.3)
Sinus of Valsalva	30.7±5.2 (16.2±2.8)→ 20 (4.8)	31.5±5.1 (15.9±2.7)→ 14 (5.0)	29.1±5.0 (16.8±3.1)→ 6 (4.5)
Sinotubular junction	27.6±4.9 (14.6±2.7)→ 28 (6.7)	28.1±4.8 (14.3±2.5)→ 19 (6.8)	26.7±5.1 (15.4±3.0)→ 9 (6.8)
Proximal ascending aorta	34.7±6.9 (18.4±3.8)→ 142 (34.3)	35.3±6.9 (17.9±3.5)→ 95 (33.8)	33.5±6.7 (19.4±4.3)→ 47 (35.3)
Aortic regurgitation			
None/mild	235 (56.8)	152 (54.1)	83 (62.4)
Moderate	133 (32.1)	94 (33.5)	39 (29.3)
Severe	46 (11.1)	35 (12.5)	11 (8.3)
Left atrial diameter, mm	33.9±6.7	34.9±5.9	31.7±7.6
LV hypertrophy	173 (41.8)	116 (41.3)	57 (42.9)
Interventricular septal thickness, mm	10.8±2.3	11.1±2.3	10.2±2.4
Left ventricular posterior wall thickness, mm	10.3±2.1	10.7±2.0	9.5±2.0
Left ventricular mass, g (indexed for BSA)	201.4±64.0 (106.9±32.2)	222.5±66.1 (112±32.2)	165.2±53.3 (94.9±28.6)
LV end-diastolic diameter, mm (indexed for BSA)	50.5±6.7 (26.7±3.8)	52.0±6.4 (26.5±3.8)	47.1±6.1 (27.2±3.7)
LV end-systolic diameter, mm (indexed for BSA)	30.8±6.0 (16.3±3.2)	32.0±6.0 (16.3±3.2)	28.3±5.2 (16.4±3.0)
LV fractional shortening, %	39.0±7.6	38.5±7.7	40.0±7.5
E/A ratio	1.7±0.6	1.7±0.6	1.65±0.7
Maximum exercise capacity, % from norm	90.4±18.4	91.2±17.9	88.7±19.6
Heart frequency, beats per minute	70.1±12.6	68.3±12.2	74.0±12.6
QRS duration, ms	99.5±14.8	102.6±14.5	93.1±13.4
PR time, ms	153.4±25.9	156.9±26.7	146±22.3
Smoking			
Never	298 (72.0)	118 (66.9)	110 (82.7)
Former	25 (6.0)	18 (6.4)	7 (5.3)
Current	91 (22.0)	75 (26.7)	16 (12.0)

Values are expressed as n(%), or mean±SD. BSA = body surface area; LV = left ventricular; SD = standard deviation. [a]Eighteen patients had an open aortic valvulotomy and balloon aortic valvuloplasty

of 414 patients were included in this study.

Table 2B.2: Predictors for peak aortic velocity progression over time

Covariates	Coefficient	SE	*p*-value
(Intercept)	3.136	0.125	0.000
Time	−0.008	0.027	0.774
Main effect			
Age (years)	0.006	0.003	0.067
Gender	−0.028	0.074	0.706
Prior aortic valve intervention	−0.102	0.069	0.137
Aortic valve calcification	−0.089	0.064	0.162
Left ventricular mass (gram)	0.001	0.001	0.366
Aortic regurgitation	0.180	0.078	0.004
Smoking	0.137	0.083	0.181
Total left ventricular load	−0.002	0.002	0.438
Interaction effect			
Age (years)	0.001	0.001	0.717
Gender	−0.012	0.015	0.430
Prior aortic valve intervention	−0.002	0.013	0.892
Aortic valve calcification	0.013	0.018	0.471
Left ventricular mass (gram)	0.001	0.001	$<$ 0.001
Aortic regurgitation	−0.026	0.021	0.413
Smoking	−0.034	0.017	0.082
Baseline peak aortic velocity (m/s)	−0.009	0.014	0.521
Total left ventricular load	−0.001	0.001	0.860

SE = standard error; Main effect = effect of a covariate on the outcome at baseline (intercept); Interaction effect = effect of a covariate on the outcome over time (slope)

Baseline characteristics are shown in Table 2B.1. All patients were asymptomatic at baseline and 98% was in sinus rhythm. Associated CHD were encountered in 45 patients (11%): aortic coarctation (n=37, repaired in 34 patients), ventricular septal defect (n=7), patent ductus arteriosus (n=6), and atrial septal defect (n=2) (not mutually exclusive). Aortic valve calcification was present in 91 patients (22%). Five patients (1.2%) were known with the diagnosis diabetes mellitus.

Median follow-up duration was 4.1 (2.5–5.1) years, yielding a total of 1,587 patient-years. On average 3.3±1.8 echocardiographic studies were available for each patient.

2B.3.1 Progression Rate of Aortic Stenosis Severity and Its Predictors

Peak aortic velocity was 3.4±0.7 m/s at baseline and did not progress significantly over time in the total study population (-0.01±0.03 m/s per year; *p*-value=0.774). However, fast progression (≥0.2 m/s/year) was noted in 56 patients (13.5%). In 13 patients (3.1%) the

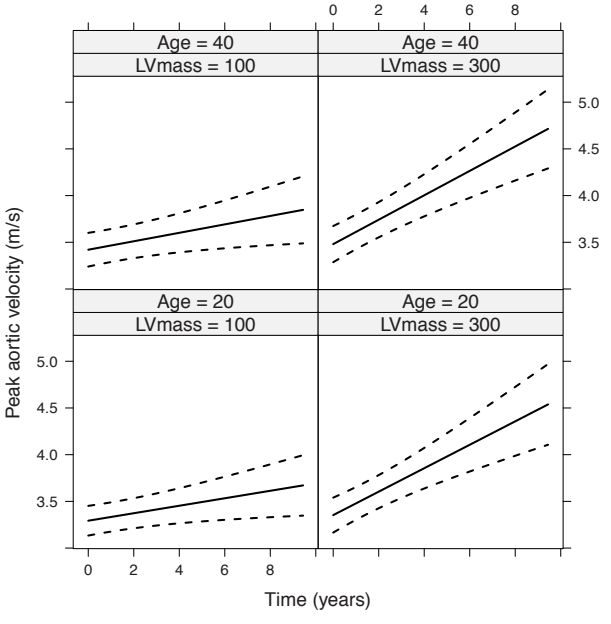

Figure 2B.1: Progression of congenital aortic stenosis over time by LV mass (p-value<0.001) and patient age (p-value=0.717). The dashed lines denote 95% confidence intervals. LV = left ventricular

progression was even $\geq$0.5 m/s per year. An increased LV mass was the only independent factor associated with faster progression of peak aortic velocity (p-value<0.001). The presence of an aortic coarctation was not significantly related to an increased LV mass (200.3$\pm$89.5 g with coarctation versus 204.6$\pm$65.4 g with no coarctation; p-value=0.720).

Progression rate was not influenced by prior intervention, gender, age, smoking history, aortic valve calcification, baseline peak aortic velocity, total LV load or aortic regurgitation (Table 2B.2). The effects of LV mass and age on peak aortic velocity progression over time are demonstrated in Figure 2B.1.

2B.3.2 Progression Rate of Aortic Dilatation and Its Predictors

Aortic dilatation mainly occurred at the level of the proximal ascending aorta: 142 patients (34%) showed dilatation at baseline, rising to 197 patients (48%) at follow-up (p-value<0.001). Increased age, prior intervention, presence of moderate-to-severe regurgitation and increased LV mass were associated with an overall larger proximal ascending aorta (Table 2B.3). There was no significant difference in ascending aortic

Table 2B.3: Predictors for ascending aortic dilatation progression over time

Covariates	Coefficient	SE	*p*-value
(Intercept)	24.900	1.184	0.000
Time	0.982	0.360	0.006
Main effect			
Age (years)	0.170	0.032	< 0.001
Gender	1.097	0.702	0.119
Prior aortic valve intervention	1.555	0.657	0.019
Baseline aortic velocity (m/s)	0.810	0.656	0.218
Left ventricular mass (gram)	0.010	0.003	< 0.001
Aortic regurgitation	2.348	0.705	0.004
Smoking	0.583	0.787	0.723
Interaction effect			
Age (years)	-0.006	0.006	0.316
Gender	0.224	0.131	0.089
Prior aortic valve intervention	0.050	0.113	0.659
Baseline peak aortic velocity (m/s)	-0.115	0.090	0.201
Left ventricular mass (gram)	-0.001	0.001	0.728
Aortic regurgitation	-0.311	0.181	0.212
Smoking	-0.131	0.141	0.275
Baseline aortic diameter >40 mm	0.179	0.133	0.181

SE = standard error; Main effect = effect of a covariate on the outcome at baseline (intercept); Interaction effect = effect of a covariate on the outcome over time (slope)

diameters between patients with bicuspid valves (94%) and patients with tricuspid, unicuspid or uncertain valve morphology (*p*-value=0.556).

The proximal ascending aortic diameter significantly increased over time with a rate of 0.66±0.23 mm per year (*p*-value=0.005). Fast progression (≥3 mm/year) was noted in 12 patients (2.9%), while 6 patients (1.4%) showed very fast progression (≥5 mm/year). The aortic dilatation progression rate tended to be faster in men compared to women (*p*-value=0.089; Figure 2B.2). Age, prior intervention, smoking, presence of moderate-to-severe regurgitation, baseline aortic dilatation >40 mm and LVmass did not influence aortic dilatation progression rate (Table 2B.3). Furthermore, aortic growth was not influenced by baseline peak aortic velocity (*p*-value=0.201; Figure 2B.3).

2B.3.3 Clinical Outcome

During the follow-up period 5 deaths occurred at a mean age of 48±10 years (0.32% per patient-year). Clinical cause of death was: 1 leukaemia, 3 sudden deaths and 1 arrhythmia (no detailed information available). No autopsies were performed. A 36-year-old patient presented in the emergency room with a Type A aortic dissection (last measured proximal ascending aortic diameter 51 mm), but was operated on successfully (rate 0.06%

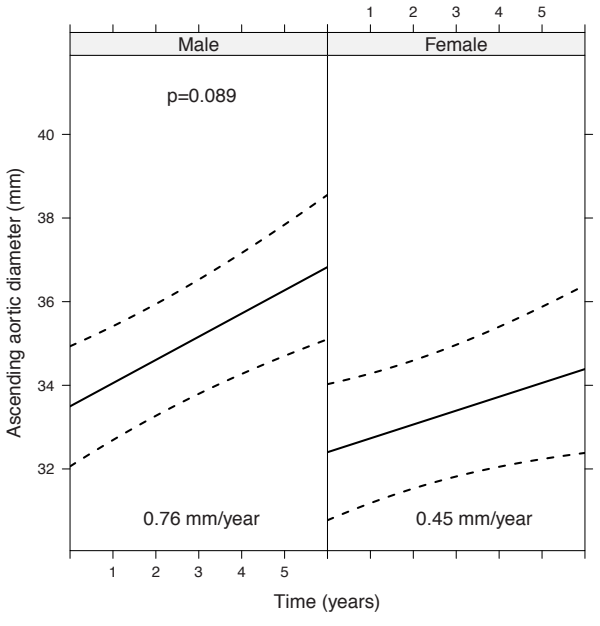

Figure 2B.2: Proximal ascending aortic dilatation progression rate over time by gender. The dashed lines denote 95% confidence intervals

Table 2B.4: Joint model (combining longitudinal and survival data) for intervention-free survival

	Hazard ratio (95% CI)	*p*-value
Age (>30 years)	1.04 (1.02–1.07)	< 0.001
Gender	1.51 (0.86–2.63)	0.150
Prior aortic valve intervention	1.77 (1.04–3.02)	0.036
Left ventricular mass	1.01 (0.99–1.02)	0.084
Former smoking	1.17 (0.48–2.85)	0.726
Current smoking	0.91 (0.50–1.65)	0.751
Aortic stenosis progression rate (mixed-effects model)	5.11 (3.47–7.53)	< 0.001

CI = confidence interval

per patient-year of follow-up). In addition, 4 patients experienced an episode of endocarditis at a mean age of 27±6 years (0.25% per patient-year). Three patients were hospitalized for

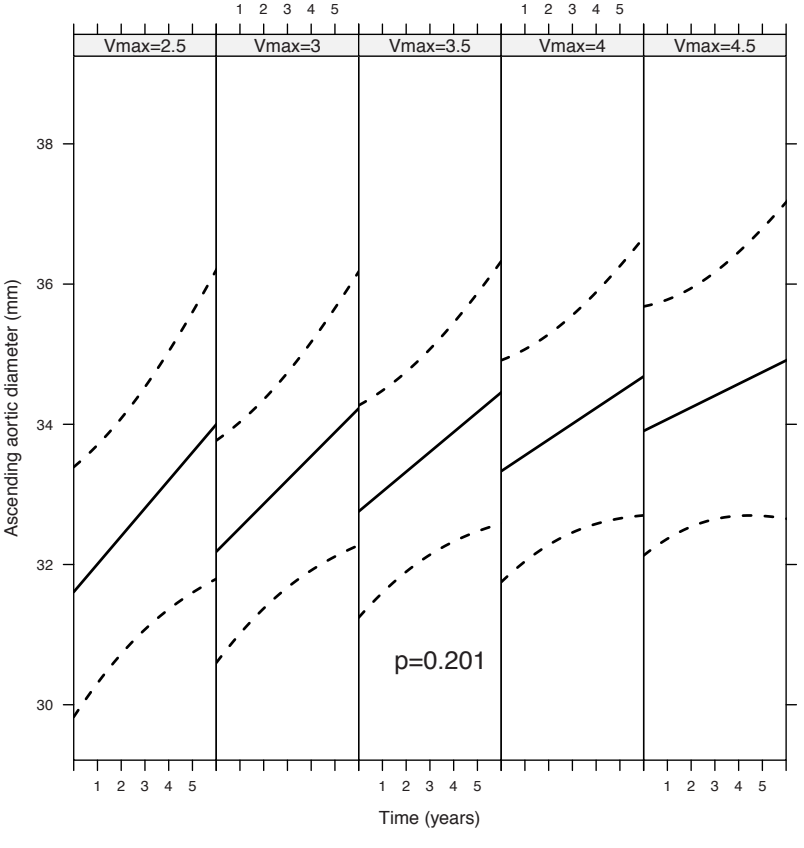

Figure 2B.3: Proximal ascending aortic dilatation progression rate over time by AS severity. The dashed lines denote 95% confidence intervals. AS = aortic stenosis; Vmax = peak aortic velocity in m/s

left-sided heart failure due to severe AS at a mean age of 32±8 years (0.19% per patient-year).

Seventy patients underwent AVR at a mean age of 36±10 years (4.4% per patient-year). Peak aortic velocity at the final echocardiographic study before intervention was 4.4±0.7 m/s. Performed operations included: 25 mechanical valves (35%), 25 Bentall procedures (35%), 10 tissue valves (14%), 5 Ross procedures (7%), 4 balloon valvuloplasties (6%) and 1 surgical valvulotomy (1%). In addition, 2 patients underwent aortic valve-sparing operations.

Overall estimated intervention-free survival was 87±2% at 3 years and 78±4% at 5 years (Figure 2B.4(A)). Median intervention-free survival for patients with an aortic peak velocity >4 m/s was 5 years (Figure 2B.4(B)). AS progression rate was the most powerful predictor

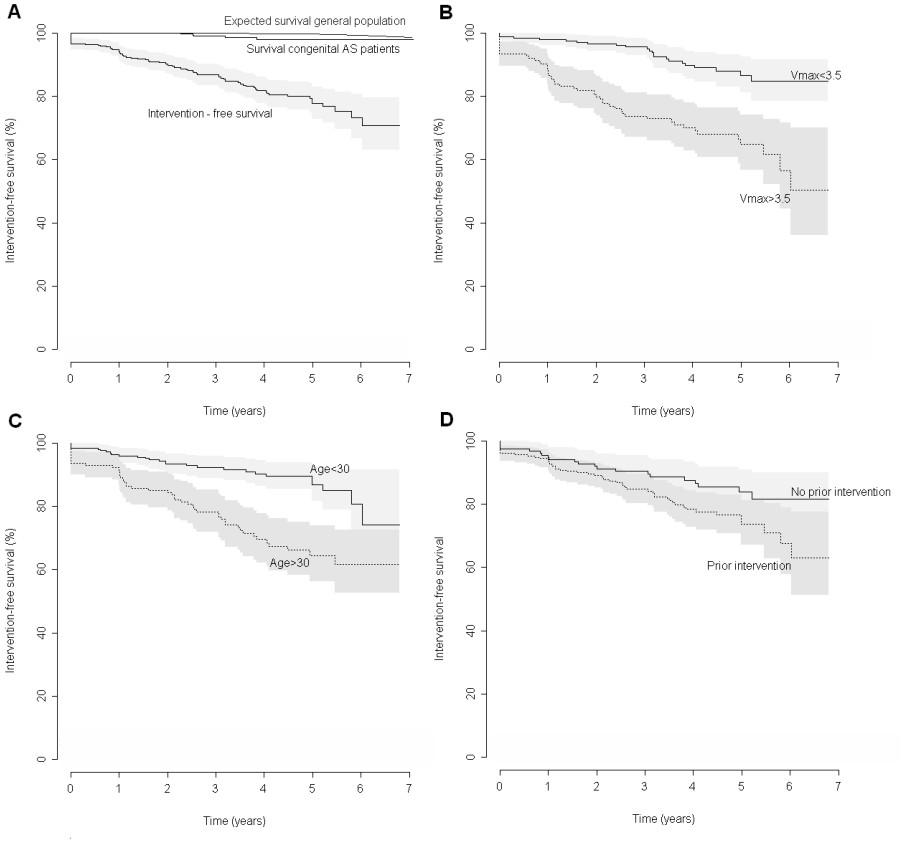

Figure 2B.4: Kaplan–Meier curves. (A) Cumulative Kaplan–Meier survival and intervention-free survival for the congenital AS patients and expected survival of the age-matched Dutch population. (B) Cumulative Kaplan–Meier intervention-free survival for congenital AS patients according to baseline peak aortic velocity (p-value<0.001). (C) Cumulative Kaplan–Meier intervention-free survival for congenital AS patients aged according to age at baseline (p-value<0.001). (D) Cumulative Kaplan–Meier intervention-free survival for congenital AS patients with and without prior aortic valve intervention (p-value=0.036). The grey-toned areas denote the 95% confidence intervals. AS = aortic stenosis; Vmax = peak aortic velocity in m/s

for AVR (Table 2B.4). Increased age (>30 years) and prior aortic valve intervention were also found to be significant predictors of outcome (Table 2B.4; Figures 2B.4(C) and (D)). In addition, an increased LV mass tended to influence intervention-free survival (Table 2B.4).

2B.4 Discussion

To our knowledge this is the first large multicenter cohort study evaluating the progression rate of asymptomatic congenital valvular AS in young adults. Given the scarcity of data about the progression of congenital AS in young adults, these results will contribute to our understanding of the clinical course of congenital AS in adulthood and guide clinical management.

2B.4.1 Progression of AS Severity

Overall, peak aortic velocity did not change over time in our cohort during the median follow-up of 4.1 years, though a subset of patients did show fast progression. This seems to be comparable to previously reported slow progression rates around 0.08 m/s per year in young adults with congenital AS (Yap et al., 2007; Beppu et al., 1993; van der Linde et al., 2011b). This accumulated evidence shows that in general the progression rate in congenital AS is lower than in degenerative calcific AS with reported progression rates around 0.3 m/s per year (Rosenhek et al., 2004). In contrast to the study by Yap et al. (2007) according to our results older age is not associated with faster progression in these young adult patients.

Interestingly, we identified LV mass to be strongly associated with progression of congenital AS, irrespective of total LV load or the presence of an aortic coarctation. Ventricular remodelling and development of LVH have classically been interpreted as a physiological mechanism used by the LV to compensate for the chronic pressure overload (Sasayama et al., 1976). However, recent insights have questioned whether this hypothesis is true. Perhaps LVH is not just a consequence of AS, but otherwise involved in the disease mechanism. Many studies have reported that the hypertrophic response to AS is not uniform in patients with comparable AS severity and regression of LVH after surgical correction is also variable (Tzikas et al., 2011; Petrov et al., 2010; Morris et al., 1994; Dellgren et al., 1999). Perhaps other factors than the pressure overload play a role in the adaptive hypertrophic response, for example gender and genetic predisposition (Morris et al., 1994; Dellgren et al., 1999; Piro et al., 2010). Furthermore, one might even argue whether evolution of LVH is adaptive or inappropriately maladaptive. Recently, the unfavourable prognostic implications of LVH were elegantly demonstrated in patients with severe degenerative AS (Cioffi et al., 2011; Kupari et al., 2005). In our young adult patients with congenital AS, the association between increased LV mass and faster AS progression emphasizes the unfavourable impact of LVH on clinical outcome. Nowadays controversy exists about how the degree of LVH should influence timing of surgery. The current European guidelines carefully state that asymptomatic patients with severe congenital AS and excessive LVH ($\geq$15 mm), unless this is due to hypertension, may be considered for AVR; while the North American guidelines do not mention LVH as consideration for AVR (Baumgartner et al., 2010; Warnes et al., 2008; Silversides et al., 2010). Basic research is warranted to elucidate the mechanisms behind the development of LVH in order to identify those patients that are at risk of LVH-related worse

outcome and will benefit from more aggressive thresholds to proceed to surgery.

2B.4.2 Progression of Aortic Dilatation

As expected, proximal aortic dilatation was present in almost half of our study population. Older age, history of prior aortic valve intervention, moderate-to-severe aortic regurgitation and LVH were all associated with the presence of proximal aortic dilatation, but none of these factors influenced the rate of aortic dilatation. Since previous studies only investigated aortic dilatation in mixed groups of BAV patients (inclusion not restricted to patients presenting with AS), it is incorrect to directly extrapolate those findings to our study group. However, these studies agree regarding the fact that patients of older age or with moderate-to-severe aortic regurgitation are more likely to have a dilated aorta (Thanassoulis et al., 2008; Della Corte et al., 2007; Keane et al., 2000).

Table 2B.5: Predictors for BSA-indexed ascending aortic dilatation progression over time

Covariates	Coefficient	SE	p-value
(Intercept)	16.411	0.688	0.000
Time	0.338	0.124	0.007
Main effect			
Age (years)	0.055	0.019	0.004
Gender	−1.670	0.407	$<$ 0.001
Prior aortic valve intervention	0.574	0.381	0.134
Baseline peak aortic velocity >3.5 m/s	0.404	0.382	0.291
Left ventricular mass (gram)	0.003	0.001	0.055
Aortic regurgitation	0.543	0.280	0.053
Smoking	0.070	0.458	0.879
Interaction effect			
Age (years)	−0.003	0.003	0.383
Gender	0.078	0.070	0.265
Prior aortic valve intervention	0.026	0.059	0.659
Left ventricular mass (gram)	−0.001	0.001	0.948
Aortic regurgitation	−0.141	0.964	0.145
Smoking	−0.045	0.075	0.544
Baseline aortic diameter >40 mm	0.037	0.071	0.604
Baseline peak aortic velocity >3.5 m/s	−0.075	0.063	0.234

SE = standard error; Main effect = effect of a covariate on the outcome at baseline (intercept); Interaction effect = effect of a covariate on the outcome over time (slope)

We found that proximal aortic dilatation steadily progressed with a rate of 0.7 mm per year. This seems to be comparable to other studies in BAV patients, which report rates ranging from 0.2 to 1.9 mm/ year (Ferencik and Pape, 2003; Novaro and Griffin, 2004; La Canna et al., 2006; Thanassoulis et al., 2008; Davies et al., 2007). Furthermore, our results are in line with the rate of progression (0.4 mm per year) reported in a small prospective study of adult

congenital AS patients (van der Linde et al., 2011b). Interestingly, the rate of progressive aortic dilatation was faster in male than in female patients. When we indexed the aortic diameter for BSA (Table 2B.5), this gender difference no longer existed and no other risk factors for faster aortic dilatation were identified. Therefore we speculate that the faster aortic growth in men is associated with their larger absolute aortic size. Despite evidence supporting the use of relative rather than absolute aortic size (Davies et al., 2006) our results suggest that absolute aortic size is an important predictor for aortic growth and might be the preferred measurement for clinical management of adult congenital AS patients. In addition, the gender difference in aortic growth rate might be explained by hormonal differences, genetic predispositions, hypertension or other gender differences, as remains to be elucidated in the future.

Surprisingly, the presence or progression of aortic dilatation was not related to AS severity in this large cohort of adult congenital AS patients. This argues against the so called haemodynamic theory, stating that aortopathy in BAV is caused by abnormal haemodynamic stress on the aortic wall due to turbulent flow as a result of abnormal valve morphology and cusp orientation (Girdauskas et al., 2011). There are conflicting data on this topic, since some studies did find a correlation between the degree of AS and aortic size (Della Corte et al., 2007), whereas others did not (Ferencik and Pape, 2003; Hahn et al., 1992). Our data strengthen the upcoming theory that aortic dilatation in BAV patients is not solely dependent on haemodynamics, but rather is a result of aortic wall fragility secondary to genetic factors and a common developmental defect involving both the aortic valve and the aortic wall (Girdauskas et al., 2011).

2B.4.3 Aortic Dissections

Aortic dissection is, without any doubt, the most feared complication of BAV-associated aortic dilatation. Therefore it is remarkable that only 1 case of aortic dissection occurred in our large cohort with almost 1,600 patient-years of follow-up. This converts to an aortic dissection risk of 0.06% per patient-year of follow-up in asymptomatic young adult patients with congenital AS. Although the prevalence of aortic dissection was estimated to be much higher in the past, two other large cohort studies with BAV patients also reported a low rate of aortic dissections (respectively 0.09% and 0.06% per patient-year of follow-up) (Tzemos et al., 2008; Michelena et al., 2011). Whether these low rate estimates indicate that we really do not have to fear aortic dissections, or reflect that prophylactic aortic surgery >50 mm efficiently prevents aortic dissections, remains a point of debate.

2B.4.4 Survival

Survival was good compared to the expected survival of the general population, but the 3 sudden deaths remain worrisome. Unfortunately no autopsy was performed to establish the

cause of death. A close look at the last available data before sudden death suggests that these patients were slightly older and had a slightly higher peak aortic velocity, greater LV mass and lower LV fractional shortening than the total cohort, but had a normal aortic diameter. However, these 3 cases do not allow statistical assessment of risk factors for sudden death.

2B.4.5 Clinical Implications

In the total study population of patients with predominantly mild-to-moderate AS, AS severity remained stable over time. However, patients with LVH showed faster disease progression, and should be monitored cautiously. In addition, LVH might be useful as an indicator for timing of earlier aortic valve intervention. Furthermore, while proximal ascending aortic dilatation was common, the risk for aortic dissection in adult congenital AS patients was low (0.06% per patient-year of follow-up). Noteworthy, proximal ascending aortic dilatation progressed steadily over time, and faster in male than in female patients. Consequently, these results stress the importance of careful and serial monitoring of the aorta patients with congenital AS. Aortic valve intervention rate is high, in particular in patients with progressive AS and history of prior aortic valve intervention.

2B.4.6 Study Limitations

This study inherits all limitations of a retrospective study design. A selected group of patients was included: patients with prior AVR and those without serial echocardiographic measurements were excluded. By including patients with a history of balloon valvuloplasty and open valvulotomy in childhood, one might question whether this is truly a natural history study. Furthermore, our study population consisted of patients receiving care in specialized CHD centres and might not be representative owing to referral bias. The use of prospective databases has limited the survival bias and extent of missing data. A potential limitation, caused by the fact that echocardiography was not performed precisely every year, was dissolved by the use of the linear mixed-effects models that take different lengths of follow-up into account. We admit that echocardiography might not have been the best tool for aortic diameter follow-up; however availability of computed tomography or magnetic resonance in this large cohort was limited. Finally, we did not assess the impact of BAV morphology or pregnancy on progression.

2B.5 Conclusions

In patients with mild-to-moderate congenital AS, AS generally does not progress over time. However patients with LVH are at risk for fast disease progression and should be monitored cautiously. Aortic dissections were rare despite the presence of proximal ascending aortic dilatation in half of the patients. The aorta grows steadily over time and thus needs to

be monitored repeatedly. Despite an excellent overall survival, intervention-free survival is impaired, particularly in patients >30 years old with a history of prior aortic valve intervention and severe or fast progressing AS.

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CHAPTER 2C

Autograft and Pulmonary Allograft Performance in the Second Post-Operative Decade After the Ross Procedure: Insights from the Rotterdam Prospective Cohort Study

This Chapter is based on: Mokhles, M.M., Rizopoulos, D., Andrinopoulou, E.R., Bekkers, J.A., Roos-Hesselink, J.W., Lesaffre, E., Bogers, A.J. and Takkenberg J.J. (2012). Autograft and pulmonary allograft performance in the second post-operative decade after the Ross procedure: insights from the Rotterdam prospective cohort study. *European Heart Journal*, 33:2213 – 2224.

Abstract

Aims: The objective of the present study was to report our ongoing prospective cohort of autograft recipients with up to 21 years of follow-up.

Methods and results: All consecutive patients (n = 161), operated between 1988 and 2010, were analysed. Mixed-effects models were used to assess changes in echocardiographic measurements (n = 1,023) over time in both the autograft and the pulmonary allograft. The mean patient age was 20.9 years (range 0.05–52.7) and 66.5% were male. Early mortality was 2.5% (n = 4), and eight additional patients died during a mean follow-up of 11.6±5.7 years (range 0–21.5). Patient survival was 90% (95% confidence interval (CI), 78–95) up to 18 years. During the follow-up, 57 patients required a reintervention related to the Ross operation. Freedom from autograft reoperation and allograft reintervention was 51% (95% CI 38–63) and 82% (95% CI 71–89) after 18 years, respectively. No major changes were observed over time in autograft gradient, and allograft gradient and regurgitation. An initial increase of sinotubular junction and aortic anulus diameter was observed in the first 5 years after surgery. The only factor associated with an increased autograft reoperation rate was pre-operative pure aortic regurgitation (hazard ratio 1.88; 95% CI 1.04–3.39; *p*-value = 0.037).

Conclusion: We observed good late survival in patients undergoing autograft procedure without reinforcement techniques. However, over half of the autografts failed prior to the end of the second decade. The reoperation rate and the results of echocardiographic measurements over time underline the importance of careful monitoring especially in the second decade after the initial autograft operation and in particular in patients with pre-operative aortic regurgitation.

2C.1 Introduction

The Ross procedure (or pulmonary autograft procedure), first introduced by Donald Ross in 1967, has become a widely accepted option for aortic valve replacement in a selected group of patients (Ross, 1967; Ross et al., 1992; Kouchoukos et al., 1994).

Although the operative mortality and long-term survival have been satisfactory, a major drawback of this procedure is the progressive dilatation of the autograft root, often combined with autograft valve insufficiency, necessitating reoperation (Kouchoukos et al., 2004; Luciani et al., 2003; Klieverik et al., 2007a; Stulak et al., 2010; Bekkers et al., 2010).

Data on patient survival, durability of the autograft and the pulmonary allograft, and the incidence of potential risk factors for valve dysfunction and reoperation after the Ross procedure are scarce beyond the first decade (Klieverik et al., 2007b; David et al., 2010b). In this regard, we report the results of the longest and most complete ongoing prospective cohort of autograft recipients, with a follow-up now reaching up to an unprecedented 21 years.

2C.2 Methods

2C.2.1 Patient Population

Between September 1988 and November 2010, 161 consecutive patients underwent the autograft procedure in our institution. The patients included in this study are also part of the German-Ross registry (Sievers et al., 2010). Approval from the Institutional Review Board was obtained for this prospective follow-up study; all patients gave their written informed consent.

2C.2.2 Operative Techniques

Timing of surgery was determined in a regular heart team meeting between (congenital) cardiologists and cardiac surgeons during which all cases were discussed. The decision whether to operate or not was based on contemporary clinical practice. Most procedures (72%) were performed by two surgeons. The remainder of the procedures was performed by another four surgeons. The surgical procedures were performed using standard cardiopulmonary bypass with moderate hypothermia, myocardial protection with crystalloid cardioplegia (St Thomas Hospital solution), and topical cooling. Additional deep hypothermia with total circulatory arrest was employed for surgery on the aortic arch.

In 155 patients, the root replacement technique was employed, and the pulmonary autograft was inserted at the level of the anulus, with care taken to reduce the subannular muscular rim of the autograft to 3 to 4 mm. The proximal suture line of the autograft was constructed, with interrupted sutures in 19% (n=30) of the procedures and running sutures in the remainder. In 159 of the 161 patients, no root reinforcement measures were taken. In two patients, an autologous pericardial strip supported the proximal suture line.

Three patients required concomitant coronary artery bypass grafting due to a procedural complication. The details of these patients have been previously reported (Klieverik et al., 2007a).

2C.2.3 Allograft Properties

In all patients, the right ventricular outflow tract (RVOT) was reconstructed using an allograft. The Rotterdam Heart Valve Bank provided most of the allografts (n=131), which were allocated by Bio Implant Services, Leiden, The Netherlands. The remaining allografts were shipped from Hospital Clinic I, Barcelona, Spain (n=16), Deutsches Herzzentrum, Berlin, Germany (n=7), the Karolinska Homograft Bank, Stockholm, Sweden (n=4), and the National Heart Hospital, London, UK (n=3). In 98%, a pulmonary allograft was used and 99% of the allografts were cryopreserved. Patient's body surface area was used as a guideline to determine the allograft diameter. No attempt was made to achieve ABO blood type or HLA

type matching. Previous publication from our centre showed that blood group compatibility and assignment of quality codes do not have an impact on allograft durability (Mokhles et al., 2011b).

2C.2.4 Data Collection

Hospital mortality and morbidity were registered and the causes of death were documented. Hospital mortality was defined as death of the patient within hospital or within 30 days after surgery. All patients were followed-up prospectively, contacted annually, and interviewed over telephone. Patients >16 years underwent standardized echocardiography biannually (Willems et al., 2001). In case of suspected complications, the attending physician was contacted for verification. The total follow-up was 1,875 patient-years and was 98.1% complete. Three patients moved abroad and were lost to follow-up (data from these patients were included in the analyses until the moment when they moved abroad). Valve-related events were defined according to the guidelines for reporting morbidity and mortality after cardiac valvular operations (Akins et al., 2008). Sudden, unexplained, unexpected deaths (SUUD) without further clinical data or autopsy were classified as valve-related deaths according to these guidelines (Akins et al., 2008). Failure of the autograft or pulmonary allograft was determined at the time of reoperation or death. Patient survival started at the time of Ross operation and ended at the time of death or at the last follow-up. Survival of the autograft or pulmonary allograft started at the time of operation and ended when a reoperation or reintervention was done, when the patient died, or at the last follow-up. Echocardiographic measurements were systematically and prospectively obtained for all patients until the time of death or autograft explant. The echocardiographic follow-up was 94% complete. The database was frozen on 31 December 2010.

2C.3 Statistical Analyses

2C.3.1 Analyses of Clinical Data

Patient data were entered into a computerized relational database (Microsoft Access 2000). The statistical software SPSS for Windows version 10 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Patient survival was estimated using the Kaplan–Meier method (Kaplan and Meier, 1958). The log-rank test was used to assess the effect of potential risk factors on patient survival, freedom from valve-related reoperation, and freedom from valve-related events. To investigate independent risk factors for mortality and morbidity caused by allograft failure, the Cox proportional hazard model was used. Risk factors were selected with a backward stepwise method (required significance of p-value>0.10 for elimination from the model and p-value<0.05 for retention in the model). Given the relatively small number of deaths, no multivariable analysis was performed for mortality in our patient

population. Kaplan–Meier survival estimates were compared with the survival of the general population matched for age, sex, year of surgery, and years of follow-up, using the Dutch population life table (Dutch Life Tables, 2009).

2C.3.2 Analyses of Serial Echocardiographic Data

Although the statistical analysis of serial echocardiographic data is often performed by means of the Kaplan–Meier method, the echocardiographic data in the present study were analysed with mixed-effects models instead. Mixed-effects modelling allows for more accurate analyses of dependent data such as hierarchical data, observations taken on related individuals (e.g. siblings), or measurements collected over time on the same individuals (e.g. echocardiographic measurements) (Pinheiro and Bates, 2000; Verbeke and Molenberghs, 2000). This approach of longitudinal data analyses is also proposed by the 2008 guidelines for reporting mortality and morbidity after cardiac valvular interventions, (Akins et al., 2008).

Mixed-effects models were used to assess changes in echocardiographic measurements over time while accounting for the correlation between repeated follow-up measurements in each patient. For the continuous outcomes, linear mixed models were used, whereas for the ordinal outcomes, mixed-effects continuation ratio models were employed. To allow for more flexibility in the specification of the patient-specific longitudinal trajectories, we utilized natural cubic splines with three internal knots placed at the corresponding percentiles of the follow-up times. Residual plots were used to validate the model's assumption, and when appropriate transformations of the outcome variables were performed. Missing echocardiogram measurements were assumed to be missing at random (Harrell, 2001; Verbeke and Molenberghs, 2000). In both the univariable and multivariable analyses, F-tests were used to assess which variables/prognostic factors were most associated with the echocardiographic measurements.

All analyses were performed with the R statistical software (version 2.13.2, 2011. R Development Core Team 2011, R Foundation for Statistical Computing, Vienna, Austria).

All statistical tests with a p-value of 0.05 or lower were considered significant.

2C.4 Results

2C.4.1 Patient and Operation Characteristics

The mean age of the patients was 20.9 ± 13.7 years (range 0.05–52.7). Patient characteristics are shown in Table 2C.1. Twelve patients underwent previous aortic valve replacement (AVR): six subcoronary allografts, three biological prostheses, and three mechanical prostheses were used. Perioperative data are shown in Table 2C.2.

Table 2C.1: Pre-operative characteristics of 161 patients

Baseline characteristics	All patients (N=161), n(%)	<18 years (N=75), n(%)	18–30 years (N=43), n(%)	>30 years (N=43), n(%)
Median age ± SD, range (years)	20.9±13.7 (0.05–52.7)	8.6±5.9 (0.05–17.8)	24.7±3.3 (18.33–24.69)	38.5±6.1 (30.0–52.7)
Gender				
Males	107 (66.5)	54 (72.0)	26 (60.5)	27 (62.8)
Females	54 (33.5)	21 (28.0)	17 (39.5)	16 (37.2)
Prior cardiac surgery				
Prior AVR	12 (7.5)	0 (0.0)	6 (14.0)	6 (14.0)
Aetiology				
Endocarditis	8 (4.9)	3 (4.0)	1 (2.3)	4 (9.4)
Congenital (including bicuspid)	123 (76.4)	70 (93.3)	30 (69.8)	23 (53.5)
Other (mainly prosthetic valve)	18 (11.2)	2 (2.7)	10 (23.3)	6 (14.0)
Degenerative/rheumatic	11 (6.8)	0 (0.0)	1 (2.3)	10 (23.3)
Aneurysm/dissection	1 (0.6)	0 (0.0)	1 (2.3)	0 (0.0)
Diagnosis				
AR	46 (28.6)	13 (17.3)	15 (34.9)	18 (41.9)
AS	47 (29.2)	19 (25.3)	14 (32.6)	14 (32.6)
AR + AS	68 (42.2)	43 (57.3)	14 (32.6)	11 (25.6)
Systolic LVF				
Good (EF > 50%)	135 (83.8)	63 (84.0)	36 (83.7)	35 (81.4)
Impaired (EF 40–50%)	17 (10.6)	9 (12.0)	3 (7.0)	5 (11.6)
Moderate/bad (EF < 40%)	9 (5.5)	2 (2.6)	4 (9.3)	3 (7.0)
Sinus rhythm	161 (100)	75 (100)	43 (100)	43 (100)
Creatinine (mmol/L)	61.7±24.4 (12–157)	41.4±15.9 (12–89)	75.6±19.5 (49–157)	78.6±15.4 (42–121)
NYHA class				
I	68 (42.2)	42 (56.0)	15 (34.9)	11 (25.6)
II	60 (37.3)	20 (26.7)	18 (41.9)	22 (51.2)
III	25 (15.5)	7 (9.3)	9 (20.9)	9 (20.9)
IV	8 (4.9)	6 (8.0)	1 (2.3)	1 (2.3)
Type of operation				
Emergency	2 (1.2)	1 (1.3)	1 (2.3)	0 (0.0)
Urgent	25 (15.5)	18 (24.0)	2 (4.7)	5 (11.6)
Elective	134 (83.2)	56 (74.7)	40 (93.0)	38 (88.4)

AS = aortic stenosis; AR = aortic regurgitation; AVR = aortic valve replacement; EF = ejection fraction; LVF = left ventricular function; SD = standard deviation

Table 2C.2: Perioperative characteristics of 161 patients

Baseline characteristics	All patients (N = 161), n (%)	<18 years (N = 75), n (%)	18–30 years (N = 43), n (%)	>30 years (N = 43), n (%)
Aortic valve Gender				
Bicuspid	99 (61.5)	49 (65.3)	27 (62.8)	23 (53.5)
Tricuspid	51 (31.7)	26 (34.7)	10 (23.3)	15 (34.9)
Prosthesis	11 (6.8)	0 (0.0)	6 (13.9)	5 (11.6)
Surgical technique				
Autograft root replacement	155 (96.3)	75 (100)	43 (100)	37 (86.0)
Inlay autograft	6 (3.7)	0 (0.0)	0 (0.0)	6 (14.0)
Concomitant procedures				
CABG	3 (1.9)	0 (0.0)	1 (2.3)	2 (4.7)
LVOT enlargement	16 (9.9)	10 (13.3)	4 (9.3)	2 (4.7)
Mitral valve surgery	2 (1.2)	1 (1.3)	0 (0.0)	1 (1.3)
Other[a]	20 (12.4)	12 (16.0)	4 (9.3)	4 (9.3)
CPB time (min)	200±68 (114–685)	175±54 (118–465)	214±55 (114–366)	227±84 (142–685)
Cross-clamp time (min)	141±32 (90–240)	125±28 (90–240)	151±33 (90–238)	156±27 (117–225)
Circulatory arrest (min)	30±29 (11–64) (n = 3)	15 (n = 1)	64 (n = 1)	11 (n = 1)
Complications				
Bleeding/tamponade	21 (13.0)	2 (2.7)	10 (23.3)	9 (20.9)
Pacemaker	2 (1.2)	1 (1.3)	0 (0.0)	1 (2.3)
Perioperative MI	1 (0.6)	0	1 (2.3)	0 (0.0)
Early mortality	4 (2.5)	1 (1.3)	2 (4.7)	1 (2.3)

CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; LVOT = left ventricular outflow tract; MI = myocardial infarction. [a]Includes patients requiring tailoring of the ascending aorta or subvalvular membrane resection

2C.4.2 Hospital Mortality and Late Survival

Hospital mortality was 2.5% (four patients) (Table 2C.2). Two patients, both female, died perioperatively. One 26-year-old male patient died due to massive pulmonary emboli shortly after the operation. Furthermore, one 24-year-old female patient with Turner syndrome and extreme left ventricular (LV) hypertrophy died due to mediastinitis and sepsis 13 days after surgery.

The mean follow-up duration was 11.6±5.7 years (range 0–21.5 years; median 12.7 years; interquartile range 8.6–15.3 years). During the follow-up, eight more patients died. Three were valve-related. One patient died suddenly 13.9 years after autograft operation at the age of 50 years. The other patient with SUUD died 10.7 years after autograft operation at the age of 39 years. The third patient with valve-related death was a 12-year-old girl with severe juvenile rheumatic disease and severe aortic regurgitation and mitral valve incompetence resulting in progressive heart failure. She died 6 months after operation. Furthermore, there were five non-valve-related deaths, of which four were cardiac deaths. Causes of the non-valve-related deaths included (1) septic shock (Candida albicans) in one infant 51 days after autograft operation; (2) heart failure resulting in cardiogenic shock in another infant 1.7 years after autograft operation; (3) gastroenteritis (Staphylococcus aureus) resulting in septic shock and multiorgan failure 14.6 years after autograft operation; (4) heart failure due to restrictive cardiomyopathy 16.3 years after autograft operation, and (5) an acute myocardial infarction in an adult patient 4.7 years after autograft operation and 2 months after autograft reoperation for structural valve deterioration with the implantation of a mechanical prosthesis.

Overall, survival was 89% (95% confidence interval (CI) 78–95) up to 18 years of follow-up (Figure 2C.1(A)).

The instantaneous hazard of mortality was highest in the immediate post-operative period. This hazard then declined in the first 6 years after surgery, but started to slightly increase again after this period (Figure 2C.1(A)).

At the most recent follow-up, 81 (54%) of our patients were in New York Heart Association (NYHA) functional class I, 38 (26%) were in NYHA functional class II, 16 (11%) were in NYHA functional class III, and 5 (3%) were in NYHA functional class IV. NYHA functional class was unknown in 9 (6%) patients at the most recent follow-up.

Table 2C.3 displays the risk factors associated with long-term mortality after autograft procedure that were identified in univariate analyses.

Long-term mortality rates of our patient population are relatively low and comparable with that of the general population in the first decade. However, the survival rate of Ross patients shows, in our experience, a decline in the second post-operative decade compared with the general population (Figure 2C.1(B)).

Table 2C.3: Potential predictors of mortality, autograft reoperation, and allograft reoperation

Predictor	Survival, Hazard ratio (95% CI)	*p*-value	Autograft reop, (95% CI)	*p*-value	Allograft reop, (95% CI)	*p*-value
Gender	1.78 (0.44–7.17)	0.24	0.63 (0.32–1.22)	0.16	0.87 (0.33–2.30)	0.77
Age	0.99 (0.94–1.05)	0.99	1.02 (0.99–1.04)	0.20	0.98 (0.95–1.02)	0.29
NYHA						
I	Reference		Reference		Reference	
II	2.39 (0.22–26.44)	0.29	1.17 (0.60–2.29)	0.67	0.59 (0.18–1.96)	0.38
III or IV	10.58 (1.23–90.67)	0.02	1.88 (0.90–3.95)	0.11	1.55 (0.51–4.76)	0.45
Hypertension	11.07 (1.23–99.42)	0.03	1.08 (0.15–7.85)	0.95	NA	NA
Previous AV surgery	0.02 (0.00–11.37)	0.24	0.53 (0.27–1.06)	0.48	0.60 (0.20–1.83)	0.49
Creatinine	1.01 (0.97–1.04)	0.84	1.01 (0.99–1.03)	0.13	0.99 (0.97–1.01)	0.29
LV function	1.03 (0.39–2.75)	0.87	1.34 (0.92–1.94)	0.13	1.04 (0.55–1.97)	0.91
Timing						
Elective	Reference		Reference		Reference	
Urgent	3.13 (0.74–13.25)	0.99	0.89 (0.37–2.11)	0.99	1.97 (0.65–6.01)	0.99
Inclusion technique	NA	NA	0.45 (0.06–3.24)	0.42	–	–
Cross-clamp time	1.01 (0.99–1.03)	0.89	1.00 (0.99–1.01)	0.83	1.00 (0.98–1.02)	0.99
Perfusion time	1.01 (0.99–1.02)	0.17	1.00 (0.99–1.01)	0.79	1.00 (0.99–1.01)	0.73
Bicuspid AV	0.33 (0.08–1.38)	0.27	0.97 (0.52–1.78)	0.88	–	–
Aorta ascendens aneurysm	NA	NA	1.58 (0.67–3.75)	0.30	1.15 (0.27–5.03)	0.85
Aortic regurgitation	7.40 (1.49–36.85)	0.03	1.88 (1.04–3.39)	0.03	–	–
Adult age (>18 years)	1.05 (0.25–4.47)	0.86	1.63 (0.84–3.17)	0.15	0.75 (0.30–1.89)	0.55

Results were obtained from univariate analyses. AV = aortic valve; LV = left ventricle; NA = not assessable; NYHA = New York Heart Association Class; CI = confidence interval

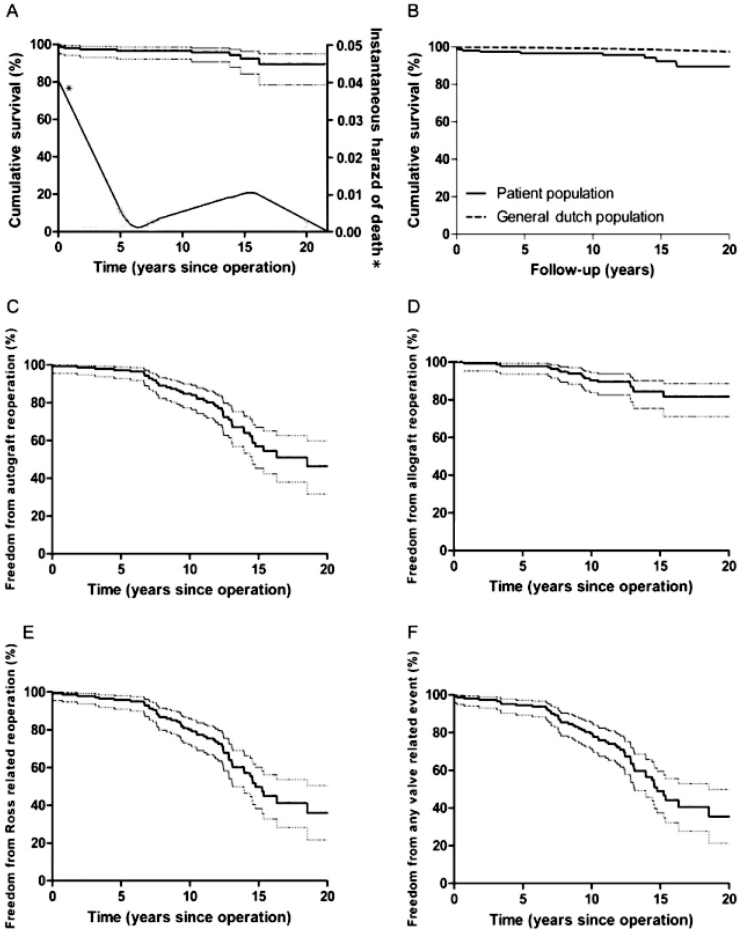

Figure 2C.1: Kaplan–Meier plot of (A) patient survival after the autograft procedure (the asterisk represents instantaneous hazard of death). (B) survival comparison of autograft patients with that of general population. (C) freedom from autograft reoperation. (D) freedom from allograft reoperation. (E) freedom from autograft or allograft reoperation. (F) freedom from any valve-related event

2C.4.3 Survival Rate in Different Age Categories

Patient survival in the age category 2 weeks to 18 years was 94% (95% CI 87–99) at both 10 years as well as up to 18 years of follow-up. Univariate analyses indicated

that previous aortic valve surgery (p-value=0.030) and pre-operative aortic anulus aneurysm (p-value=0.048) were associated with impaired survival during the follow-up in this patient group.

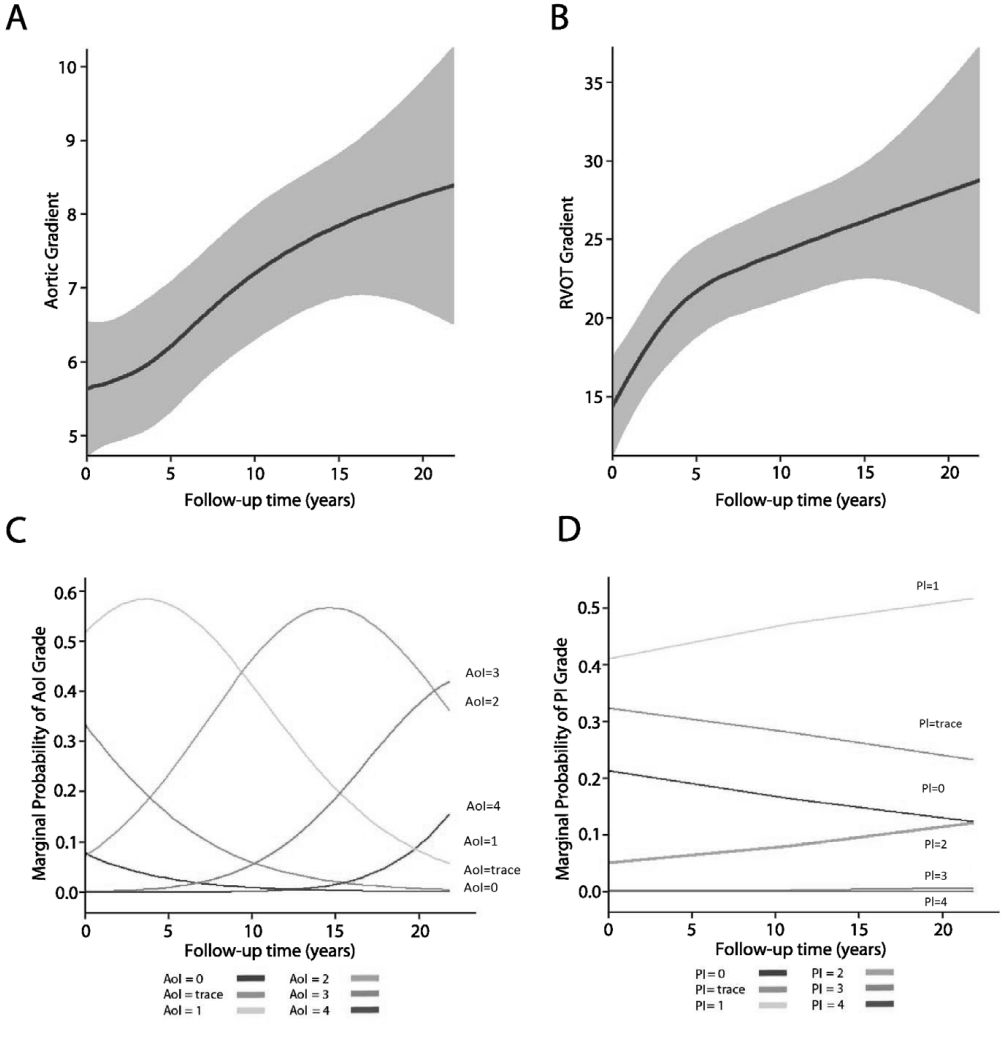

Figure 2C.2: Mixed-effects models of echocardiogram variables after the autograft procedure. (A) transaortic gradients. (B) transpulmonary gradient. (C) marginal probability of aortic insufficiency grades; (D) marginal probability of pulmonary insufficiency grades

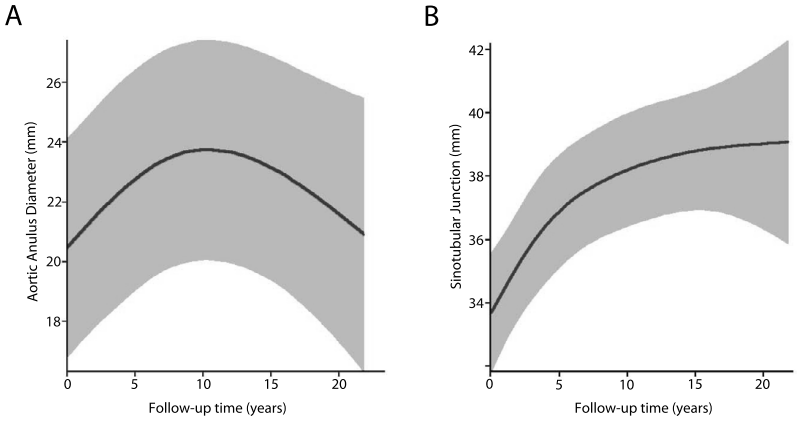

Figure 2C.3: Mixed-effects models of (A) aortic anulus diameter increase over time and (B) sinotubular junction diameter increase over time

Patient survival in the age category 18 to 30 years was 98% (95% CI 84–99) after 10 years of follow-up and 95% (95% CI 80–98) up to 18 years of follow-up. Hypertension (p-value=0.011), previous aortic valve surgery (p-value=0.030), bicuspid aortic valve (p-value=0.007), and pre-operative aortic anulus aneurysm (p-value=0.043) were correlated with impaired survival in this patient group.

Patient survival in the age category $\geq$30 years was 100% after 10 years of follow-up and 76% (95% CI 24.95) up to 18 years of follow-up. The use of inclusion technique (p-value=0.038) and pre-operative aortic anulus aneurysm (p-value=0.043) were associated with impaired survival in this group of patients.

2C.4.4 Reoperation

Fifty-seven patients required a reintervention related to the Ross operation. Of these, 33 patients required isolated pulmonary autograft replacement, 9 patients required simultaneous replacement of both the pulmonary autograft and allograft, 5 patients required isolated pulmonary allograft replacement, 2 patients with neo-aortic root dilatation required reimplantation of the autograft after replacement of the aortic root with Vascutec prostheses, 1 patient underwent autograft repair according to Yacoub's method (Yacoub et al., 1998) and 1 patient underwent reoperation after a recurrent episode of rheumatic fever involving the autograft. Furthermore, two patients underwent a reoperation without valve replacement (one patient underwent enlargement of the pulmonary outflow tract due to supravalvular pulmonary

stenosis and the other patient required reoperation for constrictive pericarditis). In addition, two patients underwent balloon valvuloplasty of the RVOT to relieve supravalvular pulmonary stenosis.

Percutaneous pulmonary allograft replacement with the Melody valve was required in two patients.

Progressive dilatation of the neo-aortic root was the main cause for autograft reoperation (n=40). Causes for pulmonary allograft reintervention were mainly structural failure, calcification, or degeneration of the valve. In our study group, four patients required a second reintervention on the pulmonary allograft during the follow-up.

All reoperations on the autograft were performed through a median sternotomy, with cardiopulmonary bypass and moderate hypothermia. We mostly used central canulation in the ascending aorta and right atrium or caval veins. To anticipate possible perforation of the heart or aorta when reopening the chest, we instituted cardiopulmonary bypass with canulation of the femoral vessels and deep cooling in four patients before performing the sternotomy. Crystalloid cardioplegia and topical cooling were used for myocardial protection. Total circulatory arrest with deep hypothermia was needed in 11 patients, with ascending aorta or arch reconstruction. In patients without aortic root dilatation, the valve leaflets were excised, followed by mechanical valve implantation. The neo-aortic root was in most cases dilated without any signs of root or valve calcification. After opening the autograft root, the autograft valve leaflets were inspected, and most of them were excised and the coronary buttons mobilized. Excess autograft wall tissue was removed, leaving parts of the autograft at the annular level in situ. Standard valved conduit implantation was performed. When appropriate, the valve leaflets were spared, using the aortic valve reimplantation technique.

Freedom from reoperation for autograft failure was 84% (95% CI 77–92) and 51% (95% CI 38–62) after 10 and 18 years, respectively (Figure 2C.1(C)). Freedom from reintervention for allograft failure was 90% (95% CI 83–94) and 81% (95% CI 71–88) after 10 and 18 years, respectively (Figure 2C.1(D)). Freedom from reintervention for autograft or allograft failure was 80% (95% CI 72–86) and 41% (95% CI 28–53) after 10 and 18 years, respectively (Figure 2C.1(E)).

Risk factors that were associated with autograft reoperation in the univariate analyses are shown in Table 2C.3. There was no re-operative mortality.

2C.4.5 Reoperation Rate in Different Age Categories

In young patients up to 18 years of age at the time of the Ross procedure, freedom from reoperation for autograft failure was 84% (95% CI 71–92) and 62% (95% CI 39–79) after 10 and 18 years of follow, respectively. In the univariate analyses, pre-operative AR (p-value=0.041), higher creatinine (p-value=0.031), and higher age (p-value=0.009) were associated with autograft failure in these young patients. However, none of these factors remained significant in the multivariate analyses. Freedom from reintervention for allograft

Table 2C.4: Risk factors associated with changes in echocardiographic measurements during follow-up

Echocardiographic measurement	Risk factors	Univariable analyses coef (±SE)	*p*-value	Multivariable analyses coef (±SE)	*p*-value
Aortic gradient	Female gender	0.39(0.14)	0.007	0.40 (0.14)	0.005
	Older age	0.01(0.01)	0.014	0.01 (0.01)	0.009
AR	Impaired LVF	−0.70(0.24)	0.003	[a]	[a]
Aortic anulus	Female gender	−4.54(0.81)	< 0.001	-3.77 (0.79)	<0.001
	Pre-operative creatinine	0.06(0.02)	0.015	0.04 (0.02)	0.02
	Pre-operative AR	2.24(0.90)	0.01	1.83 (0.83)	0.028
STJ	Female gender	−5.31(1.02)	< 0.001	[a]	[a]
Allograft gradient	Female gender	−0.63(0.29)	0.029	[a]	[a]
Allograft regurgitation	Hypertension	2.21(1.02)	0.030	0.02 (0.01)	0.02
	Older age	0.03(0.01)	0.008	[a]	[a]

AR = aortic regurgitation; LVF = left ventricular function; STJ = sinotubular junction: SE = standard error. [a] No longer significant in the multivariable model

failure was 86% (95% CI 71–94) and 81% (95% CI 64–91) after 10 and 18 years of follow-up, respectively. No potential risk factors could be identified for allograft failure in this specific patient group. Freedom from reintervention for autograft or allograft failure was 77% (95% CI 62–87) and 49% (95% CI 25–68) after 10 and 18 years, respectively.

In young adult patients between 18 and 30 years of age, freedom from reoperation for autograft failure was 80% (95% CI 64–90) and 37% (95% CI 19–56) after 10 and 18 years of follow-up, respectively. Pre-operative aortic sinus aneurysm (p-value=0.025) was the only risk factor found to be associated with autograft failure. Freedom from reintervention for allograft failure was 87% (95% CI 72–94) and 81% (95% CI 64–91) after 10 and 18 years of follow-up, respectively. No risk factors were found for allograft failure. Freedom from reintervention for autograft or allograft failure was 73% (95% CI 56–84) and 32% (95% CI 15–50) after 10 and 18 years, respectively.

In patients of $\geq$30 years, freedom from reoperation for autograft failure was 90% (95% CI 76-96) and 58% (95% CI 19-56) after 10 and 18 years of follow-up, respectively. Freedom from reintervention for allograft failure was 98% (95% CI 84-99) and 76% (95% CI 40-92) after 10 and 18 years of follow-up, respectively. No risk factors were found for autograft or allograft failure. Freedom from reintervention for autograft or allograft failure was 90% (95% CI 76-96) and 45% (95% CI 22-66) after 10 and 18 years, respectively.

2C.4.6 Other Valve-Related Events

Two patients developed endocarditis of the autograft during the follow-up (0.11%/patient-year). In one patient, the endocarditis was complicated by stroke. Furthermore, one patient developed endocarditis of the allograft (0.05%/patient-year) which was treated with antibiotics. One patient developed pulmonary emboli (0.05%/patient-year). Bleeding events, valve thrombosis, or non-structural failure was not observed.

Freedom from any valve-related event was 79% (95% CI 71–85) and 40% (95% CI 27–52) after 10 and 18 years, respectively (Figure (F)).

2C.4.7 Functional Performance of the Autograft and Allograft Over Time

During the study period, 1,023 echocardiograms were reviewed for 161 subjects. Figure 2C.2 shows time-related changes in autograft gradient (Figure 2C.2(A)), allograft gradient (Figure 2C.2(B)), autograft regurgitation (Figure 2C.2(C)) and allograft regurgitation (Figure 2C.2(D)). Figure 2C.3 shows time-related changes in aortic anulus diameter (Figure 2C.3(A)) and sinotubular junction (STJ) (Figure 2C.3(B)).

Risk factors associated with changes in echocardiographic measurements during the follow-up are shown in Table 2C.4. Female gender was found to be consistently associated with better echocardiographic outcomes. Pre-operative aortic regurgitation was found to be

consistently associated with worse echocardiographic outcomes.

2C.5 Discussion

The present study is the first to show that long-term patient survival after the Ross procedure is relatively good in contemporary practice, even at the end of the second post-operative decade. Compared with the original pioneer series by Donald Ross (1967–84), which reported an early mortality of 13% and a 20-year survival of only 61% in hospital survivors, our results illustrate the tremendous innovations that have taken place in cardiac surgery over the past decades. The present study also shows that, with increasing follow-up time, in particular the autograft has a limited durability. In addition, mixed-effects model analyses of echocardiographic measurements do not show major changes in transaortic gradients during the follow-up period. The results of mixed-effects models do, however, show that freedom from autograft regurgitation grades 3–4 was only 66% after 18 years of follow-up. Regarding neo-aortic dimensions, the mixed-effects model shows an initial increase in the STJ diameter in the first five post-operative years, which was then followed by a constant phase. Furthermore, an initial slight increase in aortic anulus diameter was observed in the first 10 post-operative years.

2C.5.1 Survival After the Ross Procedure

Although initially there was concern about the outcome of the Ross procedure, several short and mid-term studies have proven that the procedure can be performed with low operative risk and survival rates comparable with the general population (Klieverik et al., 2007a; Luciani et al., 2005; El-Hamamsy et al., 2010b).

It remains unclear whether this excellent survival is a consequence of autograft attributes (living valve with superior haemodynamics and low valve-related event occurrence rates) (Verbeke and Molenberghs, 2000) or the careful selection of patients for the Ross procedure (Mokhles et al., 2011a).

The present study adds to current knowledge that although long-term mortality rates are relatively low and comparable with that of the general population in the first decade, as reported by several other authors (Klieverik et al., 2007a; Sievers et al., 2010; El-Hamamsy et al., 2010b), the survival rate of Ross patients in our experience shows a decline in the second post-operative decade compared with the general population. Of the four observed deaths in the second post-operative decade, two were valve-related (SUUD). Although the numbers are small, this observation suggests that valve-related mortality hazard may increase in the second postoperative decade after the Ross procedure.

2C.5.2 Autograft Performance

The longevity of the autograft within our patient population is a point of concern. At the end of the second decade, over half of the patients were reoperated for autograft failure.

The main cause for reoperation after the Ross operation is dilatation of the neo-aortic root. Owing to this dilatation, coaptation of the cusps is lost and aortic regurgitation occurs. The exact cause of autograft root dilatation is unknown. It is speculated that several factors may contribute to dilatation of the aortic root. Younger patient age (Luciani et al., 2005), congenital aortic valve disease (Settepani et al., 2005), rheumatic valve disease (Sampath Kumar et al., 2006), and pre-operative aortic regurgitation (Laudito et al., 2001) and dilatation (Luciani et al., 2005) are the most commonly reported patient-related determinants of durability of the autograft valve. It should also be noted that the outcome of the Ross procedure varies considerably between different centres (El-Hamamsy et al., 2010b) and surgical techniques employed and by individual variation of the application of the root replacement technique (Takkenberg et al., 2009). Furthermore, due to significantly increased mechanical stress, post-operative hypertension may potentially have a negative effect on autograft durability (Carr-White et al., 2000; Yacoub et al., 2006).

The presence of pre-operative aortic regurgitation was an independent risk factor of autograft failure during the follow-up. Furthermore, the longitudinal analyses of echocardiographic data indicated that the presence of pre-operative aortic regurgitation was significantly associated with the increased aortic anulus diameter during the follow-up. Pre-operative aortic regurgitation was not associated with the STJ diameter during the follow-up at all. This suggests that pre-operative aortic regurgitation might specially be a risk factor for the dilatation of the aortic anulus after the Ross procedure.

The association between pre-operative aortic regurgitation and autograft failure is in agreement with other recent publications on this subject (David et al., 2010b; Laudito et al., 2001; Ryan et al., 2011; Elkins et al., 2001). Two studies hypothesize that annular dilatation associated with aortic regurgitation may be a factor, and one suggests a role for altered geometry and tissue characteristics of the subvalvular LV outflow tract resulting from chronic aortic regurgitation (Laudito et al., 2001; Elkins et al., 2001).

2C.5.3 Allograft Performance

In contrast to the performance of autografts, allografts performed adequately within our patient population, with freedom from reoperation for allograft failure of 81% after 18 years of follow-up. Although there are no studies at the moment with such a long term follow-up as the present study, the freedom from allograft failure that we have observed after 10 years of follow-up in our patient population was comparable with that of the other series (Kouchoukos et al., 2004; Elkins, 1999). The main reason for allograft reoperation in the present study was degeneration with calcification of the allograft. Pulmonary allograft stenosis is indeed another important issue that has to be taken into account when considering the Ross procedure. The

stenosis appears to represent an early post-operative inflammatory reaction to the pulmonary allograft that leads to extrinsic compression and/or shrinkage and is characterized by intimal hyperplasia at the distal anastomosis and an inflammatory mediated external compression by fibrous tissue (Carr-White et al., 2001).

2C.5.4 Clinical Implications

The observed high reoperation rate after the Ross procedure has tempered our initial enthusiasm for the procedure: in our early experience, we applied the Ross procedure generously in children and young adults, performing up to 18 Ross procedures per year, whereas in more recent years this number has gone down to 1 or 2 per year, mainly in young children.

In most of our patients (n=159, 99%), no reinforcement procedures were taken. It has been shown that in patients undergoing the Ross procedure, autograft reinforcement procedures are associated with lower aortic regurgitation development rates and reduced reoperation rates for autograft failure (Charitos et al., 2009). This is of particular importance since autograft reoperation rate in the present study was mainly driven by root dilatation. Furthermore, it should be noted that surgical techniques employed can considerably influence the outcome after the Ross procedure. A recent publication from the German–Dutch Ross registry showed that freedom from autograft or allograft reoperation was 92% at 10 years and 87% at 15 years in young and middle-aged patients operated with the subcoronary technique (Charitos et al., 2012). These reported results are better than those observed in our study population where mainly (96%) the root replacement technique was used. The widely varying durability results obtained with different surgical techniques applied in the Ross procedure illustrates the technical complexity of the procedure and the requirement of a particular surgical expertise with this procedure.

The Ross procedure represents only a fraction of all aortic valve replacement in contemporary practice (Treasure et al., 2011). Obviously, surgical expertise required to perform a Ross procedure is a limiting factor, although one may hypothesize that by avoiding this technically challenging procedure with potentially increased early risks, we are withholding young adult patients from a potentially better solution in the long run (Treasure et al., 2011). Several other options exist in replacement of the diseased aortic valve in young adult patients: mechanical prostheses, biological prostheses, or homografts.

Although mechanical valves provide excellent durability and low re-operative hazard (Vongpatanasin et al., 1996; Hammermeister et al., 2000), the choice for the mechanical valve implies lifelong anticoagulation and is associated with an increased risk for thrombo-embolic and bleeding events (Vink et al., 2003; Takkenberg et al., 2004). The use of anticoagulation may also complicate pregnancy because of the foetal and maternal complications of taking warfarin (Wong et al., 1993; Chan et al., 2000), and may require lifestyle adjustments in this relatively young and active patient group. Also, the haemodynamic performance of

mechanical valves is less favourable compared with autograft valves (Porter et al., 1999). Furthermore, prosthetic valve endocarditis occurs in up to 6% of mechanical valve recipients and is associated with considerable mortality (Vongpatanasin et al., 1996). However, it still remains unclear whether the excellent survival observed in Ross patients is a consequence of autograft attributes (living valve with superior haemodynamics and low valve-related event occurrence) or the careful selection of patients for the Ross procedure. A recent publication from our group showed that in comparable patients, there is no late survival difference in the first post-operative decade between the Ross procedure and mechanical aortic valve implantation with optimal anticoagulation self-management (Mokhles et al., 2011a).

Bioprostheses are frequently used as an aortic valve substitute and have a low thrombogenicity and absent need for lifelong anti-thrombotic therapy. Recently published studies reporting the results of Hancock II bioprosthesis have shown a freedom from reoperation of only 30–50% after 20 years of follow-up (David et al., 2010a; Valfre et al., 2010).

Homograft valves have, similar to the autograft procedure, the advantage of a low risk for thrombo-embolism and absent need of lifelong anticoagulation. However, the results of a recently published prospective randomized trial between the Ross procedure and the aortic homograft, both implanted as full roots, showed that the performance of allografts was inferior to that of autografts (El-Hamamsy et al., 2010b). Furthermore, the performance of the homograft valves have also been shown to be inferior compared with xenografts with more modern tissue processing including anticalcification processes (El-Hamamsy et al., 2010a).

In light of the limitations of contemporary prosthetic valve options, the optimal prosthesis choice for young adults remains controversial. Therefore, an individualized approach is needed in the selection of the optimal prosthetic valve. This approach should combine the evidence on outcome with different therapeutic strategies with the preferences of the informed patient since the inherent limitations of each prosthetic valve can be valued differently by individual patients.

2C.5.5 Strengths and Limitations

The present study is the longest and most complete prospective cohort study allowing for new insights into patient outcome and autograft and pulmonary allograft function well into the second post-operative decade. In addition of reporting hard clinical endpoints, the number of available echocardiograms and the powerful longitudinal data analysis techniques enabled us to be the first to provide insight into autograft and allograft valve function over time until the end of second decade. The long-term evidence of patient outcome and valve performance is helpful in the selection of most optimal prosthetic aortic valve since it provides an unprecedented time horizon regarding the Ross procedure.

The present study has several limitations. The survival of patients is reported at 18 years of follow-up and future studies are required to confirm the results of the present study. An

additional limitation is the absence of a control group in the present study. Furthermore, the results of present study only apply to the unsupported root replacement technique, which is both a strength and a limitation of the data. Finally, the generalizability of our study results requires further investigation.

2C.6 Conclusions

The present study shows that, in patients who undergo autograft procedure without any reinforcement techniques, the autograft procedure indeed meets the prospect with respect to relatively good long-term survival. However, the observation that over half of the autografts failed prior to the end of the second decade is a point of concern. The reoperation rate and echocardiographic function over time underline the importance of careful monitoring, especially in the second decade after the initial autograft operation and particularly in patients with pre-operative aortic regurgitation.

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CHAPTER 3

Joint Modelling of Two Longitudinal Outcomes and Competing Risk Data

This Chapter is based on: Andrinopoulou, E.R., Rizopoulos, D., Takkenberg, J.J. and Lesaffre, E. (2014). Joint modeling of two longitudinal outcomes and competing risk data. *Statistics in Medicine*, 33:3167 – 3178.

Abstract

Aortic gradient and aortic regurgitation are echocardiographic markers of aortic valve function. Both are biomarkers repeatedly measured in patients with valve abnormalities, and thus, it is expected that they are biologically interrelated. Loss to follow-up could be caused by multiple reasons, including valve progression related, such as an intervention or even the death of the patient. In that case, it would be of interest and appropriate to analyze these outcomes jointly. Joint models have recently received a lot of attention because they cover a wide range of clinical applications and have promising results. We propose a joint model consisting of two longitudinal outcomes, one continuous (aortic gradient) and one ordinal (aortic regurgitation), and two time-to-events (death and reoperation). Moreover, we allow for more flexibility for the average evolution and the subject-specific profiles of the continuous repeated outcome by using B-splines. A disadvantage, however, is that when adopting a nonlinear structure for the model, we may have difficulties when interpreting the results. To overcome this problem, we propose a graphical approach. In this Chapter, we apply the proposed joint models under the Bayesian framework, using a dataset including serial echocardiographic measurements of aortic gradient and aortic regurgitation and measurements of the occurrence of death and reoperation in patients who received a human tissue valve in the aortic position. The interpretation of the results will be discussed.

3.1 Introduction

In the field of Cardio-Thoracic surgery, valve function is monitored periodically over time after heart valve surgery. Aortic gradient and aortic regurgitation are both echocardiographic markers that measure valve abnormalities. Moreover, because the life expectancy of the valve is limited, patients may often require an intervention or may die during the follow-up period. The motivation of this research comes from a study, conducted in the Erasmus Medical Centre, which includes all patients who received a human tissue valve allograft in the aortic position in the Department of Cardio-Thoracic Surgery in a period of 21 years. These patients were followed prospectively over time by annual telephone interviews and biennial standardized echocardiographic assessment of the valve function, Bekkers et al. (2011). Particularly, echocardiographic examinations were scheduled at 6 months and 1 year postoperatively and biennially thereafter. From 1987 until 2008, 283 patients older that 16 years who survived aortic valve or root replacement with an allograft valve were followed until 08-Jul-2010. During follow-up, 57 (20%) patients died and 74 (26%) patients required a reoperation on the allograft. Figure 3.1 illustrates the cumulative incidence functions for the two events. We observed that patients showed a higher hazard of death the first nine years and a higher hazard of reoperation afterwards. A total of 1,252 echocardiographic measurements of aortic gradient and aortic regurgitation were performed. Each subject was monitored at different time points and had a different number of visits (median number = 4, range = 1 to 11) and

median years of follow-up equal to 6.7 (range from 0 to 19.5 years). Aortic gradient (mmHg) is a continuous variable, while aortic regurgitation has an ordinal scale (grade: 0 (none), 0.5 (trace), 1+, 2+, 3+, and 4+). High values of aortic gradient and aortic regurgitation indicate a worsening of the patient's condition with an increased risk of death or reoperation. Aortic gradient and aortic regurgitation measure the valve function, and hence it is expected that they are biologically interrelated. Furthermore, both death and reoperation could result in missing data not at random (Little and Rubin, 2002) because they are highly related to the disease condition of the patient. In order to analyze this type of data we rely on the joint modelling framework. Specifically, in this work we build on previous approaches (Li et al., 2010) and develop a joint model for two longitudinal outcomes, one continuous and one ordinal, and competing risk failure time data.

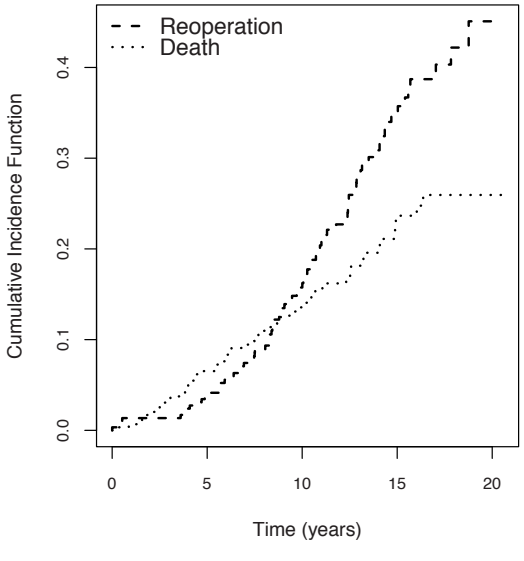

Figure 3.1: Cumulative Incidence function for death and reoperation

The joint modelling of longitudinal and time-to-event data is an active area of statistics research that has received a lot of attention in the recent years. The reason for increased interest is that joint models can be used when focusing either on the longitudinal outcome and we wish to correct for non-random dropout or on the survival outcome when we wish to account for the effect of an endogenous time-dependent covariate. There are numerous papers in the literature that have proposed several extensions of the standard joint model introduced

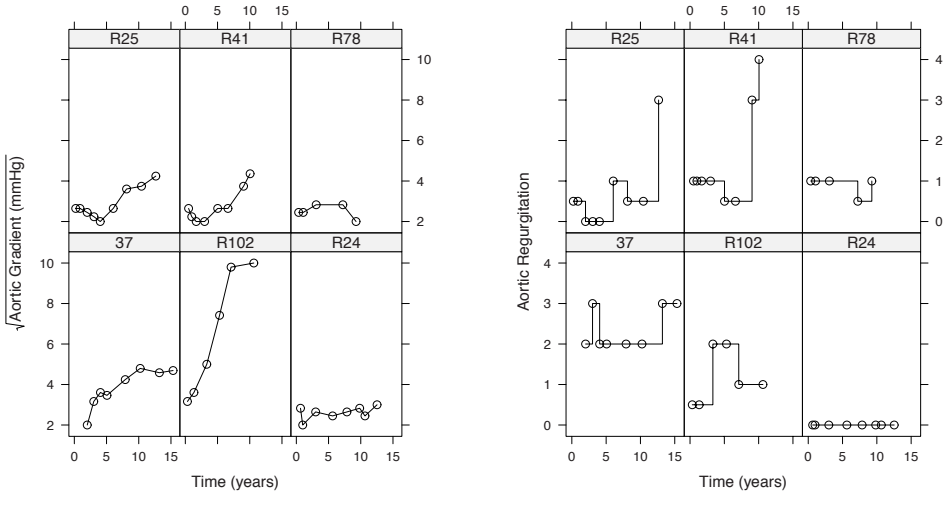

Figure 3.2: Subject-specific profiles for six patients for aortic gradient and aortic regurgitation

by Faucett and Thomas (1996) and Wulfsohn and Tsiatis (1997). These extensions include, among others, the consideration of a flexible specification of the subject-specific profiles (Brown and Ibrahim, 2003), nonparametric modelling of the random effects distribution (Song et al., 2002), the consideration of multiple longitudinal outcomes (Rizopoulos and Ghosh, 2011; Brown et al., 2005), competing risks problems (Huang et al., 2011; Elashoff et al., 2008), and the calculation of dynamic predictions and accuracy measures (Rizopoulos, 2011; Proust-Lima and Taylor, 2009). Nice overviews of some early work in this field are given by Tsiatis and Davidian (2004) and Yu et al. (2004). Furthermore, a comprehensive introduction and several extensions of the joint modelling framework, including applications in R, are presented in Rizopoulos (2012).

Many patients show nonlinear longitudinal trajectories, especially for aortic gradient. As an illustration, Figure 3.2 depicts the profiles of patients R25, R41, R78, 37, R102 and R24. These plots indicate that wrongly assuming linearity may compromise the results of the analysis. Therefore, we propose a flexible joint model which aims to capture the nonlinear average evolution and subject-specific profiles of the aortic gradient. Moreover, we propose a time-independent parametrization for the connection between the longitudinal and survival part, in which the event times depend on the subject-specific level of the longitudinal profile. In fact we are more interested in assessing the degree of association between the trend of the repeated outcomes and time-to-events, than accurately determining the estimate of the underlying process of the heart disease.

The rest of the Chapter is organized as follows. Section 3.2 describes the joint submodels and presents the Bayesian estimation procedure. Section 3.3 illustrates the performance of the joint model on the cardio data, and Section 3.4 presents the results of a limited simulation study. Finally, Section 3.5 contains a discussion.

3.2 Submodels and Definition

3.2.1 Longitudinal Outcomes

Assuming n subjects under study, we let $y_{1i}(t)$ and $y_{2i}(t)$ denote the follow-up measurements for aortic gradient and aortic regurgitation, respectively, for patient i ($i = 1,\ldots,n$) and at time t. These measurements are obtained at specific time points t_{ij} that can be different for each subject, thus $y_{1ij} = \{y_{1i}(t_{ij})\}$ and $y_{2ij} = \{y_{2i}(t_{ij})\}$ where $j = 1,\ldots,n_i$ refers to the repeated measurement of the i-th patient. To describe the subject-specific evolution over time of the longitudinal outcomes, we rely on mixed-effects models. In particular, for the continuous aortic gradient, we postulate

$$y_{1i}(t) = x_{1i}^{\top}(t)\beta_1 + z_{1i}^{\top}(t)b_{1i} + \varepsilon_i(t), \tag{3.2.1}$$

where β_1 denotes the vector with the regression coefficients of the design matrix for the fixed effects $x_{1i}^{\top}(t) = [\{x_{1i}^{time}(t)\}^{\top}, \{x_{1i}^{base}(t)\}^{\top}, \{x_{1i}^{int}(t)\}^{\top}]$ that consist of time, baseline covariates and their interaction respectively; and $z_{1i}^{\top}(t) = \{z_{1i}^{time}(t)\}^{\top}$ denotes row vectors of the design matrix for the random effects b_{1i}. The random effects are assumed to follow a normal distribution with mean zero and covariance matrix Σ_{b_1}, independent of the error terms $\varepsilon_i \sim N(0, \sigma^2 I_{n_i})$. Typically, in the specification of the linear mixed model a simple structure is assumed for the time effect, such as random intercepts and linear random slopes. However, such a simple structure may not be adequate in our study. In Figure 3.2, it is shown that the assumption of a linear profile for the patients is too strong and may not capture the real aortic gradient evolution. Thus, to relax this assumption in our analysis, a mixed-effect model with a smooth function for the time effect on aortic gradient using for example B-spline basis functions may be more appropriate. Hence, in equation (3.2.1), $x_{1i}^{\top}(t) = [\{x_{1i}^{bsp}(t)\}^{\top}, \{x_{1i}^{base}(t)\}^{\top}, \{x_{1i}^{int}(t)\}^{\top}]$ and $z_{1i}^{\top}(t) = \{z_{1i}^{bsp}(t)\}^{\top}$, where bsp represents the B-spline function.

A standard model for aortic regurgitation is the mixed-effects proportional odds model, which is based on cumulative probabilities. However, in our setting, a patient with a severe aortic regurgitation has passed through the early stages of the disease conditions before, making it more important to investigate the probability of the disease worsening by one level when the patient has passed through the lower levels. This can be captured by the continuation ratio (CR) model which is an alternative modelling framework for ordinal data and is based on conditional probabilities (Harrell, 2001). Specifically, under the CR model, the probability of being in category s conditional on being at most in category s is modeled in contrast to the

cumulative probability of category s as assumed in a proportional odds model. The CR model is more likely to fit ordinal responses in which subjects move incrementally from one stage to another, which we believe is the case here. Another advantage of the CR model is that it can be easily fitted using a mixed-effects binary logistic likelihood function, after certain rows of the design matrix of the fixed and random effects are suitably replicated, and the response is transformed to a Bernoulli random variable. However, a disadvantage is that more complex calculations are required to obtain marginal probabilities. A detailed description of this family of models is presented in Section 3.6.1.

Let $\pi_{is}(t)$ be the probability of being in category s conditional on being at most in category s, the design matrices of the fixed and random effects, and the random effects. To account for the correlations in the repeated aortic regurgitation measurements we postulate a CR mixed-effects model to investigate the evolution over time, that is

$$\pi_{is}(t) = \mathrm{P}(y_{2i}(t) = s \mid y_{2i}(t) \leq s, .) = \frac{\exp\left(x_{2i}^{\top}(t)\beta_2 + z_{2i}^{\top}(t)b_{2i}\right)}{1+\exp\left(x_{2i}^{\top}(t)\beta_2 + z_{2i}^{\top}(t)b_{2i}\right)}, \tag{3.2.2}$$

where $x_{2i}^{\top}(t)$ denotes row vectors of the design matrix for the fixed effects regression coefficients β_2, representing the overall intercept, the dummy variables for the categories, time, baseline covariates, and their interaction. Moreover, $z_{2i}^{\top}(t)$ denotes row vectors of the design matrix for the random effects $b_{2i} \sim N(0, \Sigma_{b2})$. The '.' symbol indicates that the model is conditional on the covariates and the random effects. For the same patient, the term $\exp(\beta_2)$ can be interpreted as the effect of one unit increase of the q-th covariate on the odds of category s, holding all other covariates constant.

Furthermore, to build the correlation between the aortic gradient and aortic regurgitation we assume a multivariate normal distribution for the random effects b_i, that is

$$b_i = \begin{pmatrix} b_{1i} \\ b_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, D = \begin{pmatrix} \Sigma_{b1} & \Sigma_{b12} \\ \Sigma_{b12} & \Sigma_{b2} \end{pmatrix} \right),$$

where Σ_{b12} block contains the covariances between the two sets of random effects.

3.2.2 Competing Risk Failure Times

For the survival part, let T_i denote the observed failure time for patient i, taken as $T_i = \min(T_{1i}^*, T_{2i}^*, C_i)$ with T_{ki}^* indicating the true failure time that the i-th individual experiences for each event $k = 1, 2$ and C_i the censored time. Moreover, let $\delta_i = 0, 1, 2$ be the event indicator $0 = censored$, $1 = reoperation$ and $2 = death$. To model the risks of each of the competing events, we postulate the proportional hazard models:

$$h_{ik}(t, \theta_s) \quad = \quad h_{0k}(t) \exp\{w_i^{\top}\gamma_k + (\tilde{\beta}_1 + b_{1i})^{\top}\alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^{\top}\alpha_{2k}\}, \quad t > 0,$$

where θ_s is the parameter vector for the survival outcomes, $w_i^{\top}$ denotes row vectors of the design matrix of the baseline covariates, γ_k is the corresponding regression coefficients vector,

and α_{1k} and α_{2k} are the coefficients that link the longitudinal and survival parts. Particularly, they denote the strength of the association between aortic gradient and aortic regurgitation with death and reoperation, respectively. We denote $\tilde{\beta}_1$ and $\tilde{\beta}_2$ the coefficients for aortic gradient and aortic regurgitation from the fixed effects that correspond to the coefficients from the random effects. Moreover, b_{1i} and b_{2i} denote the random coefficients from the models for aortic gradient (3.2.1) and for aortic regurgitation (3.2.2). A piecewise constant baseline hazard function is assumed $h_{0k}(t) = \sum_{q=1}^{m} \xi_{qk} I(t_{q-1} < t \leq t_q)$, where we consider (m-1) intervals with t_q $\{q = 1, \ldots, m\}$ being the knots, and $I(.)$ the indicator function.

To better understand the connection between the survival and longitudinal parts in our model, we explain in the succeeding texts the meaning of the α parameters with a simple example where we assume a linear mixed-effects model for the aortic gradient with linear time effect and a random intercept, that is

$$y_{1i}(t) \quad = \quad \beta_{10} + t\beta_{11} + b_{10i} + \varepsilon_i(t),$$

and a CR mixed-effects model with linear time and a random intercept for aortic regurgitation, that is

$$\pi_{is}(t) = \mathrm{P}(y_{2i}(t) = s \mid y_{2i}(t) \leq s, .) = \frac{\exp\left(\sum_{s=0}^{S} \beta_{2s} + t\beta_{2(S+1)} + b_{20i}\right)}{1 + \exp\left(\sum_{s=0}^{S} \beta_{2s} + t\beta_{2(S+1)} + b_{20i}\right)},$$

where $\pi_{is}(t)$ denotes the probability of being in category s conditional on being at most in category s, time and the random intercept. Moreover, β_{2s}, $s = 0, \ldots, S$, denotes the overall intercept and the dummy variables for the categories.

The model for the two competing events takes the form

$$h_{ik}(t, \theta_s) \quad = \quad h_{0k}(t) \exp\{w_i^{\top} \gamma_k + (\beta_{10} + b_{10i})^{\top} \alpha_{1k,0} + (\beta_{20} + b_{20i})^{\top} \alpha_{2k,0}\}.$$

Hence, for one unit increase in the intercept of aortic gradient for patient i the hazard ratio of the k-th event is $\exp(\alpha_{1k,0})$. Similarly, $\exp(\alpha_{2k,0})$ is the hazard ratio for the k-th event when the intercept of aortic regurgitation for the i-th patient in the first category is increased by one unit.

However, when positing nonlinear profiles for any of the two outcomes, the interpretation of the α parameters becomes more challenging. The problem is that now, the nonlinear time effect is not described by a single coefficient but rather multiple coefficients, which unfortunately do not have a direct interpretation. In Figure 3.3, we present an example of a B-spline with 4 degrees of freedom and 8 knots corresponding to 4 basis functions. The gray-colored line represents the aortic gradient profile of a hypothetical subject, while the black lines represent the B-spline basis functions. In each of the two panels of this plot, we assume a higher weight for a different basis function to investigate the effect of time on the subject-specific aortic gradient. It can be seen that different adjacent subintervals of time are affected depending on which basis function has the higher weight (i.e. coefficient). The model

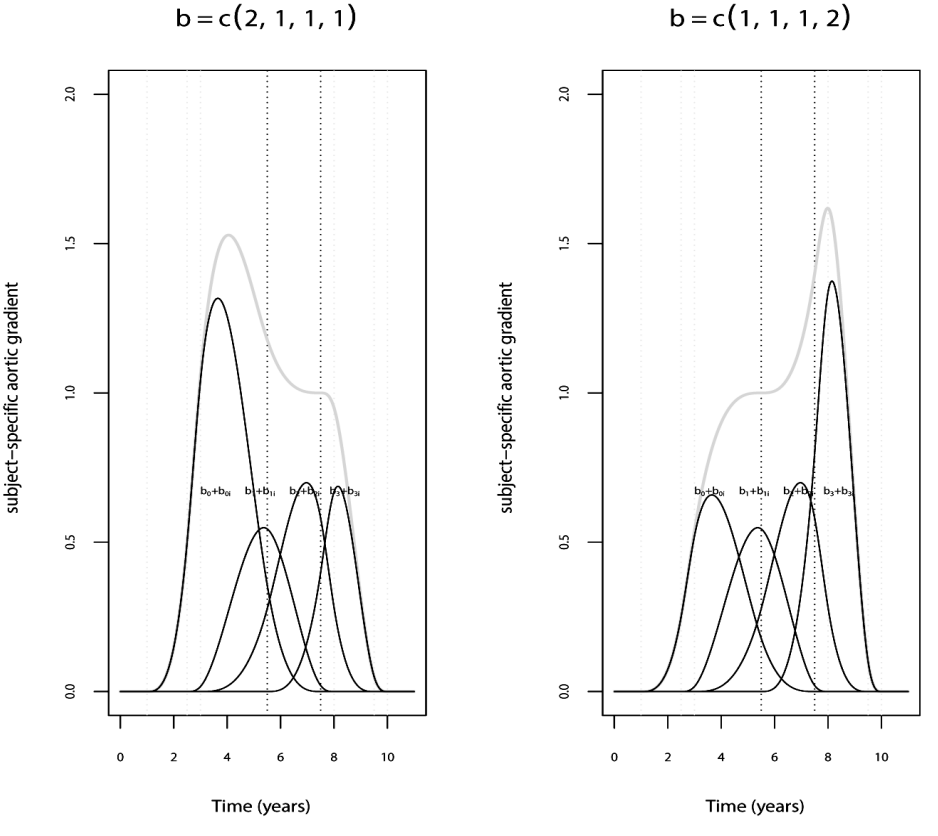

Figure 3.3: B-splines representation with 4 degrees of freedom and 8 knots

for the two competing events assuming nonlinear aortic gradient profiles will therefore take the form

$$\begin{aligned} h_{ik}(t,\theta_s) &= h_{0k}(t)\exp\{w_i^\top \gamma_k + (\beta_{10}+b_{10i})^\top \alpha_{1k,0} + \\ &\quad \sum_{p=1}^{P}(\beta_{1p}+b_{1pi})^\top \alpha_{1k,p} + (\beta_{20}+b_{20i})^\top \alpha_{2k,0}\}, \end{aligned}$$

where P indicates the number of basis functions. The interpretation of the corresponding coefficients of the relative risk submodels now becomes that for every unit increase of the subject-specific aortic gradient for the i-th patient $(\beta_{1p}+b_{1pi})$ at a specific time interval, the hazard ratio of the k-th event is $\exp(\alpha_{1k,p})$, where p indicates the basis function.

For the estimation of our joint model's parameters, we adopt a Bayesian formulation, and derive posterior inferences using a Markov chain Monte Carlo (MCMC) algorithm assuming standard non-informative prior distributions for the parameters. More details can be found in Section 3.6. Specifically, Section 3.6.2 provides the likelihood and the MCMC implementation, Section 3.6.3 presents the full conditionals for all the parameters and Section 3.6.4 consist of the code for WinBUGS that has been used. The MCMC algorithm has also been implemented using R and it is available upon request.

3.3 Analysis of the Cardio Dataset

In this Section we present the analysis of the cardio data introduced in Section 3.1. We are mainly interested in the association between aortic gradient and aortic regurgitation with time-to-death and time-to-reoperation. As mentioned before, the longitudinal trajectories are nonlinear, making it interesting to investigate both a linear and a nonlinear structure for the mixed-effects submodel of aortic gradient. Particularly for the nonlinear submodel, we assumed a simple cubic B-spline for time with two internal knots (λ) at 2.1 and 5.5 year (corresponding to 33.3% and 66.7% of the observed follow-up times) in both fixed and random part. For the model of aortic regurgitation, we assumed a simple model with linear time and a random intercept, because the separate CR model did not converge. Moreover, we corrected for age and gender in both submodels of aortic gradient and aortic regurgitation. Specifically, the mixed-effects models with the linear and the nonlinear time are

$$y_{1i}(t) = \beta_{10} + Age_i\beta_{11} + Gender_i\beta_{12} + t\beta_{13} + b_{10i} + tb_{11i} + \varepsilon_i(t),$$

and

$$y_{1i}(t) = \beta_{10} + Age_i\beta_{11} + Gender_i\beta_{12} + \sum_{p=1}^{P} B(t,\lambda)\beta_{1(p+2)} + b_{10i} + \sum_{p=1}^{P} B(t,\lambda)b_{1pi} + \varepsilon_i(t),$$

where P is the number of the basis functions and $B(t,\lambda)$ denotes a B-spline basis matrix for a simple cubic spline of time with λ being the knots. The CR mixed-effects model takes the form

$$\begin{aligned}\pi_i^*(t) &= \mathrm{P}(y_{2i}^*(t) = 1 \mid y_{2i}^*(t) \leq 1, .) = \\ &\frac{\exp\left(\sum_{s=0}^{4}\beta_{2s} + Age_i\beta_{25} + Gender_i\beta_{26} + t\beta_{27} + b_{20i}\right)}{1 + \exp\left(\sum_{s=0}^{4}\beta_{2s} + Age_i\beta_{25} + Gender_i\beta_{26} + t\beta_{27} + b_{20i}\right)},\end{aligned}$$

where β_{2s}, $s = 0,\ldots,4$ denote an overall intercept and the dummy variables for the categories of the ordinal outcome and $\pi_i^*(t)$ is the probability of the transformed aortic regurgitation y_{2i}^* being 1 at time t conditional on being at most 1. Moreover, it is conditional on age, gender, time, and the random intercept which are denoted in the model as '.'.

Table 3.1: Posterior means, standard errors and the 95% equal tail credible intervals for the joint model fitted for the cardio data when assuming linear time for aortic gradient

	Mean	SE	2.5%	97.5%
Longitudinal process (aortic gradient)				
Intercept	2.89	0.07	2.76	3.02
Time	0.20	0.02	0.17	0.24
Age	−0.20	0.06	−0.32	−0.09
Gender (female)	0.17	0.12	−0.08	0.41
σ	0.62	0.02	0.59	0.66
Longitudinal process (aortic regurgitation)				
Intercept	2.34	0.25	1.85	2.85
cohortY<=1	−1.47	0.18	−1.83	−1.12
cohortY<=2	−4.40	0.23	−4.86	−3.94
cohortY<=3	−7.58	0.33	−8.22	−6.95
cohortY<=4	−10.84	0.53	−11.92	−9.84
Time	0.12	0.02	0.09	0.15
Age	−0.28	0.16	−0.58	0.03
Gender (female)	0.71	0.33	0.05	1.35
Survival process (death)				
Age	1.11	0.20	0.74	1.51
Gender (female)	−0.26	0.32	−0.91	0.35
α_{b11}	−0.59	0.27	−1.16	−0.09
α_{b12}	2.66	1.24	0.22	5.09
α_{b2}	0.07	0.07	−0.07	0.22
Survival process (reoperation)				
Age	−0.41	0.15	−0.72	−0.12
Gender (female)	−0.41	0.29	−0.98	0.15
α_{b11}	0.03	0.19	−0.37	0.39
α_{b12}	4.64	0.76	3.29	6.26
α_{b2}	0.03	0.06	−0.09	0.14
DIC				−4,412.34

SE = standard error; DIC = deviance information criterion

For the survival models we used a proportional hazards model with a piecewise constant baseline hazard function with $Q = 5$ intervals at time points that correspond to the 20%, 40%, 60% and 80% quantiles of the uncensored event times. Furthermore, age and gender at baseline were included as confounder. Specifically, the joint models that we fitted take the form

$$\begin{aligned} h_{ik}(t,\theta_s) &= h_{0k}(t)\exp\{Age_i\gamma_{1k} + Gender_i\gamma_{2k} + (\beta_{10}+b_{10i})\alpha_{1k,0} + \\ &\quad (\beta_{11}+b_{11i})\alpha_{1k,1} + (\beta_{20}+b_{20i})\alpha_{2k,0}\}, \end{aligned}$$

Table 3.2: Posterior means, standard errors and the 95% equal tail credible intervals for the joint model fitted for the cardio data when assuming nonlinear time for aortic gradient

	Mean	SE	2.5%	97.5%
Longitudinal process (aortic gradient)				
Intercept	3.14	0.14	2.86	3.43
bs(Time, 5)1	−0.25	0.21	−0.67	0.17
bs(Time, 5)2	0.41	0.15	0.12	0.71
bs(Time, 5)3	1.12	0.30	0.54	1.73
bs(Time, 5)4	3.13	0.47	2.24	4.08
bs(Time, 5)5	2.71	0.74	1.32	4.21
Age	−0.21	0.06	−0.32	−0.10
Gender (female)	0.16	0.12	−0.06	0.40
σ	0.58	0.02	0.55	0.62
Longitudinal process (aortic regurgitation)				
Intercept	2.33	0.24	1.86	2.81
cohortY<=1	−1.46	0.18	−1.82	−1.11
cohortY<=2	−4.37	0.23	−4.84	−3.92
cohortY<=3	−7.54	0.32	−8.19	−6.92
cohortY<=4	−10.79	0.53	−11.89	−9.79
Time	0.12	0.02	0.09	0.15
Age	−0.27	0.16	−0.58	0.03
Gender (female)	0.71	0.32	0.08	1.34
Survival process (death)				
Age	1.26	0.24	0.82	1.78
Gender (female)	−0.38	0.42	−1.24	0.42
α_{b11}	−1.05	0.94	−2.90	0.87
α_{b12a}	0.004	1.46	−2.90	2.84
α_{b12b}	0.13	0.98	−1.91	2.04
α_{b12c}	−0.53	1.38	−2.95	2.48
α_{b12d}	0.49	1.18	−1.86	2.74
α_{b12e}	0.33	1.34	−2.32	2.84
α_{b2}	0.18	0.39	−0.57	1.03
Survival process (reoperation)				
Age	−0.50	0.19	−0.88	−0.13
Gender (female)	−0.51	0.37	−1.26	0.20
α_{b11}	−0.38	0.86	−2.12	1.34
α_{b12a}	−0.14	1.32	−2.76	2.49
α_{b12b}	0.53	0.91	−1.32	2.34
α_{b12c}	−0.16	1.32	−2.47	2.56
α_{b12d}	0.53	1.19	−1.88	2.70
α_{b12e}	0.17	1.29	−2.53	2.51
α_{b2}	0.08	0.36	−0.62	0.84
DIC				−5,024.46

bs = Bsplines; SE = standard error; DIC = deviance information criterion

and

$$h_{ik}(t,\theta_s) = h_{0k}(t)\exp\{Age_i\gamma_{1k} + Gender_i\gamma_{2k} + (\beta_{10}+b_{10i})\alpha_{1k,0} + \sum_{p=1}^{P}(\beta_{1p}+b_{1pi})\alpha_{1k,p} + (\beta_{20}+b_{20i})\alpha_{2k,0}\},$$

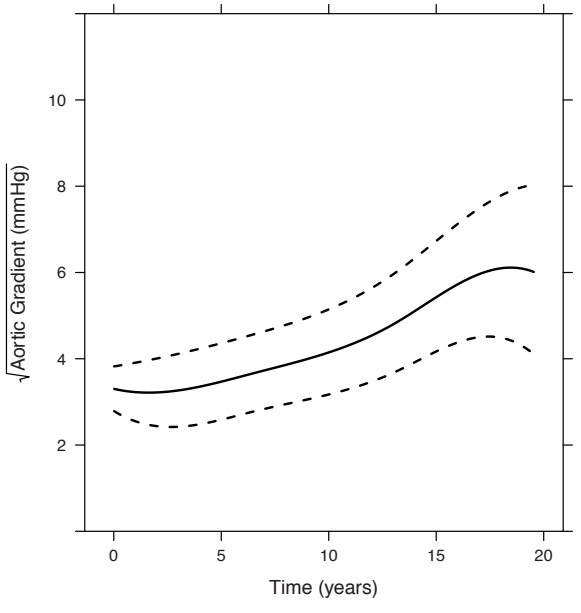

Figure 3.4: Effect plot for the squared root of aortic gradient for a male patient with mean age

for the linear and nonlinear aortic gradient evolution, respectively. We used non-informative prior distributions. Particularly, we have taken $Normal(\mu = 0, \sigma^2 = 100)$ for the parameters β_1, β_2, b_{1i}, b_{2i}, α_{1k}, α_{2k}, γ_k and ξ_{qk}, $Gamma(\alpha = 0.001, \beta = 0.001)$ for $1/\sigma^2$, and $Wishart(A_1 = diag(1), \rho = 2)$ for D^{-1}. We run the MCMC with a single chain for 550,000 iterations, and we discarded 50,000 iterations as burn-in. Convergence was monitored by trace plots and the Geweke diagnostic test. Due to the large number of parameters to estimate, convergence of the Markov chains was slow, in particular, for the parameters of the linear mixed-effects models and the parameters that connect the longitudinal and time-to-reoperation outcomes.

The results of the joint model are presented in Tables 3.1 and 3.2, for the linear and the nonlinear terms of time for aortic gradient, respectively. Since the deviance information criteria (DIC) of the linear model is $-4{,}412.34$ and of the nonlinear is $-5{,}024.46$, the nonlinear profile of the aortic gradient appears to provide better fit to the data.

Due to the fact that the coefficients of the B-splines in the nonlinear mixed model do not have a clear physical interpretation, we used plots to illustrate the shapes of the average evolution of aortic gradient over time and therefore the association between the survival and the longitudinal parts. An increased aortic gradient over time can be seen in Figure 3.4, which

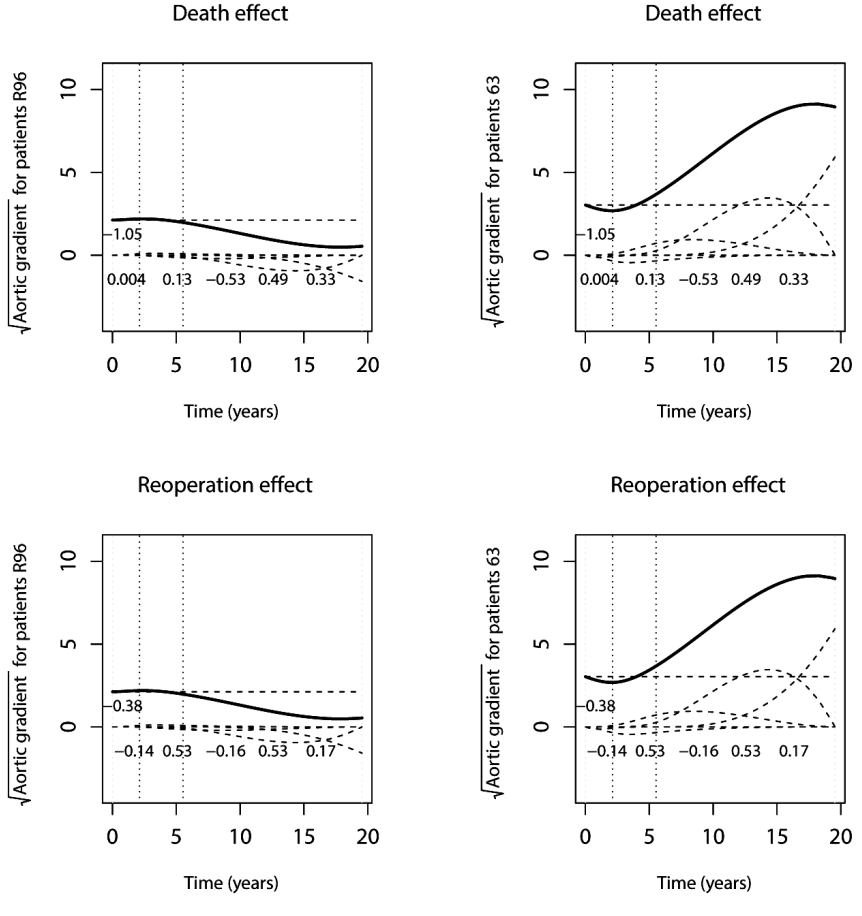

Figure 3.5: Effect plots for the subject-specific square root of aortic gradient for two patients (solid lines). The dashed lines represent B-splines basis functions of the subject-specific square root of aortic gradient. The values denote their effect on time-to-death and time-to-reoperation

presents the nonlinear aortic gradient evolution, until the 17th year. After that time point there are few observations. Furthermore, we observe a significant effect of age on aortic gradient and of time and gender on aortic regurgitation. For the results for the survival submodels, we observe that young patients have a higher risk of reoperation and older with death, while gender appears not to be an important factor. Moreover, a weak correlation was found between aortic gradient and aortic regurgitation with the risk of an event. However, to better understand the association between aortic gradient and the events when using nonlinear time terms, we

present in Figure 3.5 the subject-specific aortic gradient profiles for two patients. The values in the plots represent the effect of the particular subject-specific aortic gradient on each of the events. Hence, for patients R96 and 63, the effect of their aortic gradient levels at baseline on the risk of reoperation is -0.38.

The models with the linear and the nonlinear term of time for aortic gradient provide us some opposite results (Table 3.1 and Table 3.2). Specifically, differences can be noticed at the parameters that associate the longitudinal and survival outcomes, where in the linear case, some of them appear to be significant.

Table 3.3: Simulation results including the true parameter values, the mean of the means (over the MCMC samples) for each parameter and the mean of the standard deviations (over the MCMC samples) for each parameter

	True values	Mean	SD
β_{11}	2.980	2.978	0.074
β_{11}	0.170	0.175	0.018
σ	0.638	0.608	0.021
β_{20}	-3.132	-3.139	0.278
β_{21}	1.683	1.684	0.222
β_{22}	4.799	4.803	0.291
β_{23}	7.820	7.881	0.446
β_{24}	10.591	10.671	0.994
β_{25}	-0.142	-0.143	0.027
γ_D	0.0002	0.0002	0.00009
α_{1D}	-0.012	-0.012	0.015
α_{12D}	-0.003	-0.003	0.017
α_{2D}	0.004	0.004	0.014
γ_R	-0.048	-0.054	0.017
α_{1R}	-0.149	-0.305	0.336
α_{12R}	2.546	2.598	1.286
α_{2R}	0.001	0.012	0.138

D = death; R = reoperation; SD = standard deviation

3.4 Simulations

A simulation was set up to evaluate the performance of the proposed joint model. The design of the simulated data was almost similar to the joint models that were fitted on the cardio data. In particular, we assumed 150 patients and planned a follow-up period randomly selected from 1 to 8 years equally spaced. The median number of visits is equal to 4, and 13% of the patients have only a single measurement. More details can be found in Section 3.6.5.

Table 3.3 presents the results from the simulated data. As it can be seen, the proposed

joint model is performing well with estimates close to the true values. Specifically, we find the lowest mean absolute error to be for the time-to-death estimates. Moreover, for the CR mixed-effects submodel and the time-to-reoperation submodel, we observe a mean absolute error equal to 0.02, while for the linear mixed-effects model it is equal to 0.0091.

3.5 Discussion

Motivated by the clinical interest of associating the valve function with the patients' risks, we proposed an extended joint model which handles one continuous (aortic gradient) and one ordinal (aortic regurgitation) longitudinal outcome and a competing risk setting (time-to-death or reoperation). We used mixed-effects models for the longitudinal responses and particularly, the CR mixed-effects model for analyzing the ordinal outcome. A limited simulation study showed good performance of the proposed model. In this Chapter, the survival outcomes are coupled with the subject-specific profiles of both longitudinal outcomes making it interesting to investigate the connection when using flexible functions to smooth the linear assumptions for time in the mixed-effects models. Major benefits of the proposed joint model include the ability of the physician to investigate the progression of aortic stenosis and aortic regurgitation of the patients and to associate it with the risk of dying or requiring a reoperation on the same valve. Moreover, our joint model is applicable to a range of biomedical research settings that jointly investigate a continuous longitudinal outcome, an ordinal longitudinal outcome, and two competing risk events.

An interesting extension would be to model additional longitudinal outcomes and time-to-event outcomes. From the clinical point of view, this will be more informative because there are more than two potential biomarkers for investigating heart valve disorders, and often, there is interest in additional endpoints than reoperation and death. Moreover, in this work, we assumed that the random effects link the marker evolutions with the risk of each event by

$$h_{ik}(t,\theta_s) = h_{0k}(t)\exp\{w_i^\top \gamma_k + (\tilde{\beta}_1 + b_{1i})^\top \alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^\top \alpha_{2k}\}.$$

However, another frequently used parameterization is to connect the survival submodels with the underlying value of the biomarkers at a specific time point as presented in equation (3.5.3). Furthermore, we could also investigate whether other characteristics of the patients' longitudinal profiles of aortic gradient and aortic regurgitation may be associated with the risk for death or reoperation, such as the rate of increase/decrease of the biomarker's levels (3.5.4), or a summary of the whole longitudinal trajectories (3.5.5).

$$h_{ik}(t,\theta_s) = h_{0k}(t)\exp\{w_i^\top \gamma_k + f_{1i}(t)\alpha_{1k} + f_{2i}(t)\alpha_{2k}\}, \tag{3.5.3}$$

$$h_{ik}(t,\theta_s) = h_{0k}(t)\exp\{w_i^\top \gamma_k + f_{1i}(t)\alpha_{1k} + f'_{1i}(t)\alpha^d_{1k} + f_{2i}(t)\alpha_{2k} + f'_{2i}(t)\alpha^d_{2k}\}, \tag{3.5.4}$$

$$h_{ik}(t,\theta_s) = h_{0k}(t)\exp\{w_i^\top \gamma_k + \int_0^t f_{1i}(t)\alpha^d_{1k}ds + \int_0^t f_{2i}(t)\alpha^d_{2k}ds\}, \tag{3.5.5}$$

where $f_{1i}(t) = x_{1i}^{\top}(t)\beta_1 + z_{1i}^{\top}(t)b_{1i}$ and $f_{2i}(t) = x_{2i}^{\top}(t)\beta_2 + z_{2i}^{\top}(t)b_{2i}$ denote time-dependent functions of the two longitudinal outcomes respectively that depend on the random effects and on the true biomarkers. Moreover, $f'_{1i}(t) = \frac{\mathrm{d}f_{1i}(t)}{\mathrm{d}t}$ and $f'_{2i}(t) = \frac{\mathrm{d}f_{2i}(t)}{\mathrm{d}t}$ are the first order derivatives of the $f_{1i}(t)$ and $f_{2i}(t)$ functions. Finally, a by-product of our developments is prediction on the patient's status for example after a medical intervention. Such predictions could also be used to evaluate the performance of the proposed model under different parameterizations.

Table 3.4: CR transformed data example

id	visit	Y	cohort	visit*	Y^*
1	1	2	$\leqslant 2$	1	1
			$\leqslant 3$	1	0
			$\leqslant 4$	1	0
1	2	2	$\leqslant 2$	2	1
			$\leqslant 3$	2	0
			$\leqslant 4$	2	0
1	3	1	$\leqslant 2$	3	0
			$\leqslant 3$	3	0
			$\leqslant 4$	3	0
2	1	4	$\leqslant 4$	1	1
2	1	3	$\leqslant 3$	1	1
			$\leqslant 4$	1	0

3.6 Appendix

3.6.1 Continuation Ratio Model

There are two different types of CR models, the backward and the forward. For the cardio data we assumed a backwards CR model, which is used when progression through disease states from none to severe is represented by increasing values and the interest lies in the estimation of the odds of more severe disease compared to less severe disease. The restructure of the data assuming the backwards method is performed as follows. If Y is the ordinal response with $k+1$ categories ($k = 0, 1, 2, \ldots, k$) the first subset of the data of the higher category consists of all observations. The observations with response category equal to k are assigned the new binary response equal to 1 and the remaining observations equal to 0. The second subset of data consists of the observation with $Y \leqslant k-1$. Again the observations of the second subset with response category equal to $k-1$ are assigned as 1 and the remaining as 0. This procedure continuous until $k = 1$. An example of the transformed data is given at Table 3.4. We obtain k-1 dummy variables (cohorts) where k is the number of categories, representing the cut-point variable yields the regression coefficients of the CR

model. Thus for the backwards method, by assuming 4 categories we obtain 3 cut-point for the comparisons between category 4 vs categories 1 through 3, category 3 vs categories 2 through 1 and category 2 vs category 1.

3.6.2 Bayesian Approach for Parameter Estimation

3.6.2.1 Likelihood

The posterior distribution of the joint model is written as

$$\begin{aligned} \mathrm{P}(\theta \mid y_{1ij}, y^*_{2ij}, T_i, \delta_i) \quad \propto \quad & \mathrm{P}(y_{1ij} \mid b_{1i}, \theta_{y_1}) \mathrm{P}(y^*_{2ij} \mid b_{2i}, \theta_{y_2}) \mathrm{P}(T_i, \delta_i \mid b_{1i}, b_{2i}, \theta_s) \times \\ & \mathrm{P}(b_{1i} \mid \theta_{y_1}) \mathrm{P}(b_{2i} \mid \theta_{y^*_2}) \mathrm{P}(\theta_{y_1}) \mathrm{P}(\theta_{y^*_2}) \mathrm{P}(\theta_s), \end{aligned}$$

where $\theta = (\theta^T_{y_1}, \theta^T_{y^*_2}, \theta^T_s)^T$ denotes the parameter vector for the longitudinal and survival outcomes. Respectively, θ_{y_1} is the parameter vector for the aortic gradient, $\theta_{y^*_2}$ for transformed aortic regurgitation as described in Section 3.6.1 and θ_s for the competing risk part.
The overall likelihood contribution for the i-th subject is given by

$$\begin{aligned} \mathrm{P}(y_{1i}, y^*_{2i}, T_i, \delta_i \mid b_i; \theta) = & \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{ -\frac{1}{2\sigma^2} \sum_{j=1}^{n_i} (y_{1ij} - x^\top_{1ij}\beta_1 - z^\top_{1ij} b_{1i})^2 \right\} \times \\ & \prod_{j=1}^{n_i} \left\{ \frac{\exp(x^\top_{2ij}\beta_2 + z^\top_{2ij} b_{2i})}{1 + \exp(x^\top_{2ij}\beta_2 + z^\top_{2ij} b_{2i})} \right\}^{y^*_{2ij}} \left[1 - \left\{ \frac{\exp(x^\top_{2ij}\beta_2 + z^\top_{2ij} b_{2i})}{1 + \exp(x^\top_{2ij}\beta_2 + z^\top_{2ij} b_{2i})} \right\} \right]^{1 - y^*_{2ij}} \times \\ & \prod_{k=1}^{K} [\sum_{q=1}^{m} \xi_{qk} I(t_{q-1} < T_i \le t_q) \exp\{ w_i^\top \gamma_k + (\tilde{\beta}_1 + b_{1i})^\top \alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^\top \alpha_{2k} \}]^{I(\delta_i = k)} \times \\ & \exp\left\{ - \sum_{k=1}^{K} [\exp\{ w_i^\top \gamma_k + (\tilde{\beta}_1 + b_{1i})^\top \alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^\top \alpha_{2k} \}] \sum_{q=1}^{m_i} \xi_{qk} T_{iq} \right\}, \end{aligned}$$

where $T_{iq} = \min(T_i, t_q) - \min(T_i, t_{q-1})$ denote the intervals for the piecewise constant baseline hazard, t_q $\{q = 1, \ldots, m\}$ the knots and m_i the index of the knot for which $t_{m_i - 1} < T_i \le t_{m_i}$.

3.6.2.2 Priors and MCMC Implementation

We used standard non-informative prior distributions for the parameters. In particular, for the regression coefficients β_1, β_2, the survival coefficients γ_k, the association coefficients α_{1k}, α_{2k} and the baseline hazards for the survival submodel ξ_{qk} normal priors were taken. For the variance-covariance matrix of the random effects we have taken inverse Wishart prior, while for the variance of the error terms for the continuous longitudinal outcome inverse gamma

prior was taken. We derived the full conditional distributions of all parameters in the joint models. Gibbs sampling was combined with Metropolis-Hastings sampling. Particularly, for the parameters $1/\sigma^2$ and D^{-1} Gibbs sampling was applied since the full conditional distributions are standard. For the other parameters the Random Walk Metropolis algorithm was applied, tuned such that the acceptance rate lies between 20% and 40%.

3.6.3 Posteriors

3.6.3.1 Full Conditionals for the Mixed-Effects Submodels

The full conditional distribution of the coefficients of the linear mixed-effects submodel β_1 is

$$
\begin{aligned}
P(\beta_1 \mid .) \propto & \prod_{i=1}^{n} \exp\Big\{ -\frac{\tau}{2} \sum_{j=1}^{n_i} (y_{1ij} - x_{1ij}^\top \beta_1 - z_{1ij}^\top b_{1i})^2 \Big\} \times \\
& \prod_{k=1}^{K} [\sum_{q=1}^{m} \xi_{qk} I(t_{q-1} < T_i \le t_q) \exp\{w_i^\top \gamma_k + (\tilde{\beta}_1 + b_{1i})^\top \alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^\top \alpha_{2k}\}]^{I(\delta_i = k)} \times \\
& \exp\Big\{ -\sum_{k=1}^{K} [\exp\{w_i^\top \gamma_k + (\tilde{\beta}_1 + b_{1i})^\top \alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^\top \alpha_{2k}\}] \sum_{q=1}^{m_i} \xi_{qk} T_{iq} \Big\} \times \\
& \exp\Big\{ -\frac{1}{2} (\beta_1 - \mu_{\beta 1})^\top \tau_{\beta 1} (\beta_1 - \mu_{\beta 1}) \Big\}
\end{aligned}
$$

where $\mu_{\beta 1}$, $\tau_{\beta 1}$ are the parameters of the prior of β_1 and τ equal to $1/\sigma^2$.

The full conditional distribution of the coefficients of the CR mixed-effects submodel β_2 is

$$
\begin{aligned}
P(\beta_2 \mid .) \propto & \prod_{i=1}^{n} \prod_{j=1}^{n_i} \pi_{ij}^{y_{2ij}^*} \{1 - \pi_{ij}\}^{\{1 - y_{2ij}^*\}} \times \\
& \prod_{k=1}^{K} [\sum_{q=1}^{m} \xi_{qk} I(t_{q-1} < T_i \le t_q) \exp\{w_i^\top \gamma_k + (\tilde{\beta}_1 + b_{1i})^\top \alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^\top \alpha_{2k}\}]^{I(\delta_i = k)} \times \\
& \exp\Big\{ -\sum_{k=1}^{K} [\exp\{w_i^\top \gamma_k + (\tilde{\beta}_1 + b_{1i})^\top \alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^\top \alpha_{2k}\}] \sum_{q=1}^{m_i} \xi_{qk} T_{iq} \Big\} \times \\
& \exp\Big\{ -\frac{1}{2} (\beta_2 - \mu_{\beta 2})^\top \tau_{\beta 2} (\beta_2 - \mu_{\beta 2}) \Big\}
\end{aligned}
$$

where $\mu_{\beta 2}$ and $\tau_{\beta 2}$ are the parameters of the prior of β_2.

The full conditional distribution of the random effects of the linear mixed-effects submodel b_{1i} is

$$P(b_{1i} \mid .) \propto \exp\Big\{ -\frac{\tau}{2} \sum_{j=1}^{n_i} (y_{1ij} - x_{1ij}^{\top}\beta_1 - z_{1ij}^{\top} b_{1i})^2 \Big\} \times$$
$$\prod_{k=1}^{K} [\sum_{q=1}^{m} \xi_{qk} I(t_{q-1} < T_i \le t_q) \exp\{w_i^{\top}\gamma_k + (\tilde{\beta}_1 + b_{1i})^{\top}\alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^{\top}\alpha_{2k}\}]^{I(\delta_i = k)} \times$$
$$\exp\Big\{ -\sum_{k=1}^{K} [\exp\{w_i^{\top}\gamma_k + (\tilde{\beta}_1 + b_{1i})^{\top}\alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^{\top}\alpha_{2k}\}] \sum_{q=1}^{m_i} \xi_{qk} T_{iq} \Big\} \times$$
$$\mid \tau_{b1} \mid^{1/2} \exp(-\frac{1}{2} b_{1i}^{\top} \tau_{b1} b_{1i})$$

where τ_{b1} is the inverse variance of the prior of b_{1i}.

The full conditional distribution of the random effects of the CR mixed-effects submodel b_{2i} is

$$P(b_{2i} \mid .) \propto \prod_{j=1}^{n_i} \pi_{ij}^{y^*_{2ij}} \{1 - \pi_{ij}\}^{\{1 - y^*_{2ij}\}} \times$$
$$\prod_{k=1}^{K} [\sum_{q=1}^{m} \xi_{qk} I(t_{q-1} < T_i \le t_q) \exp\{w_i^{\top}\gamma_k + (\tilde{\beta}_1 + b_{1i})^{\top}\alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^{\top}\alpha_{2k}\}]^{I(\delta_i = k)} \times$$
$$\exp\Big\{ -\sum_{k=1}^{K} [\exp\{w_i^{\top}\gamma_k + (\tilde{\beta}_1 + b_{1i})^{\top}\alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^{\top}\alpha_{2k}\}] \sum_{q=1}^{m_i} \xi_{qk} T_{iq} \Big\} \times$$
$$\mid \tau_{b2} \mid^{1/2} \exp(-\frac{1}{2} b_{2i}^{\top} \tau_{b2} b_{2i})$$

where τ_{b2} is the inverse variance of the prior of b_{2i}.

The full conditional distribution of the inverse variance of the linear mixed-effects submodel τ is

$$P(\tau \mid .) \propto \prod_{i=1}^{n} \frac{1}{\sqrt{2\pi}} \tau^{1/2} \exp\Big\{ -\frac{\tau}{2} \sum_{j=1}^{n_i} (y_{1ij} - x_{1ij}^{\top}\beta_1 - z_{1ij}^{\top} b_{1i})^2 \Big\} \tau^{A_\tau - 1} \exp(-B_\tau \tau)$$

$[\tau \mid .] \sim \Gamma[A_\tau + \frac{N}{2}, \sum_{j=1}^{n_i} (y_{1ij} - x_{1ij}^{\top}\beta_1 - z_{1ij}^{\top} b_1)^2 + B_\tau]$,
where A_τ and B_τ are the parameters of the prior of τ.

The full conditional distribution of the inverse covariance-variance of the random part of the mixed-effects submodels τ_b is

$$\begin{aligned} P(\tau_b \mid .) &\propto \prod_{i=1}^{n} \mid \tau_b \mid^{1/2} \exp\Big(-\frac{1}{2} b_i^{\top} \tau_b b_i \Big) \mid \tau_b \mid^{\frac{n-\rho-1}{2}} \exp\Big\{ -\frac{1}{2} tr(\mid \tau_b \mid \mathrm{A}_{\tau b}^{-1}) \Big\} \\ &\propto \mid \tau_b \mid^{\frac{n-\rho}{2}} \exp\Big\{ -\frac{1}{2} (\mid \tau_b \mid b_i^{\top} b_i + \mid \tau_b \mid A_{\tau b}^{-1}) \Big\} \end{aligned}$$

$[\tau_b \mid .] \sim W[n-\rho+1, (b_i^\top b_i A_{\tau b}^{-1})^{-1}]$,
where $A_{\tau b}$ and ρ are the parameters of the prior of τ_b.

3.6.3.2 Full Conditionals for the Survival Submodels

The full conditional distributions of the coefficients of the baseline covariates of the survival submodel γ_k are

$$
\begin{aligned}
P(\gamma_k \mid .) \propto & \\
& \prod_{i=1}^{n}\prod_{k=1}^{K}[\sum_{q=1}^{m}\xi_{qk}I(t_{q-1}<T_i\le t_q)\exp\{w_i^\top\gamma_k+(\tilde{\beta}_1+b_{1i})^\top\alpha_{1k}+(\tilde{\beta}_2+b_{2i})^\top\alpha_{2k}\}]^{I(\delta_i=k)} \\
& \exp\Big\{-\sum_{k=1}^{K}[\exp\{w_i^\top\gamma_k+(\tilde{\beta}_1+b_{1i})^\top\alpha_{1k}+(\tilde{\beta}_2+b_{2i})^\top\alpha_{2k}\}]\sum_{q=1}^{m_i}\xi_{qk}T_{iq}\Big\}\times \\
& \exp\Big\{-\frac{1}{2}(\gamma_k-\mu_{\gamma k})^\top\tau_{\gamma k}^{-1}(\gamma_k-\mu_{\gamma k})\Big\}
\end{aligned}
$$

where $\mu_{\gamma k}$ and $\tau_{\gamma k}$ are the parameters of the prior of γ_k.

The full conditional distributions of the coefficients of the covariates that link the survival and the longitudinal part α_{1k} and α_{2k} are

$$
\begin{aligned}
P(\alpha_{1k} \mid .) \propto & \\
& \prod_{i=1}^{n}\prod_{k=1}^{K}[\sum_{q=1}^{m}\xi_{qk}I(t_{q-1}<T_i\le t_q)\exp\{w_i^\top\gamma_k+(\tilde{\beta}_1+b_{1i})^\top\alpha_{1k}+(\tilde{\beta}_2+b_{2i})^\top\alpha_{2k}\}]^{I(\delta_i=k)} \\
& \exp\Big\{-\sum_{k=1}^{K}[\exp\{w_i^\top\gamma_k+(\tilde{\beta}_1+b_{1i})^\top\alpha_{1k}+(\tilde{\beta}_2+b_{2i})^\top\alpha_{2k}\}]\sum_{q=1}^{m_i}\xi_{qk}T_{iq}\Big\}\times \\
& \exp\Big\{-\frac{1}{2}(\alpha_{1k}-\mu_{\alpha 1k})^\top\tau_{\alpha 1k}(\alpha_{1k}-\mu_{\alpha 1k})\Big\}
\end{aligned}
$$

where $\mu_{\alpha 1k}$ and $\tau_{\alpha 1k}$ are the parameters of the prior of α_{1k}.

$$
\begin{aligned}
P(\alpha_{2k} \mid .) \propto & \\
& \prod_{i=1}^{n}\prod_{k=1}^{K}[\sum_{q=1}^{m}\xi_{qk}I(t_{q-1}<T_i\le t_q)\exp\{w_i^\top\gamma_k+(\tilde{\beta}_1+b_{1i})^\top\alpha_{1k}+(\tilde{\beta}_2+b_{2i})^\top\alpha_{2k}\}]^{I(\delta_i=k)} \\
& \exp\Big\{-\sum_{k=1}^{K}[\exp\{w_i^\top\gamma_k+(\tilde{\beta}_1+b_{1i})^\top\alpha_{1k}+(\tilde{\beta}_2+b_{2i})^\top\alpha_{2k}\}]\sum_{q=1}^{m_i}\xi_{qk}T_{iq}\Big\}\times \\
& \exp\Big\{-\frac{1}{2}(\alpha_{2k}-\mu_{\alpha 2k})^\top\tau_{\alpha 2k}^{-1}(\alpha_{2k}-\mu_{\alpha 2k})\Big\}
\end{aligned}
$$

where $\mu_{\alpha 2k}$ and $\tau_{\alpha 1k}$ are the parameters of the prior of α_{2k}.

The full conditional distributions of the baseline hazards of the survival submodel ξ_{qk} are

$$P(\xi_{qk} \mid .) \propto$$
$$\prod_{i=1}^{n}\prod_{k=1}^{K}[\sum_{q=1}^{m}\xi_{qk}I(t_{q-1} < T_i \leq t_q)\exp\{w_i^\top\gamma_k + (\tilde{\beta}_1 + b_{1i})^\top\alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^\top\alpha_{2k}\}]^{I(\delta_i=k)}$$
$$\exp\Big\{-\sum_{k=1}^{K}[\exp\{w_i^\top\gamma_k + (\tilde{\beta}_1 + b_{1i})^\top\alpha_{1k} + (\tilde{\beta}_2 + b_{2i})^\top\alpha_{2k}\}]\sum_{q=1}^{m_i}\xi_{qk}T_{iq}\Big\} \times$$
$$\exp\Big\{-\frac{1}{2}(\xi_{qk} - \mu_{\xi qk})^\top\tau_{\xi qk}^{-1}(\xi_{qk} - \mu_{\xi qk})\Big\}$$

where $\mu_{\xi qk}$ and $\tau_{\xi qk}$ are the parameters of the prior of ξ_{qk}.

3.6.4 WinBUGS Implementation

3.6.4.1 Data

Data = { list(N = number of patients, K = 15 (the points of the Guass-Kronrod quadrature rule, explained below[1]),
offset = specifies the number of repeated measurements of each patient for aortic gradient,
offset2 = specifies the number of repeated measurements of each patient for the transformed aortic regurgitation,
X = design matrix of the fixed effects for the aortic gradient model,
X2 = design matrix of the fixed effects of the aortic regurgitation model,
y = aortic gradient, y2 = the transformed aortic regurgitation,
Z = design matrix of the random effects for the aortic gradient model,
Z2 = design matrix of the random effects of the aortic regurgitation model,
eventR = vector with the reoperation indicator,
eventD = vector with the death indicator,
zeros = a vector of zeros,
WR = design matrix including the baseline covariates of the survival model with reoperation,
WD = design matrix including the baseline covariates of the survival model with death,
ncX = number of columns of the X matrix,
ncX2 = number of columns of the X2 matrix,
ncZ = number of columns of the Z matrix,
ncZ2 = number of columns of the Z2 matrix,
ncWR = number of columns of the WR matrix,
ncWD = number of columns of the WD matrix,
W2R = design matrix of the baseline hazard for reoperation (explained below[2]),
W2D = design matrix of the baseline hazard for death (explained below[3]),
W2sR = design matrix of the baseline hazard for reoperation with the 15-point Guass-Kronrod quadrature rule (explained below[4]),
W2sD = design matrix of the baseline hazard for death with the 15-point Guass-Kronrod quadrature rule (explained below[5]),
ncW2R = number of columns of the W2R matrix,
ncW2D = number of columns of the W2D matrix,
C = integer specifying the constant used in the zeros-trick,
P = observed failure time T_i devided by 2,
wk = Guass-Kronrod quadrature rule points (explained below[1]),
nb = mumber of total random effects,
mu0 = mean of random effects,
priorMean.betas = the prior mean vector of the normal prior for the fixed effects of the linear mixed-effects model,
priorMean.betas2 = the prior mean vector of the normal prior for the fixed effects of the CR mixed-effects model,
priorTau.betas = the prior precision matrix of the normal prior for the fixed effects of the linear mixed-effects model,
priorTau.betas2 = the prior precision matrix of the normal prior for the fixed effects of the CR mixed-effects model,
priorA.tau = the prior shape parameter of the gamma prior for the precision parameter of the linear mixed-effects model,
priorB.tau = the prior rate parameter of the gamma prior for the precision parameter of the linear mixed-effects model,
priorMean.gammas = the prior mean vector of the normal prior for the regression coefficients of the survival models,

priorTau.gammas = the prior precision matrix of the normal prior for the regression coefficients of the survival models,
priorMean.alphas = the prior mean vector of the normal prior for the association parameter in the survival model,
priorTau.alphas = the prior precision matrix of the normal prior for the association parameter in the survival model,
priorMean.Bs.gammas = the prior mean vector of the normal prior for the spline coefficients of the baseline risk function,
priorTau.Bs.gammas = the prior precision matrix of the normal prior for the spline coefficients of the baseline risk function,
priorR.D = the prior precision matrix of the Wishart prior for the precision matrix of the random effects,
priorK.D = the degrees of freedom of the Wishart prior for the precision matrix of the random effects) }

3.6.4.2 Explanations and Details

1. In general, the integral of the survival function does not have a closed-form solution, and thus a numerical method must be employed for this evaluation. To approximate this integral we use the Gaussian quadrature rule and we assume a 15-point Gauss-Kronrod rule (Rizopoulos and Ghosh, 2011). Particularly

$$S(t) = \exp\left\{ -\sum_{k=1}^{K} \int_0^{T_i} h_{ik}(s)ds \right\} = \exp\left\{ -\sum_{k=1}^{K} P \sum_{u=1}^{15} \mathrm{wk}_u \, h_{ik}((T_{iq}\,\mathrm{sk}_u + \tilde{T}_{iq})/2), \right\},$$

   where $T_{iq} = min(T_i, t_q) - min(T_i, t_{q-1})$, $\tilde{T}_{iq} = min(T_i, t_q) + min(T_i, t_{q-1})$, P is the observed failure time T_i devided by 2 and wk_u and sk_u denote prespecified weights and abscissas, respectively. However, since in our case only the random effects are included in the survival model, this numerical method is simplified.

2. The rows of the design matrix of the baseline hazard indicate the patients and the columns the m-1 intervals of the piecewise constant baseline hazard. The column (interval) that includes the observed failure time T_i of each patient is denoted as 1 and the rest as 0. A simple example is followed. Let as assume 2 patients with $T_i = (1.5, 3.5)$ and the cutpoints to be $t_q = (0,1,2,3,4)$. The design matrix, then, will be:

$$\begin{pmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}.$$

3. The same matrix as explained in 2.

4. The same matrix as explained in 2, however, in that case instead of T_i we use the 15-point Gauss-Kronrod rule.

5. The same matrix as explained in 4.

3.6.4.3 Code

```
model <- function ()
{
    for (i in 1:N) {
        for (j in offset[i]:(offset[i + 1] - 1)) {
```

```
            muy[j] <- inprod(betas[1:ncX], X[j, 1:ncX]) +
                  inprod(b[i, 1:ncZ], Z[j, 1:ncZ])
            y[j] ~ dnorm(muy[j], tau)
        }
        for (j in offset2[i]:(offset2[i + 1] - 1)) {
            muy2[j] <- inprod(betas2[1:ncX2], X2[j, 1:ncX2]) +
                  inprod(b[i, (ncZ + 1):(ncZ + ncZ2)], Z2[j, 1:ncZ2])
            Pr[j] <- max(0.00001, min(0.99999, (exp(muy2[j])/
                     (1 + exp(muy2[j])))))
            y2[j] ~ dbin(Pr[j],1)
        }
        etaBaselineR[i] <- inprod(gammasR[1:(ncWR)], WR[i, 1:ncWR])
        etaBaselineD[i] <- inprod(gammasD[1:(ncWD)], WD[i, 1:ncWD])
        log.h0.TR[i] <- inprod(Bs.gammasR[1:(ncW2R)], W2R[i, 1:ncW2R])
        log.h0.TD[i] <- inprod(Bs.gammasD[1:(ncW2D)], W2D[i, 1:ncW2D])
        log.hazardR[i] <- log.h0.TR[i] + etaBaselineR[i] +
             inprod(alphasR[1:nb], b[i,1:nb])
        log.hazardD[i] <- log.h0.TD[i] + etaBaselineD[i] +
             inprod(alphasD[1:nb], b[i,1:nb])
        for (k in 1:K) {
            log.h0.sR[i, k] <- inprod(Bs.gammasR[1:(ncW2R)], W2sR[K *
                (i - 1) + k, 1:ncW2R])
            log.h0.sD[i, k] <- inprod(Bs.gammasD[1:(ncW2D)], W2sD[K *
                (i - 1) + k, 1:ncW2D])
            SurvLongR[i, k] <- wk[k] * exp(log.h0.sR[i, k] +
                 inprod(alphasR[1:nb], b[i,1:nb]))
            SurvLongD[i, k] <- wk[k] * exp(log.h0.sD[i, k] +
                 inprod(alphasD[1:nb], b[i,1:nb]))
        }
        log.survivalR[i] <- -exp(etaBaselineR[i]) * P[i] * sum(SurvLongR[i,])
        log.survivalD[i] <- -exp(etaBaselineD[i]) * P[i] * sum(SurvLongD[i,])
        phi[i] <- C - ((eventR[i] * log.hazardR[i]) +
        (eventD[i] * log.hazardD[i])) - (log.survivalR[i] + log.survivalD[i])
        zeros[i] ~ dpois(phi[i])
        b[i, 1:nb] ~ dmnorm(mu0[], inv.D[, ])
    }
    betas[1:ncX] ~ dmnorm(priorMean.betas[], priorTau.betas[,])
    betas2[1:ncX2] ~ dmnorm(priorMean.betas2[], priorTau.betas2[,])
    tau ~ dgamma(priorA.tau, priorB.tau)
    gammasR[1:(ncWR)] ~ dmnorm(priorMean.gammas[], priorTau.gammas[,])
    gammasD[1:(ncWD)] ~ dmnorm(priorMean.gammas[], priorTau.gammas[,])
    alphasR[1:nb] ~ dmnorm(priorMean.alphas[], priorTau.alphas[,])
    alphasD[1:nb] ~ dmnorm(priorMean.alphas[], priorTau.alphas[,])
    Bs.gammasR[1:(ncW2R)] ~ dmnorm(priorMean.Bs.gammas[], priorTau.Bs.gammas[,])
    Bs.gammasD[1:(ncW2D)] ~ dmnorm(priorMean.Bs.gammas[], priorTau.Bs.gammas[,])
    inv.D[1:nb, 1:nb] ~ dwish(priorR.D[, ], priorK.D)
}
```

3.6.5 Simulations

For the continuous longitudinal outcome we simulated from a linear mixed-effects given by

$$y_{1i}(t) = \beta_{10} + t\beta_{11} + b_{10i} + tb_{11i} + \varepsilon_i(t).$$

The ordinal longitudinal outcome with the same number of categories as in the cardio data was simulated from a CR model by calculating the marginal probabilities of each s category that take the form

$$P(y_{2i}(t) = s \mid .) = \Big[1 - P(y_{2i}(t) = s \mid y_{2i}(t) \geq s, \ldots)\Big]\Big[1 - \sum_{u=1}^{U} P(y_{2i}(t) = u \mid y_{2i}(t) \geq u \mid \ldots)\Big],$$

where the '.' symbol indicates the covariates and the random effects.

For simplicity, we adopt a linear effect of time without baseline covariates. In addition, we chose a random intercept and slope for the mixed-effects model of the continuous outcome and a random intercept for the CR mixed-effects model of the ordinal outcome. The visits times were simulated from a gamma distribution with mean 2.67 and variance 8.89. For the survival part, the baseline risk was simulated from a Weibull distribution $h_0(t) = \psi t^{\psi-1}$ with $\psi = 1.02$. Moreover, an exponential censoring distribution was chosen with mean equal to 25. Finally, we included baseline age which was sampled from a U[16,70]. Under the settings described above, we simulated 200 datasets.

For each simulated dataset we fitted the joint model with exactly the same design as the one we used to simulate from, based on a piecewise constant baseline risk function with internal knots at equally spaced percentiles of the observed event times. Particularly, it takes the form

$$\begin{aligned} h_{ik}(t, \theta_s) \quad = \quad & h_{0k}(t) \exp\{age_i \gamma_k + (\beta_{10} + b_{10i})\alpha_{1k,0} + (\beta_{11} + b_{11i})\alpha_{1k,1} + \\ & (\beta_{20} + b_{20i})\alpha_{2k,0}\}, \end{aligned}$$

where $h_{0k}(t) = \sum_{q=1}^{m} \xi_{qk} I(t_{q-1} < t \leq t_q)$ is the piecewise constant baseline hazard and $t_q\{q = 1, \ldots, m\}$ the knots.

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CHAPTER 4

Dynamic Prediction of Outcome for Patients with Severe Aortic Stenosis: Application of Joint Models for Longitudinal and Time-to-Event Data

This Chapter is based on: Andrinopoulou, E.R., Rizopoulos, D., Geleijnse, M.L, Lesaffre, E., Bogers, A.J. and Takkenberg, J.J. (2014). Dynamic prediction of outcome for patients with severe aortic stenosis: application of joint models for longitudinal and time-to-event data. *BMC Cardiovascular Disorders*, submitted.

Abstract

Objective: In the prediction of prognosis for new patients suffering from severe aortic stenosis (AS), a cardiologist considers not only the severity of the AS but also patient characteristics, New York Heart Association (NYHA) class, and biomarkers such as brain natriuretic peptide (BNP). Intuitively, cardiologists adjust their prognosis over time, with the change in clinical status of the patient at each outpatient clinic visit. This study aims to illustrate in a prospective cohort of patients with severe AS the use of novel statistical approaches to mimic the dynamic adjustment of patient prognosis as employed by cardiologists.

Methods: A prospective cohort of 191 patients with severe AS was followed for 2 years repeatedly collecting BNP. A 3-step approach was employed: (1) construction of a mixed-effects model describing temporal BNP progression, (2) jointly modelling the mixed-effects model with time-to-event data (death and aortic valve intervention), and (3) using the joint model to build subject-specific prediction risk models.

Results: In the mixed-effects model, an increasing BNP was associated with time (0.23 ± 0.04years), aortic valve area (AVA) (-1.48 ± 0.3cm^2), patient age (0.05 ± 0.007years), left ventricular fractional ejection fraction (-0.16 ± 0.08%), symptoms (0.43 ± 0.18) and creatinin (0.4 ± 0.09micromol/L). In the joint model, an increasing BNP over time tended to be associated with death (HR:1.64 ± 1.35).

Conclusions: By jointly modelling longitudinal BNP data with death and intervention of patients with severe AS it is possible to construct individualized dynamic event prediction models that renew over time with accumulating evidence. It provides a potentially valuable evidence-based dynamic prediction tool for everyday use in medical practice.

4.1 Introduction

In clinical practice, physicians utilize different sources of information to predict patient prognosis. For example, in diagnosing a new patient with severe aortic stenosis (AS), a cardiologist considers not only the severity of the AS (for example through aortic valve area AVA measurement) but also patient characteristics such as patient age and comorbidities, New York Heart Association (NYHA) functional class and patient history, in order to make an assessment of patient prognosis. Additionally, biomarkers such as brain natriuretic peptide (BNP) can be used to further assess AS severity and prognosis. A small AVA and a high BNP are both associated with a more severe disease and a worse outcome (Katz et al., 2012; Lancellotti et al., 2010; Otto et al., 1997).

Empirically, cardiologists adjust their prognosis over time at each outpatient clinic visit, with the change in functional class, AVA and BNP. Based on emerging evidence on determinants of the outcome in AS, and with the help of novel statistical approaches to model outcomes, it is now possible to construct dynamic prediction models for patient outcome,

employing repeatedly collected (longitudinal) data such as BNP, mimicking the dynamic adjustment of prognosis as employed intuitively by cardiologists at each outpatient clinic visit.

This Chapter aims to illustrate the use of joint models of longitudinal and time-to-event data to dynamically predict individualized event occurrence severe AS. For this purpose, data from a prospective cohort study of 191 patients with severe AS is modeled to dynamically predict prognosis of two patients: Mr. Jones and Mr Smith; who were recently diagnosed with severe AS.

4.2 Methods

4.2.1 Patient Dataset

We used the patient dataset of a previously reported prospective cohort study of 191 adult patients, who were diagnosed with severe aortic valve disease in seven cardiology clinics in the wider Rotterdam area between 2006 and 2009, and who were followed for 2 years (Heuvelman et al., 2012). Inclusion criteria were AVA $\leq$ 1 cm^2, peak transaortic jet velocity (Vmax) $\geq$ 4 m/s, or aortic valve / left ventricular outflow tract velocity time integral ratio $\geq$ 4. The patients were followed clinically, including BNP measurements, and echocardiographically at baseline and then after 6, 12 and 24 months. Baseline patient characteristics are displayed in Table 4.1. In total 561 BNP measurements were collected over a 2-year period (mean 0.9 years; range 0-2.5 years). During the follow-up period, 15% of the patients (N=28) died and 48% (N=91) received an aortic valve replacement of transcatheter aortic valve implantation.

Table 4.1: Baseline patient characteristics

	All patients (N= 191)
Male gender (n, %)	118, 62%
Age in years (mean, SD)	72.6, 11.4
Symptomatic at study entry (n, %)	132, 69%
Smoking (n, %)	115, 60%
Hypertension (n, %)	100, 52%
Diabetes (n, %)	39, 20%
Dyslipidemia (n, %)	93, 49%
AVA in cm^2 (mean, SD)	0.74, 0.27
LV ejection fraction in % (mean, sd)	61, 6.7
Creatinin in micromol/L (mean, SD)	89, 125

AVA = aortic valve area; LV = left ventricular, SD = standard deviation

4.2.2 Statistical Methods

The development of a dynamic event prediction model that takes into account both baseline patient characteristics and longitudinal BNP measurement, requires that we first describe the evolution of BNP over time, correcting for baseline variables. Second, we use this information in a time-to-event model. Finally, using the combined model, we perform dynamic event predictions. In the next paragraphs we describe in detail the statistical methods that were employed in this 3-step process, and the rationale behind these methods.

First, we fitted a mixed-effects model to describe the evolution of BNP over time. Particularly, the model included time (years) and the baseline covariates: AVA (cm^2), patient age (years), symptoms (yes/no), gender, transformed LV ejection fraction (%) and transformed creatinin (micromol/L). Transformation was done by dividing the values with the standard deviations of the specific covariates. Moreover, due to heterogeneity in the residuals plot the logarithmic scale of BNP was used. An advantage of the mixed-effects models is that they account for the positive correlation between the measurements that are observed within the same patient. For example, the values of BNP that are observed over time from the same patient are expected to be more correlated than between patients. Moreover, these models account for the biological variability in the longitudinal outcome. Specifically, if we measure BNP twice a day, we may not obtain the same result. By taking this into account using the mixed model, more reliable results will be observed.

Second, to investigate the effect of the repeated BNP measurements on death and intervention probabilities, a joint model of longitudinal and survival outcomes was constructed (Rizopoulos, 2012; Andrinopoulou et al., 2012). AVA, age, symptoms, gender, LV fraction and creatinine (all at baseline) were included as additional confounders.

Third, we considered the joint modelling framework and focused on the assessment of the predictive ability of our survival outcomes. Specifically, it was of interest to predict patient survival and aortic valve intervention-free for a new patient that has provided us with a set of BNP measurements and baseline characteristics, using the fitted joint model for all patients. Due to the fact that BNP is time-dependent and not constant between the visits and therefore providing longitudinal measurement up to a specific time, assumes survival up to this time, it was more relevant to calculate the probability of surviving a future time point, given that the patient was alive until his last follow-up visit (Rizopoulos, 2011; Proust-Lima and Taylor, 2009). Using this approach, we applied the resulting joint modelling framework to two hypothetical patients: Mr. Jones and Mr. Smith and predicted their future survival and aortic valve intervention-free probabilities. Specifically, Mr. Jones is a 72 year old male, with creatinin value at baseline 92 micromol/L, AVA of 0.96 cm^2, LV ejection fraction 61% and BNP values over time 64, 70, 72 and 78 pg/ml measured at 0.5, 0.9, 1.5 and 1.5 years. Moreover, he is asymptomatic at baseline. Additionally, Mr. Smith is a 79 year old male that has creatinin equal to 92 micromol/L, AVA equal to 0.61 cm^2, LV ejection fraction equal to 61% and he is symptomatic at baseline. Finally, his BNP values are 381, 287, 1068 and 1070 pg/ml measured at 0, 0.9, 1.2 and 2 years.

Table 4.2: Coefficients, standard error of coefficients and p-values for the mixed-effects model describing the evolution of BNP over time

	Coefficient	SE	p-value
(Intercept)	2.92	0.95	0.0025
Time (years)	0.23	0.04	< 0.0001
AVA (cm^2)	-1.48	0.3	< 0.0001
Age (years)	0.05	0.007	< 0.0001
Symptoms	0.43	0.18	0.0188
Male gender	-0.34	0.18	0.0607
*LVejection fraction (%)	-0.16	0.08	0.0486
*Creatinin (micromol/L)	0.4	0.09	< 0.0001

AVA = aortic valve area; LV = left ventricular; SE = standard error. *Trasnformed LV ejection fraction and Creatinin in the models

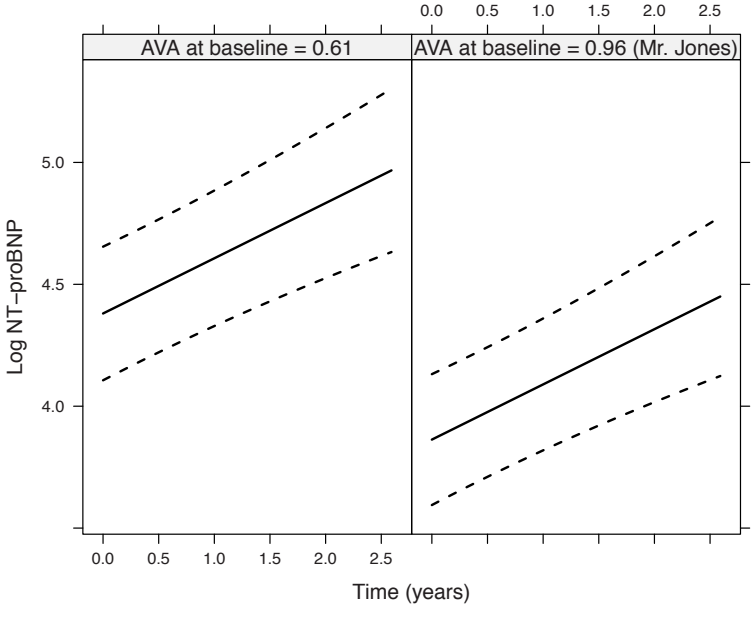

Figure 4.1: Effect plot of AVA described from the joint model for Mr. Jones and another patient with the same age, with impaired LV ejection fraction of 61, creatinin level equal to 92 and both patients with no symptoms at baseline. AVA = aortic valve area; LV = left ventricular

Table 4.3: Coefficients, standard error of coefficients and p-values for the joint model predicting survival and aortic valve intervention

	Coefficient	Hazard ratio	SE	p-value
Death				
BNP at specific time point (pg/ml)	0.5	1.65	0.3	0.0962
AVA (cm^2)	−2.61	0.07	1.5	0.0815
Age (years)	0.02	1.02	0.04	0.5674
Male gender	1.12	3.06	0.6	0.0623
Symptoms	1.87	6.49	1.05	0.0753
*LV ejection fraction (%)	0.01	1.01	0.25	0.9539
*Creatinin (micromol/L)	0.18	1.2	0.15	0.2162
Aortic valve intervention				
BNP at specific time point (pg/ml)	0.18	1.2	0.25	0.4787
AVA (cm^2)	−1.12	0.33	1.04	0.2804
Age (years)	−0.04	0.96	0.02	0.0077
Male gender	0.39	1.48	0.49	0.4287
Symptoms	1.08	2.94	0.46	0.0183
*LV ejection fraction (%)	0.24	1.27	0.21	0.2388
*Creatinin (micromol/L)	−1.43	0.24	1.31	0.2761

BNP = brain natriuretic peptide; AVA = aortic valve area; LV = left ventricular; SE = standard error. *Trasnformed LV ejection fraction and Creatinin in the models

Furthermore, we performed internal validation using a bootstrapping procedure. Specifically, we focused on discrimination, that is, how well can the model discriminate between patients who are about to experience the event within a time frame after the last measurement, from patients that are going to surpass this time frame. Since the patients were visiting their physician approximately every half year, we set this time frame. In patricularly, we rely on the receiver operating characteristic (ROC) approach to assess the predictive ability of the longitudinal biomarker BNP (Rizopoulos, 2011).

All analyses have been implemented in R.15.1, which can be downloaded as freeware at http://www.r-project.org, using the JM package (Rizopoulos, 2010).

4.3 Results

As illustrated in Table 4.2 in the mixed-effects model describing the evolution of BNP over time, all covariates have a strong association with the levels of BNP, except baseline gender. Specifically, a longer follow-up, lower AVA at baseline, older patient baseline age, symptomatic patient at baseline, lower baseline LV ejection fraction and a higher baseline serum creatinin are highly associated with an increased BNP. Moreover, Figure 4.1, shows the evolutions of BNP in time of two hypothetical patients, Mr. Jones and another patient that has the same characteristics as Mr. Jones except for the AVA level which is 0.61. It is obvious

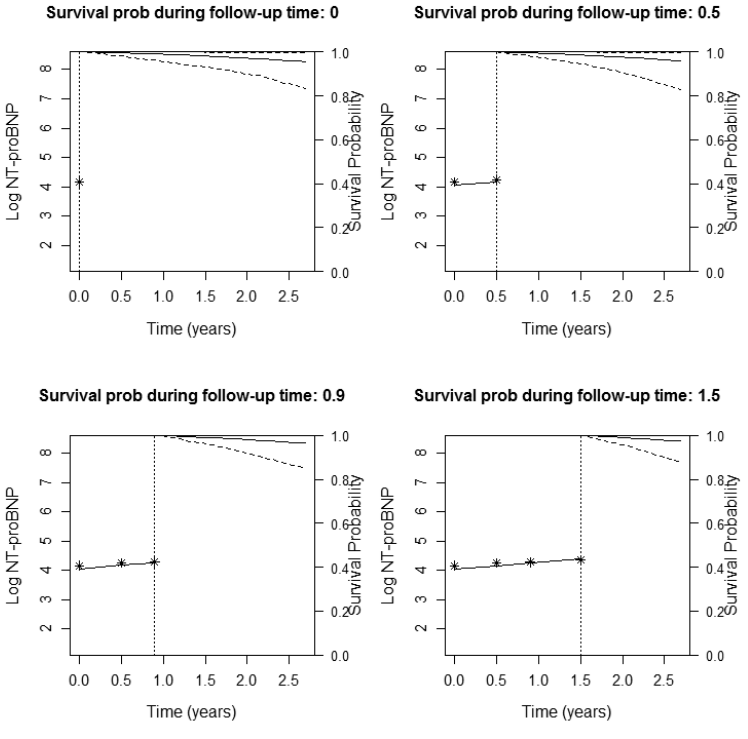

Figure 4.2: Dynamic prediction for the survival probability for Mr. Jones

in Figure 4.1 that a smaller AVA is associated with a higher BNP at baseline. Furthermore, there is no difference in the progression of BNP between the two patients. From the joint model with the survival as outcome, in Table 4.3, we observe that smaller AVA at baseline, male patient, symptoms at baseline and higher BNP at a specific time point (since we used all repeated measurements in the model for the specific covariate) tend to be associated with death. The joint model with the aortic valve intervention as outcome shows that a younger patient and symptoms at baseline are strongly associated with aortic valve intervention-free probabilities.

Figure 4.2, 4.3, 4.4 and 4.5 represent the dynamic prediction of survival and aortic valve intervention-free respectively for Mr. Jones and Mr. Smith, employing the joint modelling framework. It can be seen in Figure 4.2 that as more BNP measurements accumulated over time for Mr. Jones, the survival curve does not show big changes. Moreover, the same can be seen in Figure 4.3, where the intervention-free probabilities are presented. This can be explained by the fact that Mr. Jones' BNP measurements are relatively low and stable.

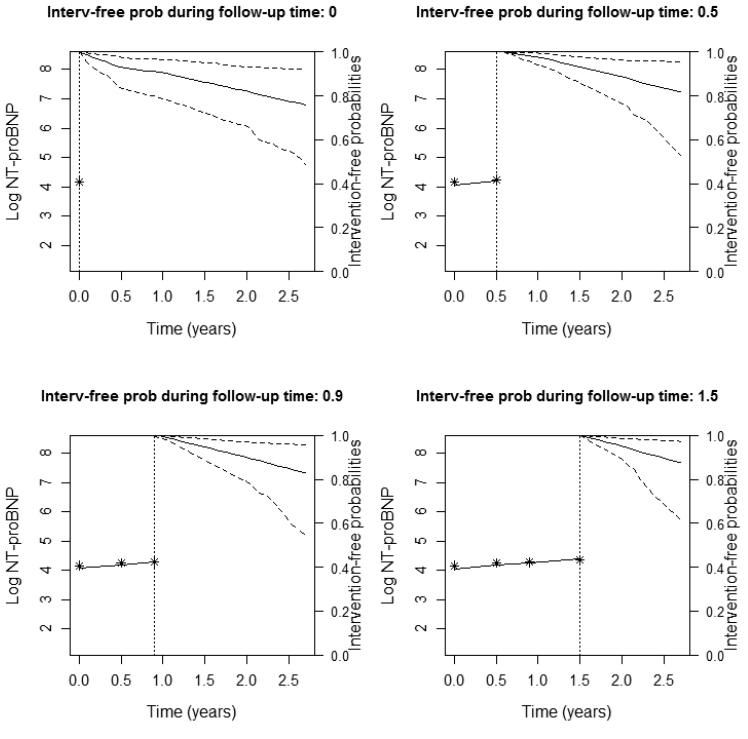

Figure 4.3: Dynamic prediction for the aortic valve intervention-free probability for Mr. Jones

In contrast, Mr. Smith has more steep curves for both expected survival and aortic valve intervention-free probabilities indicating that the patient should be monitored frequently. Specifically, one year after his first follow-up visit Mr. Smith has a survival probability of 70%, while one year after his last visit his survival probability is less than 50%. The reason could be that Mr. Smith has a high BNP value at baseline and his progression is faster within the 2 year period compared to Mr. Jones. Thus, Mr. Smith has a much lower survival probability one year after his last follow-up.

Finally, from the bootstrap method we observe the area under the ROC curve for death and reoperation to be 0.88 and 0.59, respectively. This indicates a good discriminative capability of the BNP for death, and little added value for the prediction of reoperation.

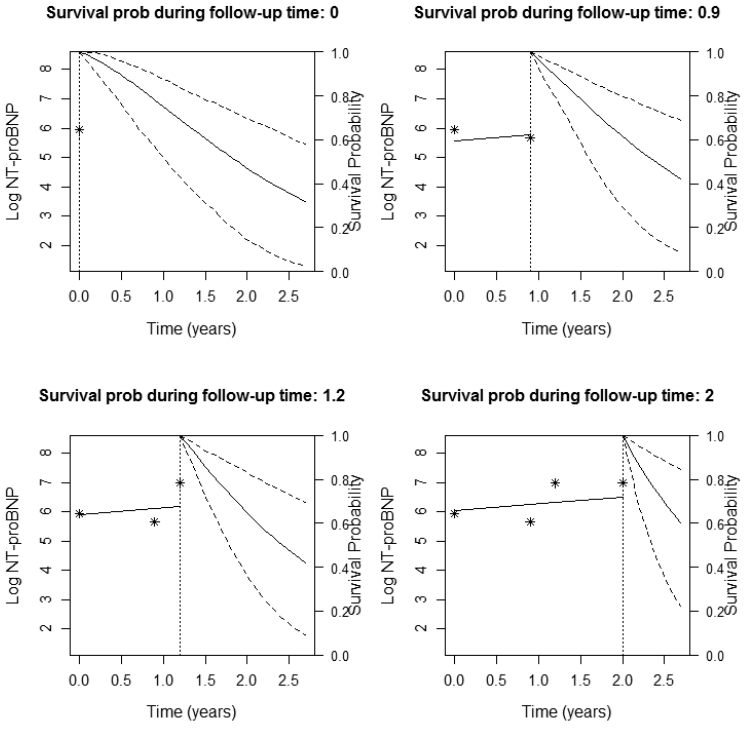

Figure 4.4: Dynamic prediction for the survival probability for Mr. Smith

4.4 Discussion

In this Chapter we illustrated the use of joint models of longitudinal and time-to-event data for individualized dynamic event prediction using serial BNP measurements in patients with severe AS. Patient prognostication may be improved by the use of such models that take into account all available medical information that accumulates over time. In the case of Mr. Jones and Mr. Smith, their probabilities of survival and aortic valve intervention-free were calculated accounting for all BNP values that accumulated over time and were updated when new BNP measurements became available. This approach provides the cardiologist with a useful evidence-based tool to assess the impact of BNP on patient prognosis. Importantly, the calculated probabilities for survival and aortic valve intervention can be used as an early warning system, allowing the necessary time for the physicians to plan an intervention. Given the impaired quality of life (QOL) of symptomatic patients with AS (van Geldorp et al., 2013b) and the considerable improvement in QOL after the aortic valve replacement, dynamic

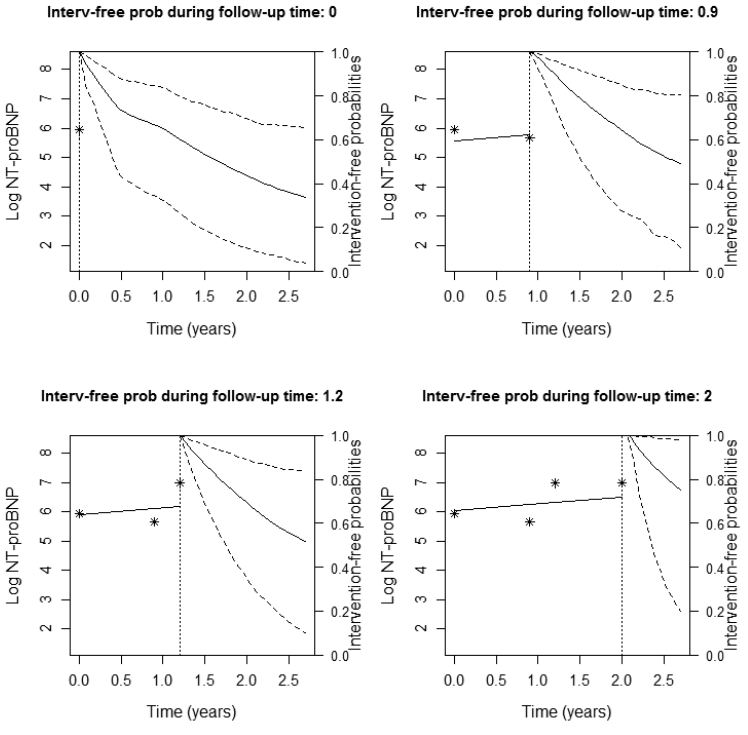

Figure 4.5: Dynamic prediction for the aortic valve intervention-free probability for Mr. Smith

event predictions may be of great value in optimizing the timing of the intervention (van Geldorp et al., 2013a).

Joint models of longitudinal and survival data (Rizopoulos, 2012) represent a powerful statistical tool capable of capturing the association between longitudinal and survival time data. An alternative approach is to utilize the time-dependent Cox model. However, this model assumes a step function between the repeated measurements, which is not realistic for biomarkers due to the fact that such cardio data as BNP values cannot be assumed to be constant between visits.

Of course, the proposed methodology has several (potential) limitations, both from a clinical and a statistical point of view. From a clinical point of view, every patient is unique, and analysis based on group data may not account for the special characteristics of an individual patient. Moreover, there are factors that are not included in the statistical models that may play an important role and thus, influence the decision making. In this respect we acknowledge that the proposed statistical methodology may be supportive in clinical

decision making, but can never replace clinical expertise. From the statistical point of view, the analysis of more than one longitudinal outcome such as BNP, AVA and symptoms over time together with survival outcomes requires advanced computational work and standard statistical packages do not yet provide these options. Moreover, there is not yet a package performing dynamic event prediction accounting for the competing risk problem: specifically, patients could die or require an intervention, in this case is aortic valve intervention. The analysis, then, becomes more complicated by the fact that the two censored outcomes are not completely independent, thus it is clear that analyzing the two outcomes separately is not appropriate and may lead to bias. However, in order to keep the analysis simple and thus to use only available packages, in this Chapter we did not account for the competing risk problem. Furthermore, a topic that was not addressed, concerns the validation of the derived predictions in terms of calibration. Within the joint modelling frame, some work has been done by Rizopoulos (2011) and Proust-Lima and Taylor (2009). Specifically, they focus on predictive accuracy measures that compare the actual value of predictions with the observed data using simulated data. Finally, a dataset consisting of more patients that are followed for a longer time period may provide better predictions for future patients.

Although all analyses were performed using standard statistical packages, a level of expertise in programming may be required. Thus, interactive web applications with friendly controls that easily incorporate plots and summaries are essential for adequate implementation of the proposed models in clinical practice may be interesting to produce. Particularly, an easy web application could give the opportunity to every physician to derive updated predictions for new patients when more longitudinal outcomes are available.

From the analysis we obtained a non significant association between aortic valve intervention and the evolution of BNP (Table 4.3). Hence, the validation showed that for the target group of patients the BNP as a marker for intervention does not exhibit great discrimination power. Although BNP profile is not a good predictor of intervention, it is reliable in predicting mortality and thus can be very helpful in planning an intervention to prevent mortality due to AS disease progression.

In conclusion, this Chapter has shown that temporal adjustment of risk prediction models for patients with severe AS, as more measurements of BNP become available over time, provide the physician with an evidence-based understanding of the prognostic implication of changes in the patient's disease condition. With the cardiovascular medical practice increasingly moving towards personalized medicine (Vahanian et al, 2012), joint models may provide an attractive tool for subject-specific predictions. The proposed joint model that was built and used to predict prognosis of patients suffering from severe AS, can be easily extended to other chronic disease entities that employ both longitudinal and survival data to dynamically assess patient prognosis.

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CHAPTER 5

Combined Dynamic Predictions using Joint Models of Multiple Longitudinal Outcomes and Competing Risk Data

This Chapter is based on: Andrinopoulou, E.R., Rizopoulos, D., Takkenberg, J.J. and Lesaffre, E. (2014). Combined dynamic predictions using joint models of multiple longitudinal outcomes and competing risk data. *Statistical Methods in Medical Research*, submitted.

Abstract

Nowadays there is increased medical interest in personalized medicine and tailoring decision making to the needs of individual patients. Within this context our developments are motivated from a Dutch study at the Cardio-Thoracic surgery department of the Erasmus Medical Centre, consisting of patients who received a human tissue valve in aortic position and who were thereafter followed echocardiographically. Our aim is to utilize the available follow-up measurements of the current patients to produce dynamically updated predictions of both survival and freedom from reintervention for future patients. In this Chapter we propose to jointly model multiple longitudinal measurements combined with competing risk survival outcomes and derive the dynamically updated cumulative incidence functions. Moreover, we investigate whether different features of the longitudinal processes would change significantly the prediction for the events of interest by considering different types of association structures, such as time-dependent trajectory slopes and time-dependent cumulative effects. Our final contribution focuses on optimizing the quality of the derived predictions. In particular, instead of choosing one final model over a list of candidate models which ignores model uncertainty, we propose to suitably combine predictions from all considered models using Bayesian model averaging (BMA).

5.1 Introduction

Motivated by current increased medical interest in personalized medicine, in this work we focus on subject-specific survival predictions (Taylor et al., 2005; Garre et al., 2008; Yu et al., 2008; Proust-Lima and Taylor, 2009; Rizopoulos, 2011). For example in the field of Cardio-Thoracic surgery and especially after a heart valve replacement, the main disadvantage of human tissue valve allografts is their limited durability due to calcification with tissue damage resulting in degeneration and dysfunction. Thus, it may be of interest for the treating physicians to develop a prognostic tool that could inform them about a future reintervention to their patients using all available repeated measurements. Specifically, the motivation comes from a study that was conducted in the Erasmus Medical Centre, Rotterdam, The Netherlands. This study includes 270 patients who received a human tissue valve allograft in aortic position in the Department of Cardio-Thoracic Surgery in a period of 21 years. Patients were followed prospectively over time and measurements of aortic gradient and aortic regurgitation were obtained at 6 months and 1 year postoperatively and biennially thereafter (Bekkers et al., 2011). The continuous variable aortic gradient measures whether the opening of the aortic valve is narrowed, while the ordinal variable aortic regurgitation measures leakage of the aortic valve. At the end of follow-up, 57 (20.1%) patients had died and 74 (26.1%) patients required a reoperation on the allograft. Since aortic gradient and aortic regurgitation are both measuring aortic heart valve abnormalities and therefore, the presence of one disease will have an influence on the other, it is of great interest from the clinical point of view to analyze

them together.

To evaluate the predictive value of the valve data on mortality and reoperation and to derive the subject-specific predictions we rely on joint models for longitudinal and time-to-event data. Joint modelling is an active area of statistics research that has received a lot of attention in recent years (Wulfsohn and Tsiatis, 1997; Tsiatis and Davidian, 2004; Rizopoulos, 2012). Moreover, these models can be used to objectively extract information from multiple markers and to employ them to dynamically update risk estimates. An advantage is that the predictions are updated as more measurements become available. Thus, the statistical predictions can be combined with the physician's expertise to yield improved health outcomes eventually.

In this paper, we extend the work presented in Andrinopoulou et al. (2014), that focuses on fitting the data using a joint model where the survival outcomes are associated with the random effects of the longitudinal outcomes. In particular, our contribution is two-fold: first, we postulate joint models assuming different functional forms to underlie the relationship between multiple longitudinal and survival outcomes and second, we focus on prediction models in the presence of competing risks. Since we are more interested in predicting future patients than simply assessing the degree of association between the trend of the repeated outcomes and time-to-events, it is important to accurately determine the estimate of the underlying process of the heart disease. Thus, we go beyond the standard joint model that utilizes only the latent value of the biomarkers and investigate whether the risk of an event could be affected also by the slope or a summary of the whole history of the longitudinal outcomes.

Finally, instead of deriving predictions based on a single model we suitably combine all considered ones. It is common practice that a model is selected from a set of different possible models upon clinical predictions are based. However, such an approach neglects model uncertainty. In addition, different models may produce more accurate predictions for different types of patients. We explicitly account for these issues and rely on Bayesian model averaging (BMA, Hoeting et al., 1999; Rizopoulos et al., 2014). Previous research using that approach in the joint modelling framework (Rizopoulos et al., 2014) derives BMA risk predictions for one event based on one continuous longitudinal outcome. In this paper we extend this idea to handle multiple longitudinal outcomes and a competing risk setting. Specifically, motivated by the heart valve study where treating physicians are more interested in risk predictions separately for reoperation and death, we derive BMA version of the cumulative incidence functions of the two events.

The rest of the Chapter is organized as follows. Section 5.2 describes the joint submodels and the Bayesian estimation procedure. Section 5.3 provides the individualized prediction mechanism and the Bayesian model averaging. Finally, Section 5.4 presents the results of the valve data and Section 5.5 closes with a discussion.

5.2 Methods

5.2.1 Submodels

Let T^*_{ki} denote the true failure time for the i-th individual ($i = 1,\ldots,n$) for each competing event $k = 1,2,\ldots,K$, and C_i the censoring time, then $T_i = \min(T^*_{1i},\ldots,T^*_{Ki},C_i)$ represents the observed failure time for the i-th patient. Moreover, $\delta_i = 0,1,2,\ldots,K$ is the event indicator where 0 indicates censoring. For the longitudinal part, we let $y_i = (y_{i1}^\top,\ldots,y_{iP}^\top)^\top$, $p = 1,\ldots,P$ denote a vector of P outcomes for the i-th patient, where y_{ip} consists of longitudinal responses that may be obtained at different time points $t_{ij,p}$ and have length n_{ip}. To describe the subject-specific evolutions over time of the longitudinal outcomes we utilize generalized linear mixed-effects models. In particular, the conditional distribution of the data, given the random effects, is taken to be member of the exponential family of distributions with mean conditional on the random effects

$$E(y_{ip}(t) \mid b_{ip}) = g_p^{-1}\{f_{ip}(t)\},$$

where $g_p^{-1}(.)$ is the inverse link function and $f_{ip}(.)$ describes the longitudinal profile for the p-th outcome

$$f_{ip}(t) = x_{ip}^\top(t)\beta_p + z_{ip}^\top(t)b_{ip},$$

where $x_{ip}(t)$ denotes the design vector for the fixed effects regression coefficients β_p and $z_{ip}(t)$ the design vector for the random effects b_{ip}.

For ordinal outcomes, we propose to use the continuation ratio (CR) mixed-effects model, postulated as

$$\mathrm{P}(y_{ip}(t) = s \mid y_{ip}(t) \le s, x_{ip}, z_{ip}, b_{ip}) = \frac{\exp\{f_{ip}(t)\}}{1+\exp\{f_{ip}(t)\}},$$

where $s = 1,\ldots,S_p$ represents the categories of each ordinal outcome. This model is based on conditional probabilities and is more appropriate when subjects move incrementally from one stage to another. Constructing a new binary $y^*_{ip}(t)$ vector and replicating rows of the $x_{ip}(t)$ and $z_{ip}(t)$ design vectors as described by Harrell (2001), the CR model can be fitted using a mixed-effects binary logistic likelihood function. Finally, we assume that a full multivariate normal distribution for the random effects describes the evolution of the longitudinal outcomes, i.e.,

$$b_i = (b_{i1}^\top,\ldots,b_{iP}^\top)^\top \sim N_p(0,D).$$

For the survival process we assume that the risk for each of the K competing events depends on the true but unobserved value of the markers at time t. Specifically, we have

$$h_{ik}(t,\theta_s) \quad = \quad h_{0k}(t)\exp\left\{\gamma_k^\top w_{ik} + \sum_{p=1}^{P}\alpha_{pk}f_{ip}(t)\right\}, \quad t > 0,$$

where θ_s is the parameter vector for the survival outcomes, w_{ik} is a vector of baseline covariates with a corresponding vector of regression coefficients γ_k, and α_{pk} denotes the strength of association between the longitudinal and survival outcomes. A B-splines baseline hazard function is assumed $\log h_{0k}(t) = \gamma_{h_0,0} + \sum_{q=1}^{Q} \gamma_{h_0,q} B_q(t,t_q)$, where $B_q(t,t_q)$ denotes the q-th basis function of a B-spline with knots $t_1,\ldots,t_Q$ and γ_{h_0} the vector of spline coefficients. We place the knots at equally spaced percentiles of the observed event times.

An issue that is often overlooked when building joint models, is the functional form that describes the longitudinal outcomes that are associated with the risk for each event. Due to the fact that different structures may provide us with different inferences and predictions, it is important to study this component of the model. Following, Brown (2009), Rizopoulos and Ghosh (2011) and Rizopoulos (2012) we postulate different functional forms to assess the predictive ability of the biomarkers. Specifically, we assume the following association structures:

$$M_1 : h_{ik}(t,\theta_s) = h_{0k}(t)\exp\left\{\gamma_k^\top w_{ik} + \sum_{p=1}^{P} \alpha_{pk} f_{ip}(t)\right\}, \tag{5.2.1}$$

$$M_2 : h_{ik}(t,\theta_s) = h_{0k}(t)\exp\left\{\gamma_k^\top w_{ik} + \sum_{p=1}^{P} \alpha_{pk} f_{ip}(t) + \sum_{p=1}^{P} \alpha_{pk}^d f'_{ip}(t)\right\}, \tag{5.2.2}$$

$$M_3 : h_{ik}(t,\theta_s) = h_{0k}(t)\exp\left\{\gamma_k^\top w_{ik} + \sum_{p=1}^{P} \alpha_{pk}^d \int_0^t f_{ip}(s)ds\right\}, \tag{5.2.3}$$

where $f'_{ip}(t) = \frac{\mathrm{d}f_{ip}(t)}{\mathrm{d}t}$ is the first order derivative of the $f_{ip}(t)$ function.

Model M_1 postulates that the risk for an event at time t depends on the mean level of the markers at the same time point t. Model M_2 is an extension of model M_1 in which not only the current value but also the slopes of the longitudinal trajectories at time t are related to the hazard. Yet another option is to relate the survival outcomes with a summary of the whole history of the markers, where as summary we take the area under the longitudinal profiles (model M_3).

Combinations of these parameterizations are possible, where in the case of $P = P_1 + P_2$ longitudinal outcomes we could have:

$$h_{ik}(t,\theta_s) \quad = \quad h_{0k}(t)\exp\left\{\gamma_k^\top w_{ik} + \sum_{p_1=1}^{P_1} \alpha_{p_1 k} f_{ip_1}(t) + \sum_{p_2=1}^{P_2} \alpha_{p_2 k}^d \int_0^t f_{ip_2}(s)ds\right\},$$

where the risk for an event at time t is associated with the underlying value of P_1 biomarkers at a specific time point and the area under the curve for P_2 biomarkers. Furthermore, different structure could be assumed for each survival model. A big range of combined models will improve the efficiency of BMA and therefore more accurate predictions will be provided.

5.2.2 Bayesian Estimation and Prior Specification

For the estimation of our joint model's parameters, we adopt a Bayesian formulation and derive posterior inferences using a Markov chain Monte Carlo (MCMC) algorithm. The likelihood of the model is derived under the assumption that the random effects account for all dependencies between the observed outcomes. Specifically, given the random effects, the longitudinal and survival processes are assumed independent and moreover, the longitudinal responses of each subject are assumed independent. In particular,

$$p(y_i, T_i, \delta_i \mid b_i; \theta) = \prod_{p=1}^{P} p(y_{ip} \mid b_{ip}, \theta_{y_p}) p\{T_i, \delta_i \mid f_{ip}(.), \theta_s\}, \tag{5.2.4}$$

$$p(y_{ip} \mid b_{ip}; \theta_{y_p}) = \prod_{j=1}^{n_{ip}} p(y_{ipj} \mid b_{ip}; \theta_{y_p}), \tag{5.2.5}$$

where $\theta = (\theta_{y_p}^T, \theta_s^T)^T$ denotes the parameter vector for the longitudinal and survival outcomes. Thus, the posterior distribution is written as

$$p(\theta \mid y_{ip}, T_i, \delta_i) \propto \prod_{p=1}^{P} \prod_{j=1}^{n_{ip}} p(y_{ipj} \mid b_{ip}, \theta_{y_p}) p\{T_i, \delta_i \mid f_{ip}(.), \theta_s\} p(b_{ip} \mid \theta_{y_p}) p(\theta_{y_p}) p(\theta_s).$$

The likelihood contribution from the exponential family takes the form

$$p(y_{ip} \mid b_{ip}, \theta_{y_p}) = \exp\left\{ \sum_{j=1}^{n_{ip}} \left[y_{ipj} \psi_{ipj}(b_{ip}) - c\{\psi_{ipj}(b_{ip})\}/a(\phi) - d(y_{ipj}, \phi) \right] \right\},$$

where $\psi_{ipj}(b_{ip})$ and ϕ denote the natural and dispersion parameters in the exponential family, respectively, and $c(.)$, $d(.)$ and $a(.)$ are known functions specifying the member of the exponential family. The likelihood contribution of the survival model when assuming the parametrization of model (5.2.1) is given by

$$\begin{aligned} &p\{T_i, \delta_i \mid f_{ip}(.), \theta_s\} = \\ &\prod_{k=1}^{K} \left[\exp\left\{ \sum_q \gamma_{h_{0k},q} B_q(T_i, t_q) + \gamma_k^\top w_{ik} + \sum_{p=1}^{P} \alpha_{pk} f_{ip}(T_i) \right\}^{I(\delta_i = k)} \times \right. \\ &\left. \exp\left(-\exp(\gamma_k^\top w_{ik}) \int_0^{T_i} \exp\left\{ \sum_q \gamma_{h_{0k},q} B_q(s, t_q) + \sum_{p=1}^{P} \alpha_{pk} f_{ip}(s) \right\} ds \right) \right]. \end{aligned}$$

The integral in the definition of the survival function does not have a closed-form solution, and therefore we used a 15-point Gauss-Kronrod quadrature rule to approximate it (Press et al., 2007).

We use standard prior distributions for the parameters. In particular, for the regression coefficients β_p, the survival coefficients γ_k, the association coefficients α_{pk} and the baseline hazards for the survival submodel $\gamma_{h_{0k},q}$, normal priors are taken with mean *0* and variance *100*. For the variance–covariance matrix D of the random effects we take inverse Wishart prior with an identity scale matrix and 6 degrees of freedom. Finally, for variance parameters (e.g. for normal longitudinal outcomes) inverse gamma priors are taken with parameters that are based on the separate analysis per outcome.

All computations have been performed in R (version 3.0.1) and JAGS (version 3.3.0) and is available upon request from the first author.

5.3 Dynamic Survival Predictions

5.3.1 Predictions from a Single Model

Based on the joint models presented in Section 5.2.1, we focus on the derivation of the predictions of the survival outcomes. More specifically, we would like to predict cumulative incidence probabilities for a new patient l that has provided us with a set of longitudinal measurements $\tilde{Y}_{lp}(t) = \{y_{lp}(s_{p1}), \ldots, y_{lp}(s_{pnl}); 0 \leq s_{p1} < s_{p2} < \cdots < s_{pnl} < t, p = 1, \ldots, P\}$. Given that no event occurred up to t, it is more relevant to focus on the cumulative incidence probabilities at time $u > t$. To account for competing risks we work with the cumulative incidence function:

$$\pi_{lk}(u,t) = \mathrm{P}(T^*_{lk} < u \mid \cup_{k=1}^{K} T^*_{lk} > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{lP}(t), D_n),$$

where $D_n = \{T_i, \delta_i, y_{i1}, \ldots, y_{iP}; i = 1, \ldots, n\}$ denotes the sample on which the joint model was fitted.

Under the Bayesian formulation of the joint model, the estimation of $\pi_{lk}(u,t)$ is based on the corresponding posterior predictive distributions, namely

$$\pi_{lk}(u,t) = \int \mathrm{P}(T^*_{lk} < u \mid \cup_{k=1}^{K} T^*_{lk} > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{lP}(t); \theta) p(\theta \mid D_n) d\theta. \tag{5.3.6}$$

Using the full conditional independence assumption (5.2.4), the first term of the integrand in (5.3.6) can be written as

$$\begin{aligned}
&\mathrm{P}(T^*_{lk} < u \mid \cup_{k=1}^{K} T^*_{lk} > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{lP}(t); \theta) = \\
&\quad \int \mathrm{P}(T^*_{lk} < u \mid \cup_{k=1}^{K} T^*_{lk} > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{1P}(t), b_{lp}; \theta) \times \\
&\quad p(b_{lp} \mid \cup_{k=1}^{K} T^*_{lk} > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{lP}(t); \theta) db = \\
&\quad \int \mathrm{P}(T^*_{lk} < u \mid \cup_{k=1}^{K} T^*_{lk} > t, b_{lp}; \theta) p(b_{lp} \mid \cup_{k=1}^{K} T^*_{lk} > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{lP}(t); \theta) db.
\end{aligned}$$

Furthermore,

$$\int \mathrm{P}(T_{lk}^* < u \mid \cup_{k=1}^K T_{lk}^* > t, b_{lp}; \theta) p(b_{lp} \mid \cup_{k=1}^K T_{lk}^* > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{lP}(t); \theta) db =$$
$$\int \frac{\mathrm{P}(T_{lk}^* < u, \cup_{k=1}^K T_{lk}^* > t \mid b_{lp}; \theta)}{\mathrm{P}(\cup_{k=1}^K T_{lk}^* > t \mid b_{lp}; \theta)} p(b_{lp} \mid \cup_{k=1}^K T_{lk}^* > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{lP}(t); \theta) db =$$
$$\int \frac{CIF(u,t)}{S(t)} p(b_{lp} \mid \cup_{k=1}^K T_{lk}^* > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{lP}(t); \theta) db,$$

where $S(.)$ denotes the overall survival and $CIF(.) = \int_t^u h_{lk}(s)S(s)ds$ the cumulative incidence function. The second term of the integrant (5.3.6), $p(\theta \mid D_n)$, is the posterior distribution of the parameters given the observed data.

Here we can obtain a Monte Carlo estimate of $\pi_{lk}(u,t)$ using the following simulation scheme:

1. Draw θ^* from the MCMC sample of the posterior $p(\theta \mid D_n)$
2. Draw b_{lp}^* from $p(b_{lp} \mid \cup_{k=1}^K T_{lk}^* > t, \tilde{Y}_{l1}(t), \ldots, \tilde{Y}_{lP}(t); \theta^*)$
3. Compute $\pi_{lk}(u,t,b_{lp}^*; \theta^*) = CIF(u,t,b_{lp}^*; \theta^*)/S(t,b_{lp}^*; \theta^*)$,

We, then, repeat steps 1-3 H times and derive the estimates of the $\pi_{lk}(u,t)$ as,

$$\hat{\pi}_{lk}(u,t) = \frac{1}{H} \sum_{h=1}^{H} \pi_{lk}^{(h)}(u,t)$$

Moreover, a 95% credible interval (CI) can be obtained using the Monte Carlo sample percentiles.

5.3.2 Combined Predictions using Bayesian Model Averaging

As it was seen in Section 5.2.1, there are several ways to link the longitudinal and the survival outcomes. Moreover, we could even postulate additional joint models with different assumptions for each submodel. For instance, in some of the mixed models the subject-specific evolutions over time may be nonlinear, or we could control for different sets of baseline covariates either in the mixed-effects or relative-risk submodels. In this complex setting, a common practice is to choose a single model based on information criteria and obtain predictions from that selected model. However, this approach ignores model uncertainty. In addition, there may be different models that provide more accurate predictions for different types of subjects. An alternative solution to this problem is BMA, which proceeds by estimating a number of models and constructing a weighted average of predictions (Hoeting et al., 1999; Rizopoulos et al., 2014).

More formally, following the notation in Section 5.3.1, we would like to obtain predictions of the conditional probabilities $\pi_{lk}(u,t)$, $u > t$, for a new patient l who has provided us with a set of longitudinal outcomes $\tilde{Y}_{lp}(t) = \{y_{lp}(s_{p1}), \ldots, y_{lp}(s_{pnl}); 0 \leq s_{p1} < s_{p2} < \cdots < s_{pnl} < t, p = 1, \ldots, P\}$. Assuming models $M_1, \ldots, M_\Omega$, the averaged conditional cumulative probabilities of patient l occurring an event at time u, given that he did not have any event up to time t is given by:

$$\mathrm{P}(T^*_{lk} < u \mid \cup_{k=1}^{K} T^*_{lk} > t, D_l(t), D_n) = \sum_{\omega=1}^{\Omega} \mathrm{P}(T^*_{lk} < u \mid \cup_{k=1}^{K} T^*_{lk} > t, M_\omega, D_l(t), D_n) p(M_\omega \mid D_l(t), D_n),$$

where $D_n = \{T_i, \delta_i, y_{i1}, \ldots, y_{iP}; i = 1, \ldots, n\}$ denotes the sample on which the joint models were fitted and $D_l(t) = \{\tilde{Y}_{lp}(t), \cup_{k=1}^{K} T^*_{lk} > t\}$ denotes the data of the new patient l. The first term of the above equation denotes the conditional cumulative probabilities per model and the second term denotes the posterior weights of each of the models. To calculate the posterior probability of the models we use Bayes rule as

$$p(M_\omega \mid D_l(t), D_n) = \frac{p(D_l(t) \mid M_\omega) p(D_n \mid M_\omega) p(M_\omega)}{\sum_{q=1}^{\Omega} p(D_l(t) \mid M_q) p(D_n \mid M_q) p(M_q)},$$

where

$$p(D_l(t) \mid M_\omega) = \int p(D_l(t) \mid \theta_\omega) p(\theta_\omega \mid M_\omega) d\theta_\omega = \int \prod_{p=1}^{P} p(\tilde{Y}_{lp}(t) \mid b_{lp}, \theta_\omega) p(T_l, \delta_l \mid b_{lp}, \theta_\omega) p(b_{lp} \mid \theta_\omega) p(\theta_\omega \mid M_\omega) d\theta_\omega,$$

and

$$p(D_n \mid M_\omega) = \int p(D_n \mid \theta_\omega) p(\theta_\omega \mid M_\omega) d\theta_\omega = \int \prod_{p=1}^{P} p(y_{ip}(t) \mid b_{ip}, \theta_\omega) p(T_i, \delta_i \mid b_{ip}, \theta_\omega) p(b_{ip} \mid \theta_\omega) p(\theta_\omega \mid M_\omega) d\theta_\omega,$$

where $p(D_l(t) \mid \theta_\omega)$ and $p(D_n \mid \theta_\omega)$ are the likelihood functions for the new patient and for all the patients, respectively. Furthermore, $p(\theta_\omega \mid M_\omega)$ is the prior density of θ_ω under model M_ω. $p(D_l(t) \mid M_\omega)$ and $p(D_n \mid M_\omega)$ are obtained by means of Laplace approximations. Specifically we first integrate out the random effects and then the parameters. A priori we assume that all models are equally probable. A careful investigation of $p(M_\omega \mid D_l(t), D_n)$ reveals that different patients, but also different time points within the same patient could provide different weights. Thus, compared to the choice of a single model, the BMA provides predictions that are more accurate since for every patient and visit it uses the models that are more probable to describe the association between the longitudinal and survival outcomes.

Table 5.1: Posterior means, standard errors and 95 % equal tail credible intervals for the joint model fitted for the cardio data when assuming model M11

	Mean	SE	2.5%	97.5%
Longitudinal process (aortic gradient)				
Intercept	2.91	0.09	2.74	3.07
ns(Time, 3)1	1.40	0.20	1.00	1.78
ns(Time, 3)2	2.86	0.34	2.22	3.55
ns(Time, 3)3	2.88	0.41	2.12	3.74
Age	−0.25	0.06	−0.36	−0.13
Sex (female)	0.19	0.12	−0.04	0.41
Precision	2.88	0.18	2.54	3.24
Longitudinal process (aortic regurgitation)				
Intercept	2.85	0.30	2.27	3.46
cohortY<=1	−1.90	0.21	−2.33	−1.50
cohortY<=2	−5.52	0.30	−6.14	−4.95
cohortY<=3	−9.52	0.46	−10.49	−8.63
cohortY<=4	−14.07	0.87	−16.34	−12.80
Time	0.25	0.04	0.17	0.34
Age	−0.33	0.22	−0.74	0.10
Sex (female)	0.73	0.38	0.001	1.48
Survival process (death)				
Age	0.88	0.17	0.56	1.22
Type of operation (root replacement)	0.75	0.36	0.06	1.48
α_{AoG}	−0.42	0.15	−0.73	−0.13
α_{AoR}	0.09	0.03	0.04	0.15
Survival process (reoperation)				
Age	−0.41	0.16	−0.72	−0.10
Type of operation (root replacement)	0.57	0.31	−0.01	1.20
α_{AoG}	0.34	0.09	0.16	0.51
α_{AoR}	0.10	0.03	0.05	0.16
DIC				−5910.9

ns = natural splines; AoG = aortic gradient; AoR = aortic regurgitation; SD = standard deviation; DIC = deviance information criterion

5.4 Analysis of the Valve Dataset

In this Section we present the analysis of the cardio data introduced in Section 5.1. Our interest is to derive subject-specific risk predictions using all available information for a patient. We first started our analysis by fitting a set of joint models with different association structures and different baseline covariates. More specifically, for the linear mixed-effects model many patients show nonlinear longitudinal trajectories and therefore, we assumed natural cubic spline for time with two internal knots (λ) at 2.1 and 5.5 year (corresponding to 33.3% and 66.7% of the observed follow-up times) in both fixed and random part in the mixed-effects model of aortic gradient. Furthermore, we corrected for age (after we standardize it) and gender. Since there are more clinical relevant baseline covariates that have an effect on aortic gradient, we fitted a second mixed-effects model including also:

Table 5.2: Posterior means, standard errors and 95 % equal tail credible intervals for the joint model fitted for the cardio data when assuming model M12

	Mean	SE	2.5%	97.5%
Longitudinal process (aortic gradient)				
Intercept	3.31	0.14	3.02	3.59
ns(Time, 3)1	1.42	0.19	1.05	1.80
ns(Time, 3)2	2.89	0.30	2.31	3.50
ns(Time, 3)3	2.91	0.36	2.23	3.64
Age	−0.31	0.06	−0.43	−0.20
Sex (female)	0.10	0.12	−0.13	0.33
Type of operation (root replacement)	−0.48	0.14	−0.74	−0.22
Marfan (yes)	−0.45	0.24	−0.93	0.03
LVfunction (2)	−0.01	0.13	−0.27	0.25
LVfunction (3)	0.46	0.34	−0.21	1.12
LVfunction (4)	−0.13	0.24	−0.61	0.33
DonorAge	0.18	0.06	0.07	0.29
Diameter (mm)	−0.29	0.06	−0.41	−0.18
Precision	2.86	0.18	2.52	3.21
Longitudinal process (aortic regurgitation)				
Intercept	2.86	0.31	2.25	3.48
cohortY<=1	−1.92	0.21	−2.33	−1.50
cohortY<=2	−5.53	0.30	−6.13	−4.96
cohortY<=3	−9.51	0.45	−10.40	−8.65
cohortY<=4	−14.24	0.82	−15.92	−12.73
Time	0.25	0.04	0.18	0.34
Age	−0.30	0.20	−0.70	0.08
Sex (female)	0.74	0.41	−0.04	1.55
Survival process (death)				
Age	0.89	0.17	0.56	1.23
Type of operation (root replacement)	0.77	0.36	0.09	1.50
α_{AoG}	−0.43	0.15	−0.73	−0.14
α_{AoR}	0.10	0.03	0.04	0.16
Survival process (reoperation)				
Age	−0.40	0.15	−0.70	−0.09
Type of operation (root replacement)	0.58	0.31	−0.02	1.19
α_{AoG}	0.34	0.09	0.17	0.51
α_{AoR}	0.11	0.03	0.05	0.17
DIC				−5902.7

ns = natural splines; AoG = aortic gradient; AoR = aortic regurgitation; SD = standard deviation; DIC = deviance information criterion

marfan, left ventricular function, standardized donor age and standardize diameter of valve.

Table 5.3: Posterior means, standard errors and 95 % equal tail credible intervals for the joint model fitted for the cardio data when assuming model M21

	Mean	SE	2.5%	97.5%
Longitudinal process (aortic gradient)				
Intercept	2.90	0.08	2.74	3.05
ns(Time, 3)1	1.56	0.18	1.21	1.92
ns(Time, 3)2	3.59	0.37	2.88	4.34
ns(Time, 3)3	4.04	0.55	3.01	5.17
Age	−0.23	0.06	−0.34	−0.11
Sex (female)	0.23	0.12	−0.01	0.46
Precision	2.41	0.17	2.11	2.78
Longitudinal process (aortic regurgitation)				
Intercept	2.81	0.32	2.19	3.46
cohortY<=1	−1.91	0.21	−2.33	−1.50
cohortY<=2	−5.55	0.31	−6.16	−4.96
cohortY<=3	−9.55	0.46	−10.46	−8.70
cohortY<=4	−14.25	0.81	−15.91	−12.74
Time	0.28	0.04	0.20	0.36
Age	−0.30	0.20	−0.69	0.09
Sex (female)	0.75	0.41	−0.04	1.57
Survival process (death)				
Age	1.18	0.23	0.77	1.66
Type of operation (root replacement)	0.67	0.38	−0.07	1.45
α_{AoG}	−0.94	0.27	−1.52	−0.47
α_{AoR}	0.09	0.03	0.04	0.16
α^d_{AoG}	10.67	3.74	4.16	18.85
α^d_{AoR}	−0.36	0.32	−1.09	0.20
Survival process (reoperation)				
Age	−0.29	0.20	−0.67	0.10
Type of operation (root replacement)	0.64	0.36	−0.03	1.37
α_{AoG}	−0.31	0.26	−0.87	0.15
α_{AoR}	0.12	0.03	0.06	0.19
α^d_{AoG}	9.06	3.70	2.90	17.40
α^d_{AoR}	−0.24	0.28	−0.87	0.24
DIC				−6154.6

ns = natural splines; AoG = aortic gradient; AoR = aortic regurgitation; SD = standard deviation; DIC = deviance information criterion

Particularly, the linear mixed-effects models take the form

$$y_{1i}(t) = \begin{cases} f_{1ia}(t) + \varepsilon_i(t) = \beta_{10a} + Age_i\beta_{11a} + Sex_i\beta_{12a} + \sum_{v=1}^{V} ns(t,\lambda)\beta_{1(v+2)a} + \\ b_{10ia} + \sum_{v=1}^{V} ns(t,\lambda)b_{1via}, \\ \\ f_{1ib}(t) + \varepsilon_i(t) = \beta_{10b} + Age_i\beta_{11b} + Sex_i\beta_{12b} + TypeOp_i\beta_{13b} + Marfan_i\beta_{14b} + \\ LVfrac_i\beta_{15b} + DonAg_i\beta_{16b} + Diam_i\beta_{17b} + \sum_{v=1}^{V} ns(t,\lambda)\beta_{1(v+7)b} + \\ b_{10ib} + \sum_{v=1}^{V} ns(t,\lambda)b_{1vib}, \end{cases}$$

Table 5.4: Posterior means, standard errors and 95 % equal tail credible intervals for the joint model fitted for the cardio data when assuming model M22

	Mean	SE	2.5%	97.5%
Longitudinal process (aortic gradient)				
Intercept	3.34	0.13	3.08	3.59
ns(Time, 3)1	1.50	0.18	1.16	1.84
ns(Time, 3)2	3.72	0.36	3.01	4.44
ns(Time, 3)3	4.36	0.56	3.29	5.47
Age	−0.30	0.05	−0.40	−0.19
Sex (female)	0.16	0.11	−0.06	0.38
Type of operation (root replacement)	−0.50	0.13	−0.75	−0.25
Marfan (yes)	−0.60	0.23	−1.05	−0.15
LVfunction (2)	−0.04	0.13	−0.28	0.20
LVfunction (3)	0.32	0.31	−0.29	0.94
LVfunction (4)	−0.13	0.23	−0.58	0.32
DonorAge	0.19	0.05	0.09	0.29
Diameter (mm)	−0.29	0.05	−0.40	−0.18
Precision	2.29	0.14	2.03	2.60
Longitudinal process (aortic regurgitation)				
Intercept	2.81	0.32	2.20	3.45
cohortY<=1	−1.91	0.21	−2.33	−1.50
cohortY<=2	−5.56	0.31	−6.17	−4.96
cohortY<=3	−9.56	0.46	−10.49	−8.68
cohortY<=4	−14.26	0.81	−15.90	−12.79
Time	0.29	0.04	0.21	0.37
Age	−0.29	0.20	−0.68	0.11
Sex (female)	0.73	0.40	−0.05	1.51
Survival process (death)				
Age	1.24	0.24	0.79	1.76
Type of operation (root replacement)	0.43	0.43	−0.40	1.27
α_{AoG}	−1.16	0.28	−1.72	−0.64
α_{AoR}	0.09	0.03	0.04	0.16
α^d_{AoG}	14.38	3.78	7.22	22.27
α^d_{AoR}	−0.59	0.35	−1.37	0.01
Survival process (reoperation)				
Age	−0.26	0.22	−0.68	0.16
Type of operation (root replacement)	0.53	0.39	−0.25	1.30
α_{AoG}	−0.52	0.26	−1.07	−0.04
α_{AoR}	0.12	0.03	0.06	0.20
α^d_{AoG}	12.73	3.85	5.61	20.96
α^d_{AoR}	−0.47	0.32	−1.20	0.07
DIC				−5981.1

ns = natural splines; AoG = aortic gradient; AoR = aortic regurgitation; SD = standard deviation; DIC = deviance information criterion

where $ns(t, \lambda)$ denotes the natural cubic spline matrix with two internal knots. For the CR mixed-effects model of aortic regurgitation we assumed linear time at the fixed part and a random intercept and slope at the random part. Finally, we corrected for age (after we standardized it) and gender. The CR mixed-effects model after the transformation of the

Table 5.5: Posterior means, standard errors and 95 % equal tail credible intervals for the joint model fitted for the cardio data when assuming model M31

	Mean	SE	2.5%	97.5%
Longitudinal process (aortic gradient)				
Intercept	2.91	0.08	2.75	3.08
ns(Time, 3)1	1.39	0.18	1.04	1.76
ns(Time, 3)2	2.82	0.29	2.27	3.39
ns(Time, 3)3	2.81	0.36	2.14	3.53
Age	−0.24	0.06	−0.36	−0.12
Sex (female)	0.19	0.12	−0.04	0.41
Precision	2.85	0.18	2.52	3.22
Longitudinal process (aortic regurgitation)				
Intercept	2.91	0.29	2.34	3.49
cohortY<=1	−1.87	0.21	−2.28	−1.46
cohortY<=2	−5.48	0.29	−6.06	−4.93
cohortY<=3	−9.43	0.41	−10.30	−8.66
cohortY<=4	−13.85	0.71	−15.71	−12.70
Time	0.21	0.04	0.14	0.28
Age	−0.31	0.20	−0.73	0.07
Sex (female)	0.86	0.41	0.09	1.69
Survival process (death)				
Age	0.85	0.16	0.54	1.17
Type of Operation (root replacement)	0.30	0.32	−0.32	0.93
α^d_{AoG}	−0.05	0.02	−0.08	−0.01
α^d_{AoR}	0.003	0.002	−0.001	0.007
Survival process (reoperation)				
Age	−0.62	0.14	−0.89	−0.35
Type of operation (root replacement)	0.09	0.27	−0.45	0.63
α^d_{AoG}	0.03	0.01	0.01	0.05
α^d_{AoR}	0.001	0.002	−0.002	0.004
DIC				−6139.6

ns = natural splines; AoG = aortic gradient; AoR = aortic regurgitation; SD = standard deviation; DIC = deviance information criterion

ordinal outcome takes the form

$$\mathrm{P}(y^*_{2i}(t) = 1 \mid y^*_{2i}(t) \leq 1, Age, Sex, t, b_{20}, b_{21}) = \frac{\exp\{f_{2i}(t)\}}{1+\exp\{f_{2i}(t)\}} = \frac{\exp\left(\sum_{s=0}^{4}\beta_{2s} + Age_i\beta_{25} + Sex_i\beta_{26} + t\beta_{27} + b_{20i} + tb_{21i}\right)}{1+\exp\left(\sum_{s=0}^{4}\beta_{2s} + Age_i\beta_{25} + Sex_i\beta_{26} + t\beta_{27} + b_{20i} + tb_{21i}\right)}.$$

Table 5.6: Posterior means, standard errors and 95 % equal tail credible intervals for the joint model fitted for the cardio data when assuming model M32

	Mean	SE	2.5%	97.5%
Longitudinal process (aortic gradient)				
Intercept	3.31	0.13	3.06	3.57
ns(Time, 3)1	1.40	0.18	1.06	1.76
ns(Time, 3)2	2.81	0.29	2.26	3.39
ns(Time, 3)3	2.80	0.35	2.13	3.52
Age	−0.31	0.06	−0.42	−0.19
Sex (female)	0.11	0.11	−0.12	0.33
Type of operation (root replacement)	−0.50	0.13	−0.76	−0.24
Marfan (yes)	−0.42	0.24	−0.90	0.05
LVfunction (2)	0.02	0.14	−0.24	0.29
LVfunction (3)	0.47	0.35	−0.22	1.13
LVfunction (4)	−0.11	0.24	−0.57	0.38
DonorAge	0.18	0.06	0.07	0.29
Diameter (mm)	−0.29	0.06	−0.40	−0.18
Precision	2.83	0.18	2.48	3.19
Longitudinal process (aortic regurgitation)				
Intercept	2.91	0.32	2.32	3.56
cohortY<=1	−1.88	0.21	−2.30	−1.47
cohortY<=2	−5.50	0.31	−6.13	−4.91
cohortY<=3	−9.48	0.46	−10.40	−8.61
cohortY<=4	−13.99	0.79	−15.63	−12.50
Time	0.21	0.04	0.14	0.29
Age	−0.30	0.20	−0.70	0.08
Sex (female)	0.86	0.42	0.05	1.71
Survival process (death)				
Age	0.85	0.16	0.54	1.18
Type of Operation (root replacement)	0.30	0.31	−0.31	0.93
α^d_{AoG}	−0.05	0.02	−0.08	−0.01
α^d_{AoR}	0.003	0.002	−0.001	0.007
Survival process (reoperation)				
Age	−0.62	0.14	−0.90	−0.36
Type of operation (root replacement)	0.09	0.27	−0.44	0.63
α^d_{AoG}	0.03	0.01	0.01	0.05
α^d_{AoR}	0.001	0.002	−0.002	0.005
DIC				−6240.2

ns = natural splines; AoG = aortic gradient; AoR = aortic regurgitation; SD = standard deviation; DIC = deviance information criterion

For the survival models we used proportional hazards models assuming B-splines for the baseline hazard function as described in Section 5.2.1. Standardized age and type of operation are important clinical factors and thus were included as confounders. Moreover, to keep the analysis simple we assumed the same functional form for the longitudinal outcomes and the same model for each survival outcomes. Specifically, the joint models that we fitted take the form

$$
\begin{aligned}
M_{11} : h_{ik}(t,\theta_s) &= h_{0k}(t)\exp\{\gamma_{1k}Age_i + \gamma_{2k}TypeOp_i + \alpha_{1k}f_{1ia}(t) + \alpha_{2k}f_{2i}(t)\},\\
M_{12} : h_{ik}(t,\theta_s) &= h_{0k}(t)\exp\{\gamma_{1k}Age_i + \gamma_{2k}TypeOp_i + \alpha_{1k}f_{1ib}(t) + \alpha_{2k}f_{2i}(t)\},\\
M_{21} : h_{ik}(t,\theta_s) &= h_{0k}(t)\exp\{\gamma_{1k}Age_i + \gamma_{2k}TypeOp_i + \alpha_{1k}f_{1ia}(t) + \alpha^d_{1k}f'_{1ia}(t) +\\
&\quad \alpha_{2k}f_{2i}(t) + \alpha^d_{2k}f'_{2i}(t)\},\\
M_{22} : h_{ik}(t,\theta_s) &= h_{0k}(t)\exp\{\gamma_{1k}Age_i + \gamma_{2k}TypeOp_i + \alpha_{1k}f_{1ib}(t) + \alpha^d_{1k}f'_{1ib}(t) +\\
&\quad \alpha_{2k}f_{2i}(t) + \alpha^d_{2k}f'_{2i}(t)\},\\
M_{31} : h_{ik}(t,\theta_s) &= h_{0k}(t)\exp\{\gamma_{1k}Age_i + \gamma_{2k}TypeOp_i + \alpha^d_{1k}\int_0^t f_{1ia}(s)ds +\\
&\quad \alpha^d_{2k}\int_0^t f_{2i}(s)ds\},\\
M_{32} : h_{ik}(t,\theta_s) &= h_{0k}(t)\exp\{\gamma_{1k}Age_i + \gamma_{2k}TypeOp_i + \alpha^d_{1k}\int_0^t f_{1ib}(s)ds +\\
&\quad \alpha^d_{2k}\int_0^t f_{2i}(s)ds\}.
\end{aligned}
$$

We run the MCMC with single chains for 550,000 iterations for all models and we discarded 50,000 iterations as burn-in. Convergence was monitored by trace plots and the Geweke diagnostic test. Tables 5.1, 5.2, 5.3, 5.4, 5.5 and 5.6 show the posterior means, standard errors and corresponding 95% credible intervals for the parameters of the longitudinal and survival submodels, respectively. As it can be seen, age is significantly associated with death in all models and with reoperation in models M_{11}, M_{12}, M_{31} and M_{32} where the survival outcomes are associated with the true value and the area under the curve of the biomarkers. Moreover, type of operation seems to be a significant factor for death in models M_{11} and M_{12}. Furthermore, the underlying value, the slope and the area under the curve of aortic gradient seem to be associated with death in both models with the less and extra baseline covariates in the mixed-effect model while only M_{21} showed a non significant association of the underlying value with reoperation. Finally, from models M_{11}, M_{12}, M_{21} and M_{22} we obtain that the underlying value of aortic regurgitation is a significant factor for death and reoperation. In addition, we use the deviance information criterion (DIC) to compare the models. Specifically, from Tables 5.1, 5.2, 5.3, 5.4, 5.5 and 5.6 model M_{32} appears to provide better fit to the data.

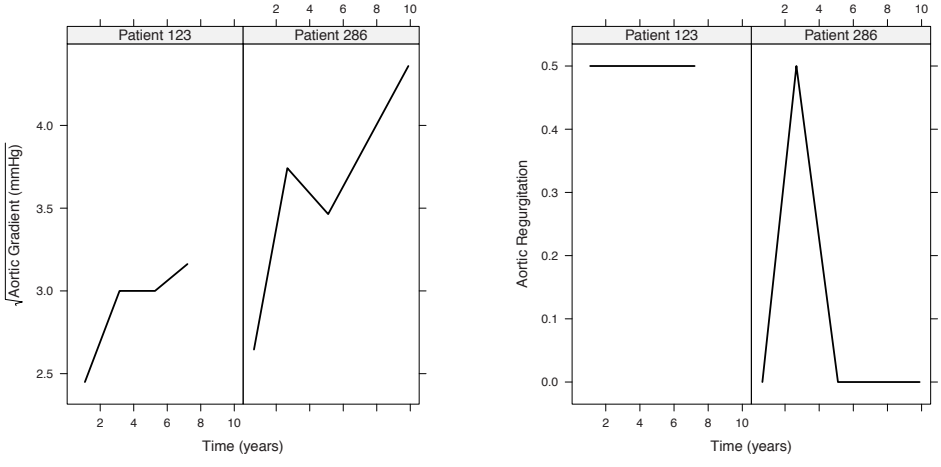

Figure 5.1: Profile plots of aortic gradient and aortic regurgitation for patient 123 and 286

We continued by calculating dynamic predictions based on the models described above. Under the fitted joint models, the conditional probabilities of death and reoperation were estimated using the Monte Carlo procedure, as described in Section 5.3.1, with $H = 300$. Specifically, we derived the predictions of two patients, patient 123 (47 year old male) and patient 286 (52 year old male), that were excluded from the dataset when fitting the joint models. In Figure 5.1, we present the longitudinal trajectories of these patients. As it can be seen, both patients show an increasing aortic gradient profile over time, but, patient 286 has higher values than patient 123. For aortic regurgitation, only patient 286 seems to change category at the second follow-up. We show the predictions of every joint model of death and reoperation for patients 123 and 286 in Figure 5.2 and 5.3, as more longitudinal measurements are available. For patient 123, when using the underlying value of aortic gradient and aortic regurgitation in the survival models (for both the model with less M_{11} and more covariates M_{12} as confounder in the longitudinal part), the conditional probabilities of death are much smaller than reoperation. The same can be seen when assuming the area under the curve model with the extra confounders M_{32}. However, when assuming the slope parameterization and the area under the curve parameterization (for the model without the extra clinical relevant covariates) the difference between the survival and free intervention probabilities is smaller (M_{21}, M_{22} and M_{31}). Specifically, the probabilities of death and reoperation seem to cross in model M_{21} while, in model M_{22} are both really small. For patient 286, a bigger difference between the death and survival probabilities is observed in model M_{31} compared to patient 123. Furthermore, in model M_{21} it is clear that the probability of death is higher the next five

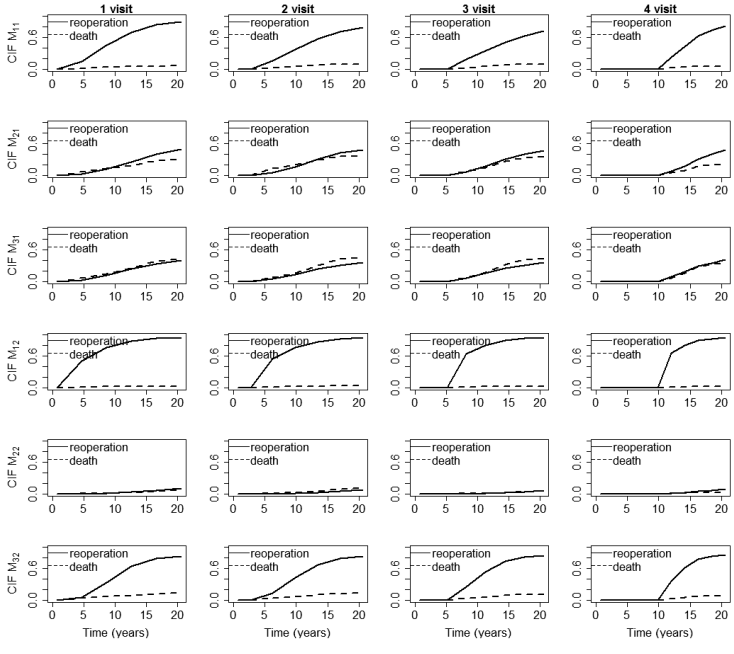

Figure 5.2: Prediction plots for patient 123 using each joint model proposed. CIF = Cumulative Incidence Function

years at the first two visits.

Table 5.7: BMA posterior weights for the six proposed joint models for patient 123 and 286 for each measurement

Patient	Time	M_{11}	M_{21}	M_{31}	M_{12}	M_{22}	M_{32}
123	1.09	0.00	0.00	0.00	0.00	0.00	1.00
123	3.15	0.00	0.00	0.00	0.82	0.00	0.18
123	5.27	0.00	0.00	0.00	0.89	0.00	0.11
123	7.20	0.00	0.00	0.00	0.00	0.00	1.00
286	0.67	0.00	0.00	0.00	0.67	0.00	0.33
286	2.67	0.00	0.00	0.00	0.00	0.00	1.00
286	5.10	0.00	0.00	0.00	0.00	0.00	1.00
286	9.89	0.00	0.00	0.00	0.01	0.00	0.99

Following, we computed the posterior weight for each model and calculate the BMA

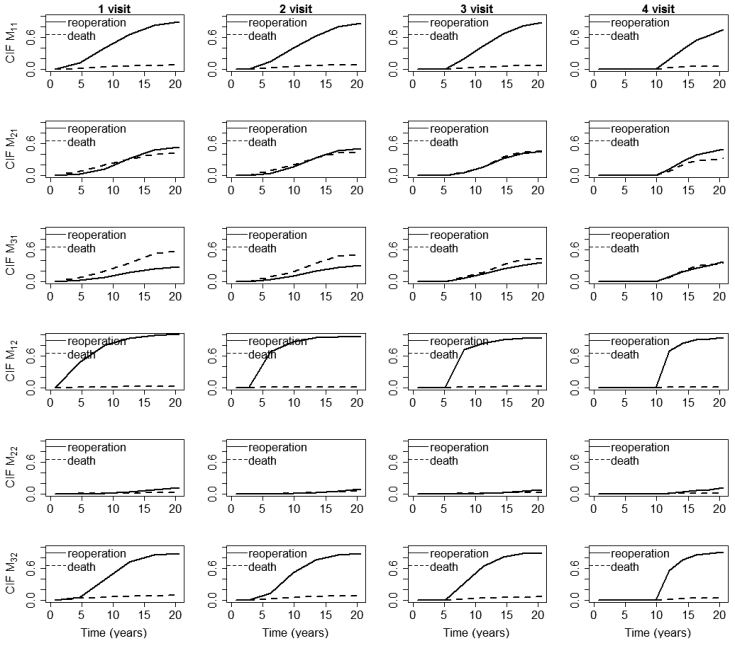

Figure 5.3: Prediction plots for patient 286 using each joint model proposed. CIF = Cumulative Incidence Function

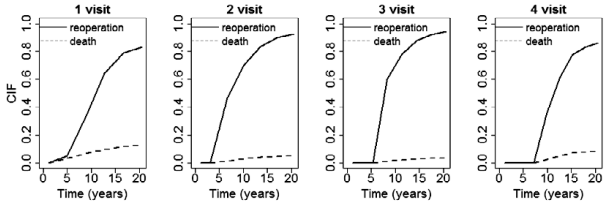

Figure 5.4: Prediction plots for patient 132 using Bayesian model averaging. CIF = Cumulative Incidence Function

predictions. In Table 5.7 we present the weights of the models for each patient and visit. It is clear that not always a single model provides the best prediction. Specifically, models M_{12} and M_{32} seem to contribute in the BMA predictions depending on the patient and the visit. As it can be seen, even within the same patient the choice of the best model could change over time. In particular, for patient 123 at the first and last visit we observe that only model M_{32} provides

Figure 5.5: Prediction plots for patient 286 using Bayesian model averaging. CIF = Cumulative Incidence Function

better predictions. However, for the second and third visit we obtain a higher contribution for model M_{12}. This could be explained by the fact that the square root of aortic gradient of the specific patient remains the same for visit 2 and 3, thus the underlying value provides us with enough information. Furthermore, for patient 286 we obtain that model M_{12} contributes 67% and model M_{32} 33% at the calculation of the predictions at visit one. After the first visit M_{32} is chosen to be the most appropriate model. From the profile plots, we obtain a decrease of the square root aortic gradient from visit 2 to 3 and an increased aortic regurgitation at visit 2, therefore the whole evolution of the outcome may be a better predictor after the second visit. In Figure 5.4 and 5.5, which present the combined predictions, we obtain high probabilities for reoperation and low for death for both patients. This is explained by the fact that both models M_{12} and M_{32} indicate the same behavior.

5.5 Discussion

Risk predictions for patients with severe valve diseases that are updated as more longitudinal measurements become available over time, provide the physician with an evidence-based understanding of disease progression. Importantly, the calculated probabilities for survival and reintervention can be used as an early warning system, allowing the necessary time for the physicians to plan an intervention. In this work we presented dynamic predictions for a competing risks setting using multiple longitudinal outcomes. Specifically, we performed different functional forms to relate the longitudinal and the survival processes and different structure (by adding clinical relevant baseline covariates) of one longitudinal model and investigate the predictions of two patients that we originally excluded from the dataset. Finally, since the choice of a single model ignores the model uncertainty issue, we combined all models and derive predictions for the survival outcomes for the same two patients using the BMA. This method explicitly accounts for model uncertainty and for the fact that not all future patients have the same prognostic model. Despite the usefulness of the BMA approach, caution is needed with respect to some issues. In particular, the specification of the prior distribution of the models is challenging and has received little

attention. Moreover, the number of models that could be combined may be high resulting to difficulties in calculating the summation. We should, furthermore, make clear that we cannot identify the true model from the pool of all candidate models.

We limited our work so that the association between aortic gradient and aortic regurgitation with the survival outcomes was the same. However, a different functional form for each biomarker would be also possible and interesting to investigate. A disadvantage, however, is that it will be more computational intensive, since more models should be performed. Moreover, additional ways to link the longitudinal and survival processes, such as the weighted area under the curve, the lag effect and the shared random effect parameterization, were not addressed in this paper. Nevertheless, a bigger dataset with patients followed for a longer period is probably needed in order to obtain a variety of evolutions and capture the special characteristics of the patients. Furthermore, we performed models including extra confounders only for the continuous longitudinal outcome. Hence, more factors in the model of the ordinal outcome and also of the survival outcomes could be included and further investigated. Finally, in this paper we did not perform any formal validation of the derived predictions. Measures for the evaluation of calibration and discrimination of prognostic survival models can be easily adapted to the competing risks setting (Schoop et al., 2011; Gail and Pfeiffer, 2005). Within the joint modelling framework, calibration and discrimination has been previously introduced (Rizopoulos, 2011; Proust-Lima and Taylor, 2009). However to our knowledge these proposed measures of calibration and discrimination are not directly applicable on competing risk settings. Thus, validation in that setting may be an interesting topic for future research.

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CHAPTER 6

Conclusions

6.1 Summary

In this thesis, we focused on the analysis of longitudinal and time-to-event outcomes motivated by the aortic valve disease datasets. We proposed the joint modelling framework which couples repeated measurements such as aortic gradient, aortic regurgitation and brain natriuretic peptide (BNP) with survival outcomes such as death and reoperation, while accounting for the special features of the data. In Chapter 2, we introduced the mixed-effects and the joint models and we investigated the different inferences that could be obtained by comparing them with simple methods that do not account for the special features of the data. In Chapter 3, we continued with an extension of the basic joint model to handle one continuous (aortic gradient), one ordinal (aortic regurgitation) longitudinal outcome and a competing risk setting (death/reoperation). Specifically, the survival outcomes were coupled with the subject-specific profiles of both longitudinal outcomes. In Chapter 4, we focused on individualized risk predictions for future patients in the clinical setting. Specifically, we predicted death and reoperation probabilities as more BNP values became available for two new patients. In Chapter 5, we extended the concept of prediction to multiple longitudinal outcomes combined with competing risk survival outcomes and we derived the dynamically updated cumulative incidence functions. Moreover, we showed that different features of the longitudinal processes, such as time-dependent trajectory slopes and time-dependent cumulative effects, but also different baseline covariates could change the prediction for the events of interest. Finally, due to the fact that the choice of a single model ignores the model uncertainty issue, we combined all proposed models using Bayesian model averaging (BMA) to derive predictions for the survival outcomes.

6.2 Discussion

The focus of this thesis was on both methodological and applied aspects of the joint modelling framework. Specifically, we illustrated the properties of the basic joint model and proposed several extensions in order to analyze the heart valve data.

In clinical practice, physicians intuitively use only a small portion of the available information to proceed to an intervention. We showed that the whole medical history of the patients could also be incorporated in a statistical model using the joint modelling approach of longitudinal and survival data. Nevertheless, medical expertise is a key ingredient that helps to define models relevant to medical practice (e.g. the choice of the covariates and the structures). Medical experience coupled with an estimate of the survival probability of a patient that accounts for all available information, would enable physicians to make better informed decisions and thus improve clinical outcome.

The underlying assumptions of a joint model are important and need to be clearly specified. In particular, these models are built under the assumption that the random effects account for all dependencies between the observed data. That is, given the random effects

both the longitudinal outcomes as well as the repeated measurements for each outcome are independent of each other and in addition, the longitudinal outcomes are independent of the time-to-events. This conditional independence assumption is directly related to the missing data mechanism (as presented in Section 1.2.3 in Chapter 1). Thus, if this proves to be incorrect, the dropout process may still depend on the unobserved responses. The key component behind the joint models are the random effects which describe the subject-specific evolutions. In the case where a patient has an increase aortic gradient evolution over time, it is highly probable that the physician will decide that an intervention is required. The missing data mechanism implies that individuals who show steep changes are more likely to occur an event. It is obvious that after the event time point, the profile of the patient changes.

The key aspect to consider in the joint models is the association between the longitudinal and survival outcomes. However, the choice between the different parameterizations depends also on the clinical question of interest. That is, whether the focus of inference is on measuring the effect of the longitudinal covariate in the survival outcome, or on investigating the association structure between the two processes. In particular, when we are more interested in assessing the degree of association between the trend of the repeated outcomes and time-to-events as presented in Chapter 3, the random effects parametrization offers a great flexibility. Nevertheless, when we wish to accurately determine the estimate of the underlying process of the heart disease in order to obtain predictions, a further investigation is required in order to obtain the true association (Chapter 5).

6.3 Future Research

During the research on analyzing the heart valve data appropriately and therefore deriving predictions, we faced some issues and investigated approaches that could open discussions for future research.

6.3.1 Translate the Joint Models into Clinical Practice

The joint model of longitudinal and survival data can be implemented in R using the **JM** or the **JMbayes** package (Rizopoulos, 2012). Specifically, the first package performs these models under a maximum likelihood approach. Various of options are available including the specification of the association structure and the baseline hazard, competing risk settings, predictions etc. However, there are some limitations such as the analysis of a categorical longitudinal response, multiple longitudinal outcomes and recurrent events processes. The **JMbayes** package fits joint models for longitudinal and survival outcomes under a Bayesian approach and has also a various of options similar to the **JM** package. Even though it does allow for more complex outcomes (e.g. categorical, left censored), it does not facilitate the analysis of multiple longitudinal outcomes and recurrent events. In this thesis, specifically in Chapter 2 and 4, we used the **JM** package to perform joint models assuming a longitudinal

and a time-to-event outcome. For the joint models of a continuous, an ordinal longitudinal outcome and a competing risk setting presented in Chapter 3 and 5, some extra programming was required. Other packages for the joint models have been also developed. Specifically, the package **joineR** fits joint models that consider a linear mixed-effects submodel for the longitudinal data and a Cox-based submodel for the survival data, linking the submodels through common random effects. Furthermore, the package **lcmm** performs latent class joint models, where the correlation between the repeated measurements in the longitudinal outcome is captured by the random effects and the association between the longitudinal with the survival outcomes by a shared latent class indicator (Proust-Lima and Taylor, 2009).

The use of such computer intensive applications requires a high level of expertise in programming and a sound methodological background. Hence, performing the analysis, even with the use of the packages, may be not possible for everyone. Interactive web applications with friendly controls that easily incorporate plots and summaries are essential for adequate implementation of the proposed models in clinical practice. Such a tool can be build with the **shiny** package. Specifically, it translates the R code into an user-interface that thereafter can be used without requiring any knowledge in programming. A web application for obtaining predictions for future patients under the package **JMbayes** already exists. Thus, this could be extended in order to account for multiple longitudinal and survival outcomes. Such an easy web application could give the opportunity to every physician to derive updated risk predictions for new patients when more longitudinal outcomes (such as aortic gradient and aortic regurgitation) are available. Integration of such a webbased tool into the patient information system would be highly desirable to optimally support clinical decision making.

6.3.2 BMA Extensions

When investigating more than one biomarker, we assumed the same parameterization for each of them. However, an interesting extension would be to investigate combinations of association structures. This could provide optimal predictive ability, since more models would be combined in the BMA. An example for $P = P1 + P2$ longitudinal outcomes would be

$$h_{ik}(t,\theta_s) = h_{0k}(t)\exp\left\{\gamma_k^\top w_{ik} + \sum_{p_1=1}^{P_1}\alpha_{p_1k}f_{ip_1}(t) + \sum_{p_2=1}^{P_2}\alpha_{p_2k}^d\int_0^t f_{ip_2}(s)ds\right\}, \qquad (6.3.1)$$

where k is the event, θ_s is the parameter vector for the survival outcomes, $h_{0k}(t)$ is the baseline hazard, w_{ik} is a vector of baseline covariates with a corresponding vector of regression coefficients γ_k and α_{p_1k} and α_{p_2k} are the coefficients that link the longitudinal and survival parts. Specifically, in (6.3.1) for a set of P_1 longitudinal outcomes, we assume the true value and for another set P_2 the area under the curve to be associated with the survival outcomes. Furthermore, different submodels could be assumed per outcome. For instance, type of operation could be a significant factor for death but not for reoperation. In addition,

the slope of aortic gradient could have an influence on death, however, the area under the curve of the same biomarker could affect significantly reoperation. An issue with such an extension is that the number of models under consideration may be large and will, therefore, make it impossible to estimate every possible model. Nevertheless, there have been several proposals in the literature which carry out BMA without requiring the evaluation of every possible model. Madigan and Raftery (1994) and Furnival and Wilson (1974) manage to reduce the number of models to be estimated, using appropriate strategies (model selection problem).

When interest is only on determining confounders for the survival outcomes, weighted estimates for the covariates considering models with different associated structures could be observed. The weights per model can be written as

$$\mathrm{P}(M_\omega \mid D_n) = \frac{\mathrm{P}(D_n \mid M_\omega)\mathrm{P}(M_\omega)}{\sum_{q=1}^{\Omega} \mathrm{P}(D_n \mid M_q)\mathrm{P}(M_q)},$$

where $p(D_n \mid M_\omega)$ is the marginal density of the original data for model ω and $\mathrm{P}(M_\omega)$ the prior of each model. We could then make inference for the whole universe of candidate models. As a result, we consider not only the uncertainty associated with the parameter estimate conditional on a given model, but also the uncertainty of parameter estimate across different models. However, this approach will lead to wider confidence intervals for the weighted coefficients.

Furthermore, in order to implement the BMA, prior information for each model must be assigned. In this thesis, we worked with equally probable models apriori. However, the specification of more flexible priors for the models may be more appropriate. Specifically, Moral-Benito (2013) propose some alternative priors.

6.3.3 Further Extensions

In this thesis, we mostly used the Bayesian approach since it facilitates computations. However, in the statistics research little work was done with regards to model averaging method using the frequentist approach (FMA). The selection of the priors of the models in the case of a large range of models may be a difficult task. Furthermore, we raise concern for the fact that the typical application of BMA involves mixing together many conflicting prior opinions regarding interest parameters. Specifically, we need to set priors for the parameters of each model and for the model itself. Thus, the FMA is an alternative method to the BMA which requires only the specification of the weights of each model. Specifically, as presented by Wang et al. (2009) and Moral-Benito (2013), weights could be based on information criteria, Mallows' criteria or cross-validation criteria.

Moreover, the validation of predictions on different cohorts is of primary importance in the process of developing a prognostic tool, especially when using a complex statistical model, and was not addressed in this thesis. We applied the BMA approach which provided us with

predictions that account for both model uncertainty and patients' unique nature. Nevertheless, we did not concentrate on how well the model predicts the observed data. Thus, standard measurements, such as calibration, may be useful to investigate.

Finally, in the standard Cox model the effect of the covariates on survival is to act multiplicatively on some unknown baseline hazard rate, therefore the relationship between the event and the factors is described by the ratio. However, in some cases, the risk difference is preferred to describe this association. Thus, in the heart valve data it may be of interest to investigate also the risk of death or reoperation with one unit increase of the echocardiographic measurements. An alternative to the Cox model would be the additive hazard model, where the covariates act in additive manner on unknown baseline hazard (Aalen, 1980; Aranda-Orda et al., 1983). Specifically, the additive hazard model can be written as

$$h_{ik}(t,\theta_s) \quad = \quad h_{0k}(t) + \gamma_k^\top w_{ik} + \sum_{p=1}^{P} \alpha_{pk} f_{ip}(t), \tag{6.3.2}$$

where α_{pk} are the coefficients that link the longitudinal and survival parts. Specifically, the coefficients can be interpreted as the increase in the hazard rate for every unit increase in the corresponding component. With regards to the likelihood under the additive hazards model (6.3.2), a further investigation is required. Even though there are many advantages in using the additive hazard regression models, they are not widely used. One reason for this is that the model is not readily available in statistical software packages. A further investigation of the predictions that this approach provides in our concept, could be performed using the BMA that includes also the additive hazard models.

6.4 Final Conclusion

We should make clear that the choice of the method should depend on the nature of the data and the interest of the physicians rather than the complexity of the method. The joint models are a useful tool when longitudinal outcomes are collected together with time-to-event data. Specifically, they incorporate all information simultaneously and provide valid and efficient inferences. Nevertheless, in the case of a cross-sectional dataset, where data are collected by observing many subjects at the same point of time, the mixed-effects and therefore the joint models are not longer needed. The choice of the statistical models is an important task and needs to be done with caution.

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Chapter 7

Nederlandse Samenvatting, Acknowledgements, CV and PhD Portfolio Summary

Nederlandse Samenvatting

Het monitoren van patiënten is essentieel bij het vroegtijdig opsporen van hartklepaandoeningen. In het bijzonder zijn de aorta gradiënt, aorta-insufficiëntie en brain natriuretisch peptide (BNP) metingen van belang bij het vaststellen van de ernst en progressie van de klepziekte. Deze metingen kunnen nuttig zijn voor de therapeutische besluitvorming, vooral wanneer deze metingen regelmatig worden uitgevoerd. Gemotiveerd door dit klinisch belang, hebben wij gebruik gemaakt van gemengde modellen voor longitudinale- en overlevingsdata. Het idee achter deze modellen is de veranderingen van de marker in de loop van de tijd goed te beschrijfven. Vervolgens worden deze veranderingen van de marker gebruikt als een tijdsafhankelijke covariaat in een overlevingsmodel. In dit proefschrift hebben we deze modellen geïntroduceerd en meerdere extensies gepresenteerd.

Allereerst onderzochten we in **hoofdstuk 2** de verschillende conclusies die kunnen worden getrokken bij het vergelijken van het gemengde model met de eenvoudige methode, die geen rekening houdt met de bijzondere kenmerken van de data. Meer in het bijzonder, hebben wij gebruik gemaakt van het 'eenvoudige' Cox model welke gecorrigeerd is voor de laatste metingen van de longitudinale uitkomst. Uit de analyse komen verschillen naar voren in de richtingen van de schatting, maar ook in de p-waarden. In dit hoofdstuk hebben wij laten zien dat de gekozen benadering invloed kan hebben op de resultaten.

In **hoofdstuk 3** zijn we verder gegaan met een uitbreiding van het gemengde model dat een ononderbroken (aorta gradiënt) uitkomst, en een ordinale longitudinale (aorta-insufficiëntie) uitkomst in een concurrerende risico setting behandelt. Wij hebben gebruik gemaakt van gemengde modellen voor de longitudinale uitkomsten en het zogenoemde "continuation ratio mixed-effects model" voor het analyseren van de ordinale uitkomst. Bovendien worden de overlevingsresultaten gecombineerd met de onderwerp-specifieke profielen van beide longitudinale uitkomsten. In dit geval is het interessant om de relatie te onderzoeken tussen flexibele functies voor tijd en de gemengde modellen (bijv. niet-lineaire). Groot voordeel van het voorgestelde gemengde model is dat het de mogelijkheid geeft aan de arts om de progressie van de ziekte van de patiënt te onderzoeken en te associëren met het risico om te sterven. Hiermee wordt de arts in staat gesteld om te oordelen of er noodzaak is tot een nieuwe operatie aan de hartklep.

In **hoofdstuk 4** hebben we ons gericht op de individuele risico voorspellingen voor toekomstige patiënten. Specifiek hebben wij het risico om te overlijden of opnieuw geopereerd te worden voorspeld naarmate er meer BNP waarden beschikbaar kwamen voor twee nieuwe patiënten. Deze methode en de ervaring van de arts zorgt voor een nauwkeurige voorspelling. Het zorgt voor een alarmsysteem voor de beoordeling van de nieuwe interventie bij de patiënt.

In **hoofdstuk 5** hebben we het voorspellingsmodel uitgebreid met meerdere longitudinale en overlevings-uitkomsten. Daarnaast hebben we onderzocht of de verschillende kenmerken van de longitudinale processen de voorspelling significant zouden veranderen. Dit hebben wij gedaan door te kijken naar de verschillende soorten van vereniging structuren, zoals

tijdsafhankelijke traject hellingen en tijdsafhankelijke cumulatieve effecten. Bovendien hebben wij dit voorzien van extra gemengde modellen met meer klinisch relevante factoren voor één van de uitkomsten. Dit is belangrijk want vanuit het klinisch oogpunt kunnen verschillende combinaties van de baseline covariaten de resultaten beïnvloeden. Omdat de keuze voor één model het modelonzekerheidsprobleem negeert, hebben we tenslotte de voorgestelde modellen gecombineerd door middel van Bayesiaanse model middeling. Met behulp van Bayesiaanse model middeling hebben we voorspellingen van de overlevingskansen van twee nieuwe patiënten berekend, die we aanvankelijk uit de dataset hadden gelaten. Daaruit blijkt dat Bayesian model middeling een vruchtbaar middel is voor flexibele voorspellingen voor toekomstige patiënten met unieke eigenschappen.

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CV

The author was born on December 31, 1987 in Athens (Greece). After finishing the Lyceum in 2005, she qualified 3rd best into the department of Statistics, Athens University of Economics and Business. During the first year of her studies she was awarded a scholarship from the State Scholarship Foundation (IKY): Distinction in education and ethics in the academic year 2005-2006 (1st year), STATISTICS section of the Athens University of Economics, Greece (26 August 2009). In 2009, she obtained her Diploma in Statistics. From 16 October 2009 until 31 July 2010 she worked for the company Aegate Hellas as a content Administrator in the department of Marketing.

In September 2010 she commenced her PhD project under the supervision of Prof. Emmanuel Lesaffre, Prof. Johanna Takkenberg and Dr. Dimitris Rizopoulos. During this research, she also participated in projects at the department of Biostatistics and Cardio-Thoracic surgery. In 2014, she will start her post-doc in the department of Biostatistics at the Erasmus MC.

PhD Portfolio Summary

Publications

- Combined Dynamic Predictions using Joint Models of Multiple Longitudinal Outcomes and Competing Risk Data. Andrinopoulou ER, Rizopoulos D, Takkenberg JJ, Lesaffre E. Submitted.
- Dynamic Prediction of Outcome for Patients with Severe Aortic Stenosis: Application of Joint Models for Longitudinal and Time-to-Event Data. Andrinopoulou ER, Rizopoulos D, Geleijnse ML, Lesaffre E, Bogers AJ, Takkenberg JJ. Submitted.
- Dynamic Predictions with Time-Dependent Covariates in Survival Analysis using Joint Modeling and Landmarking. Rizopoulos D, Murawska M, Andrinopoulou ER, Molenberghs G, Takkenberg JJ, Lesaffre E. Submitted.
- Joint Modeling of Two Longitudinal Outcomes and Competing Risk Data. Andrinopoulou ER, Rizopoulos D, Takkenberg JJ, Lesaffre E. *Statistic in Medicine*. 2014 Aug;33(18):3167 – 3178.
- Increasing Mean Arterial Blood Pressure and Heart Rate With Catecholaminergic Drugs Does Not Improve the Microcirculation in Children With Congenital Diaphragmatic Hernia: A Prospective Cohort Study. Buijs EA, Reiss IK, Kraemer U, Andrinopoulou ER, Zwiers AJ, Ince C, Tibboel D. *Pediatric Critical Care Medicine*. 2014 Mar;15(4):343 – 354.
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- Congenital valvular aortic stenosis in young adults: predictors for rate of progression of stenosis and aortic dilatation. van der Linde D, Andrinopoulou ER, Oechslin EN, Budts W, van Dijk AP, Pieper PG, Wajon EM, Post MC, Witsenburg M, Silversides CK, Oxenius A, Bogers AJ, Takkenberg JJ, Roos-Hesselink JW. *International Journal of Cardiology*. 2013 Sep;168(2):863 – 870.
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- Autograft and pulmonary allograft performance in the second post-operative decade after the Ross procedure: insights from the Rotterdam Prospective Cohort Study. Mokhles MM, Rizopoulos D, Andrinopoulou ER, Bekkers JA, Roos-Hesselink JW, Lesaffre E, Bogers AJ, Takkenberg JJ. *European Heart Journal*. 2012 Sep;33(17):2213 – 2224.

- An introduction to mixed models and joint modeling: analysis of valve function over time. Andrinopoulou ER, Rizopoulos D, Jin R, Bogers AJ, Lesaffre E, Takkenberg JJ. *The Annals of Thoracic Surgery*. 2012 Jun;93(6):1765 – 1772.

Conferences

- 35th Annual Conference of the International Society for Clinical Biostatistics (ISCB) - Vienna, Austria, 2014 (oral presentation)

- 27th International Biometric Conference (IBC) - Florence, Italy, 2014 (oral presentation)

- 6th Annual Joint Scientific Session of the Heart Valve Society of America (HVSA) and Society for Heart Valve Disease (SHVD) Valves in the Heart of the Big Apple VIII - New York, US, 2014 (oral presentation)

- 7th Biennial Congress of the Society for Heart Valve Diseases (SHVD) and Heart Valve Society of America (HVSA) - Venice, Italy, 2013 (oral presentation)

- BAYES2013 - Rotterdam, The Netherlands, 2013 (oral presentation)

- 7th meeting of the Eastern Mediterranean Region of the International Biometric Society (EMR-IBS) - Tel Aviv, Israel, 2013 (oral presentation)

- Werkgroep Epidemiologisch onderzoek Nederland (WEON) Health and disease during the life course - Rotterdam, The Netherlands, 2012 (oral presentation)

- 27th International Workshop on Statistical Modelling (IWSM) - Prague, Czech Republic, 2012 (oral presentation)

PhD Training

- Statistical Methods for Multi-Outcome Data Workshop, Cambridge, UK, 30 June – 1 July 2014 (poster presentation)

- GAMLSS in action, Rotterdam, The Netherlands, 22-23 January 2014

- Bayesian inferences for latent Gaussian models using INLA, Utrecht, The Netherlands, 24 January 2013
- Bayesian adaptive methods for clinical trials, Rotterdam, The Netherlands, 8 - 9 October 2012
- Variable selections: Spring symposium, Rotterdam, The Netherlands, 9 March 2012
- Missing data in longitudinal studies: strategies for Bayesian modelling, sensitivity analysis, and causal inference, Rotterdam, The Netherlands, 20 - 21 October 2011
- Bayesian variable selection and model choice for structured additive regression using spike-and-slab priors, Rotterdam, The Netherlands, 28 September 2011
- Joint modelling: Spring symposium, Rotterdam, The Netherlands, 11 March 2011
- The craft of smoothing, Rotterdam, The Netherlands, 20-21 December 2010

Teaching

- Teaching basic statistics with practical applications to 4th year medical students, 2014
- Supervision of 2nd year medical students in a systematic review, 2014
- Teaching basic statistics with practical applications to 1st year medical students, 2013
- Assisting survival analysis course (nihes), 2013
- Assisting repeated measurements course (nihes), 2013
- Assisting Bayesian course (nihes), 2013
- Assisting joint modelling course (nihes), 2013
- Assisting survival course (nihes), 2013
- Assisting R course (nihes), 2012
- Assisting SPSS practical for Classical Methods (nihes), 2010 and 2012
- Assisting SPSS & SAS practical for Modern Methods (nihes), 2010
- Assisting SPSS practical (nihes), 2010 and 2011

Invited Seminars

- Combined Dynamic Predictions using Joint Models of Multiple Longitudinal Outcomes and Competing Risk Data. Biostatistics seminar in VU University Medical Centre Amsterdam, The Netherlands, 2014

Awards

- Student conference award (35th Annual Conference of the International Society for Clinical Biostatistics ISCB) - Vienna, Austria, 2014
- Poster award (2nd Statistical Analysis of Multi-Outcome Data workshop SAM) - Cambridge, UK, 2014
- The award for the extraordinary student oral presentation (27th International Workshop on Statistical Modelling IWSM) - Prague, Czech Republic, 2012