Survival studies of total hip replacements and postoperative mortality

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Between 1993 and 1997 I was engaged at NAR as a statistician and computer-engineer. During these years my knowledge and interest about artificial joints was initiated.

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1. List of papers

Paper I:

Lie S.A., Havelin L., Engesæter L.B. Gjessing H.K., and Vollset, S.E. Mortality after total hip replacement, 0-10 years follow up of 39 543 patients in the Norwegian Arthroplasty Register. *Acta Orthopaedica Scand.* 2000; 71(1): 19-27

Paper II:

Lie S.A., Havelin L., Engesæter L.B., Furnes O., and Vollset, S.E. Early postoperative mortality after 67 548 total hip replacements - Causes of death and thrombosis prophylaxis in 68 Norwegian hospitals from 1987 to 1999. In press *Acta Orthopaedica Scand.*

Paper III:

Lie S.A., Engesæter L.B., Havelin L.I., Gjessing H.K., and Vollset S.E. Dependency issues in survival analyses of 55 782 primary hip replacements from 47 355 patients *Submitted*

Paper IV:

Lie S.A., Lie R.T., and Svanes C. Expected survival compared with survival of peptic ulcer patients. *Statistics in Medicine,* 1998; 17(11), 1189-99

2. Introduction

During the later decades the number of medical registries and other sources of electronically collected medical data have increased rapidly. These medical data sources may constitute prospective studies, retrospective studies, or cross sectional studies. For many studies analysis for follow-up data may be relevant. Analyses of mortality may for instance often be considered although this was not initially intended. This may be one of the reasons why survival analysis plays a central role in medical statistics (Bull and Spiegelhalter 1997). Another common use of survival techniques is for data on patient mortality or time to some disease (e.g. AIDS) or event (e.g. heart attack) occurs.

In addition to the increased amount of available data, the complexity of the collected medical data has increased, which has lead to a considerable development in the methodology for survival data (Andersen et al. 1993, Hougaard 2000, Therneau and Grambsch 2000). Several measures or outcomes for one unit (patient or cluster) are not uncommon (e.g. repeated heart attacks). Joint replacement patients can for instance have artificial joint replacements in several joints or repeated operations in the same joint. Such problems has usually been avoided or ignored for joint replacement data (Morris 1993).

The older methods for survival analysis based on actuarial calculations for survival probabilities (with discrete time intervals) or grouped data have met a new era in the capacity of modern data equipment, as for other branches in applied statistics. The product limit calculation of survival probabilities (Böhmer 1912, Kaplan and Meier 1958) and the proportional hazard regression model (Cox 1972), both utilize individual data and need more data capacity than analyses on grouped data in their calculation. These two methods have become the basis of survival analyses in medical statistics and have formed the basis for several alternatives and extensions during the later decades.

This thesis is focused on the extensive data of 70,000 total hip replacements in the Norwegian Arthroplasty Register (Havelin et al. 2000) (Paper I, II and III). In paper IV we additionally use data with 38 years of follow-up for mortality in 1097 patients with perforated peptic ulcer (Svanes et al. 1993) to discuss alternatives for calculation of expected survival curves. Patients with perforated peptic ulcer have a highly increased

mortality the first 30 days after the incident and a long-term higher mortality than the general population (Svanes et al. 1994). This contrasts with total hip replacement patients where we observed an increased mortality during the first postoperative period (Paper II), but the long-term mortality is lower than for the general population (Paper I). Some patients have hip replacement in both hips, which may be associated with increased mortality for these patients. Furthermore, patients with a revised prosthesis may have a change in their mortality.

The issue of patients with two prostheses is furthermore considered (Paper III). These patients may influence the overall results for hip prostheses, if it is ignored that bilateral prostheses may be dependent. Furthermore, prostheses from patients with bilateral operations may have a different risk for revision for their prostheses than prostheses from patients with only one prosthesis (Morris 1993, Schwarzer et al. 2001).

This thesis focuses on survival methods related to follow-up for the patients, both for time to death and time to revision surgery, incorporation that some patient may have bilateral prostheses. In analysis of patient mortality it is important to keep in mind the standard mortality for the general population. Comparison of patient mortality with the population mortality and methods incorporating population mortality rates is therefore emphasized.

3. Background

Statistical techniques for analyses of survival data have a long history and so has artificial joint replacement. The understanding of using survival techniques in analysis duration for joint replacement is however not very old. Some works have argued for the use of survival tools to calculate survival probabilities for the joint prostheses (Murray et al. 1993, Nelissen et al. 1992).

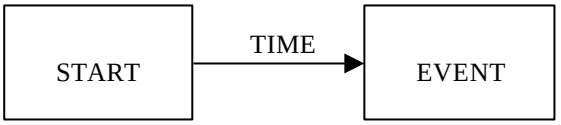
3.1. Brief overview of survival analyses

Work related to survival analyses has roots back to before 1700 (Hald 1990). Actuarial techniques for calculating survival probabilities is one of the old known methods as well as methods to calculate standardized mortality ratios (SMR´s). The actuarial methods divide the time scale of interest into intervals and hence limit the number of required calculations to obtain survival probabilities. Furthermore, the SMR was commonly applied to grouped data according to available mortality tables from some reference population, which limits the required calculation.

The two most cited works related to analysis of survival data is Kaplan and Meier's (Kaplan and Meier 1958), with more than 18 000 citations, and Cox's (Cox 1972), with more than 12 000 citations (the ISI-base). The Kaplan and Meier method was known from earlier work and they refer their work back to Böhmer (Böhmer 1912).

The basic idea of survival analysis is to study the distribution of life times till some event. Usually a well-defined start (e.g. time of an operation) and a well-defined event (e.g. death for a patient or failure of a prosthesis) are identified. Hence we observe *a time and an event* or *a time for last seen and no event*. The last possibility are called censored observations.

In order to apply the standard survival techniques, this simple schematic illustration of the study should be possible to set up, where the time to some event, which may or may not occur, are of interest:



The standardized mortality ratio (SMR) was introduced around 1750 (Keiding 1987) and is still among the most commonly used measures for comparing the mortality in a group of individuals with the mortality of a reference population. The SMR can generally be interpreted as "the observed number of deaths" divided with "the expected number of deaths" and is hence an attractive measure in analyses of patient survival. The Kaplan-Meier calculation for survival probabilities and the SMR measure gives attractive presentation for the failure characteristics of the data. Often extended analyses are desired and some class of regression model for survival data would be an option. The Cox proportional hazards model (Cox 1972) is, as mentioned, the most common technique. Alternatives would be Poisson regression (Breslow and Day 1980), which often is used on grouped data for large data sources, or Aalen's additive regression model (Aalen 1989, Aalen 1993). Poisson regression using grouped data can be designed to reflect the results from a similar Cox model with individual data (Selmer 1990). Aalen's additive regression model is another alternative which calculates additive non-parametric effects for, possibly time dependent, covariates (Aalen 1989).

3.1.1. Basic notation

Presentation of plots with survival probabilities (survival curves) have become an important tool in medical research for survival data during the recent decades. The survival function is defined as the probability of an event occurring later than time *t*,

$$S(t) = P(T > t)\,. \tag{3.1}$$

The survival curve has the central role as the non-conditional probability for an item (patients/prostheses) surviving longer than time t, while the distribution function, the probability that some event occurs before time *t*, sometimes may be used,

$$F(t) = P(T \le t) = 1 - S(t)\,. \tag{3.2}$$

The density function (for ordinary continuous data assessed with a histogram) is given as,

$$f(t) = \lim_{dt \to 0} \frac{P(T \in (t, t+dt))}{dt} = \frac{dF(t)}{dt}. \quad (3.3)$$

Furthermore, the essential hazard function, which forms the basis in most regression models for survival data, is defined as,

$$l(t) = \lim_{dt \to 0} \frac{P(T \in (t, t+dt) \mid T > t)}{dt}. \quad (3.4)$$

The hazard function can also be expressed as,

$$l(t) = \frac{f(t)}{S(t)}. \quad (3.5)$$

The relationship, in continuous time, between the survival function and the hazard function is,

$$S(t) = e^{-\int_0^t l(u)\,du}. \quad (3.6)$$

3.1.2. Concepts in survival analysis

The Kaplan-Meier method (Kaplan and Meier 1958) for calculating survival probabilities ($S(t)$) has become a standard in medical studies for survival analyses. The Kaplan-Meier method gives an attractive presentation with a simple interpretation of plots for the calculated survival probabilities. If we let $D(s)$ be the number of deaths at time s and $Y(s)$ the number of items still at risk at time s, the estimated survival probability is,

$$\hat{S}(t) = \prod_{s \le t} \left(1 - \frac{D(s)}{Y(s)}\right). \quad (3.7)$$

Furthermore, the Cox proportional hazards model (Cox 1972) for regression analyses of survival data gives a straightforward interpretation of risk factors related to the risk for failure ($l(t)$). The hazard for item i (e.g. patient) ($l_i(t)$) consists of a non-parametric baseline hazard ($l_0(t)$) common for all items, and a parametric part describing possible risk factors and potential confounders ($\exp(\mathbf{b}^T \mathbf{x}_i)$),

$$l_i(t) = l_0(t) e^{\boldsymbol{\beta}^T \mathbf{x}_i}. \quad (3.8)$$

The estimated parameters (b for β) for the risk factors is interpreted as log of the hazard ratio for unit increments of the explanatory variable (x). The model may also be used to calculate adjusted survival curves

During the recent decades there has been a rapid development in survival analysis with several books on the topic (Andersen et al. 1993, Hougaard 2000, Therneau and Grambsch 2000). Extensions and alternatives to the Cox-model have been one of the important issues in these works. Furthermore, the need for more complex models based on the increasing complexity of available data has been important. Such data may either be clustered observations within units (groups or patients) or repeated observations for the same unit.

3.2. Total hip replacements

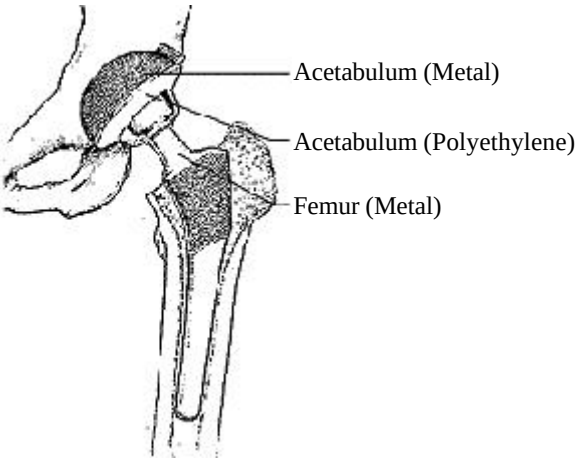
3.2.1. Hip disease

Degenerative disease or osteoarthritis of the hip, coxarthrosis, is commonly found in the population over 75 years and the prevalence of this condition increases with age (Danielsson and Lindberg 1997, Danielsson et al. 1984, Heliovaara et al. 1993). Some studies have found arthritis in approximately 50 % of adults over 65 years (Whelton et al. 2001). Seventy percent of the total hip replacement patients are women, indicating that hip disease is a typical female condition (Annual report from the Norwegian Arthoplasty Register). Individuals with hip disease will often suffer from pain, stiffening of the hip, and immobility with its social consequences. Other important categories of patients that may need hip replacements are those with inflammatory joint conditions. These patients are often younger with either rheumatoid arthritis or ankylosing spondylitis. Generally, a hip replacement is only considered if conservative treatment, medication or physical activity/therapy does not have a satisfactory effect. Two other important categories of the hip replacement patients are patients who have had a pediatric hip disease (dysplastic hips, epifysiolysis, and Perthes' disease) and patients with fracture of the femoral neck.

3.2.2. Hip arthroplasty

A total hip replacement is a biomechanical device replacing completely the native hip joint. The first known attempts to surgically remodel a destructed hip is from the 1880's (Ollier 1885) where they used soft tissues to rebuild the joint. About a decade later, Gluck was the first to use foreign materials using ivory components with nickel-plated steel screws for fixation (Gluck 1891). The term hip arthroplasty was originally used for any surgical forming or rebuilding of the hip, but this term is now used almost exclusively for total hip replacements.

A total hip replacement normally consists of a femoral component (stem) and an acetabular component (cup). The femoral component may have a shaft that is inserted into the femoral bone canal (with or without cement for fixation) and a femoral head (caput) that can be modular (replaceable). The acetabular component may consist of only a polyethylene cup or a polyethylene cup with a shell of metal (with or without cement for fixation).



The important breakthrough in hip replacement surgery came in the 1960's when Sir John Charnley introduced a new design of hip prosthesis with cement for fixation of the prosthesis to the bone (Charnley 1963). This design and method is often the reference that new products are compared to. Further development was seen in the 1970's when new operation environments and antibiotic prophylaxis were introduced (Charnley 1972a, Charnley 1972b). The basic ideas of Charnley was to use a cemented polyethylene acetebular cup and a small 22 mm femoral head, which gave low torque and low wear on a cemented femoral stem of stainless steel.

Several designs similar to the Charnley and designs with new ideas were introduced to the market in the 1970's. The Norwegian orthopedic surgeon Tor Christiansen designed a prosthesis with an anatomically more correct design with a large femoral head (caput, 37 mm) as a contrast to the small Charnley head (22 mm) (Christiansen 1969, Christiansen 1974, Sudmann et al. 1983). This design was later

found to have inferior results compared to the Charnley prosthesis and was one of the reasons for establishing the Norwegian Arthroplasty Register (Havelin et al. 1986, Sudmann et al. 1983). Other prostheses from the 1970's and 1980's which demonstrated the need for a quality control of the prosthesis market, were the uncemented Bio-Fit femur prosthesis with a smooth surface, and the double cup prostheses such as the Wagner prosthesis (Howie et al. 1990), which had inferior results compared to the Christiansen prosthesis.

The cemented prostheses (Charnley and others) have been accepted as the best replacement technique for older patients. For younger and active patients there is still a debate on which solution to choose. After poor results on the first generation of uncemented prostheses, some of the newer uncemented designs with hydroxyapatite coating to ensure bone in-growth and fixation of the prosthesis, have shown promising results at mid term follow-up (5-7 years).

The poor results of the inferior implants were often not seen before after several years when the prostheses had been used in large numbers of patients. Often an attractive new principle was the argument for the introduction of a new prosthesis on the marked, usually without any documentation of clinical results. Most of the quality tests of the early prostheses were laboratory tests carried out under a controlled environment. For instance, the Christiansen prosthesis had good friction properties in laboratory situations, but the prosthesis resulted in large amounts of wear debris in the patients, with a loose prosthesis as the result. An additional reason for the high grade of wear and poor results could also be the change from polyethylene to the plastic components of Delrin. Some early inserted Christiansen prostheses have shown good long-term results (Nesse and Ramstad 1989).

There have been a rapid increase in the annual number of total hip replacements performed worldwide. In 1980, between 300 000 and 400 000 total hip replacements were performed. Ten years later the number was approximately 800 000 annually (Levy et al. 1985), and by 1999 it had passed 1 million (Soderman 2000). If we stipulate the cost for each of these operations to $ 10 000, the annual cost worldwide is $ 10 billion.

3.2.3. Thromboprophylaxis

In the early period following a major surgery, patients have an increased mortality which is mainly due to thromboembolic events, such as pulmonary embolism (Dahl 1998, Murray et al. 1996, Planes et al. 1996, Turpie and Kher 1998). After joint replacement operations, the increase in mortality in the early postoperative period is not at the same level as after other types of surgery (Osswald et al. 1999, Seagroatt and Goldacre 1994).

During a hip replacement operation a coagulation process starts which can lead to thrombotic complications such as deep venous thrombosis or a fatal pulmonary embolism (Dahl 1997, Dahl 1999, Dahl et al. 1995, Engesaeter et al. 1984). Due to the increased mortality caused by the thromboembolic events, most patients receive some sort of thromboprophylaxis. The thromboprophylaxis is supposed to reduce the mortality only from causes of death related to thromboembolic complication. Since the rate of deaths due to thromboembolic events are very low, a large number of patients would be required in randomized trials (Collins et al. 1988, Fender et al. 1997). Other measures have therefore been used. In randomized studies measuring effects of thromboprophylaxis the ordinary outcome measure is deep venous thrombosis (DVT) (Borris et al. 1994, Comp et al. 1998, Mehta et al. 1975, O´Brian and al. 2000, Planes et al. 1996). Due to the low mortality, DVT is used as a surrogate measurement to estimate the effect of thromboprophylaxis (Murray et al. 1996). The use of DVT as a surrogate measurement of mortality may, however, be discussed (Mismetti et al. 2001, Prentice 1998).

There has been and is still a debate on the use of thromboprophylaxis, the duration of the prophylaxis, how the prophylaxis may influence the mortality, and which drugs to use (Andreassen and Dahl 1997, Bulstrode 1998, Dahl 2000, Dahl et al. 2001, Dahl et al. 2000, Frostick 2000, Hull et al. 2001a, Hull et al. 2001b). Several studies have shown an increased mortality during the early postoperative period after a total hip replacement operation (Dearborn and Harris 1998, Dunsmuir et al. 1996, Seagroatt and Goldacre 1994, Seagroatt et al. 1991). The increased mortality may be increased for as long as three months after the surgery (Seagroatt and Goldacre 1994). Since randomized trials large enough to show effects of thromboprophylaxis on mortality are difficult to carry out (O´Brian and al. 2000), meta analyses (Borris et al. 1994, Collins et al. 1988,

Freedman et al. 2000, Imperiale and Speroff 1994, Mohr et al. 1993, Murray et al. 1996) may be a suitable tool to describe possible associations between mortality and thromboprophylaxis. Large prospective studies, e. g. register studies, may also be a valuable source of describing the overall early postoperative mortality and for how long this mortality persists.

3.2.4. Arthroplasty registers

During the recent decades several national registries of joint replacements have been founded. The Swedish Knee Arthroplasty Project was established in 1975 with an individual registration of knee prosthesis patients. (Knutson et al. 1994, Robertsson et al. 2001, Robertsson et al. 2000). In 1979 the Swedish National Total Hip Arthroplasty Registry started to register all revisions of total hip prostheses performed in Sweden (Ahnfelt et al. 1990, Soderman 2000, Soderman et al. 2000). Primary operations were reported as summary numbers from the reporting hospitals until 1992. Later the registration also included individual data on primary operations (Herberts and Malchau 2000). Separate registries of other joint replacements are also present at different locations in Sweden (Rahme et al. 2001). In 1980, the Finnish Arthroplasty Register started their registration of individual data on patients with prostheses (Puolakka et al. 2001). This register is hence the oldest and largest register with individual data on primary total hip replacements on a national basis, but with limited information on the inserted prostheses. During the 1990's, registries have been initiated or established in Denmark (Lucht 2000), Iceland, New Zealand (Rothwell 1999), Switzerland, Canada, Austria, and new countries are following. There are also some regional and hospital based registries. For example the Trent Regional Hip Register (UK, established in 1990) (Fender et al. 2000) and the hip replacement register at the Mayo Clinic in Rochester, Minnesota, US (Berry et al. 1997). The basic motivation for these registries are quality control of joint replacement surgery and prosthesis brands.

The reasons for the successes of joint replacement registries and the growing numbers of such registries are several. As joint replacement operations take place in operation theatres, the opportunity to track patients is large. Furthermore, most orthopaedic surgeons have the willingness to quality control the prostheses brands and operation techniques in use. In the Scandinavian countries, the personal identification

numbers increases the possibility to track patients operated at different locations and to obtain records on the time of death.

3.2.5. The Norwegian Arthroplasty Register

Based on the poor performance of undocumented or poorly documented prostheses during the 1970's the Norwegian Orthopaedic Association established the hip replacement register in 1987, located to Haukeland University Hospital, Bergen. The founder was Professor Einar Sudmann in cooperation with Professor Lars B. Engesæter and the orthopeadic surgeon Tor Steinar Raugstad. Registration of total hip replacement operations started in September 1987, with the orthopeadic surgeon Leif I. Havelin in charge of the register. Later on, he became head of the register. To limit the workload for the participating surgeons, in order to keep up the reply percentage, the voluntary reporting of hip replacement operations was done by a one-page form. Furthermore, each hospital receives reports with their own reports, and with the possibility to compare these results with country averages. These reports also keep up the motivation of the participating surgeons and improve the quality at the hospitals.

Based on the successes of the hip register, the registry was extended to include all joint replacements (knee, elbow, toe, finger, shoulder, ankle, and wrist), in 1994 (Furnes et al. 1996).

3.2.6. Development of the data system at the Norwegian Arthroplasty Register

In 1993, the Norwegian Medical Association gave a three-year funding to start the new registry for joints other than the hip. These fundings provided the basis for my position as a database constructor at the Norwegian Arthroplasty Register, my task was to establish the database, develop the application for registration of operations, and systemize the prosthesis registry and the computer system. During the first years, a system using Paradox (Borland) was set up for this. In 1994 Haukeland Hospital updated its old mainframe (ND) system to an MS-Windows NT environment with PC units and MS-Windows Office Professional as a standard. The old hip registry was converted from the mainframe system to an MS-access database. The old text files with the hip prosthesis catalogue with more than 6 000 lines of hip prostheses was manually

converted to an MS-Access database and connected to the hip registry, a connection that gave the possibility to use the prostheses database as look-up menus. Furthermore, a system for checking of the data quality, applications for look-up tables (hospitals, diagnoses etc), and tools for the registry's annual reports were constructed. The recently established registry of joints apart from the hip was then converted into the same system. The data system for the Norwegian Arthroplasty Register consists thus of two databases for the joint replacement operations (one for hips and one for other joints), two prosthesis-databases (one for hips and one for other joints), two databases for the look-up and control tables, two databases with the applications, and finally a database with the main menu for the system. The responsibility for the technical system and data safety for the registry is now under the IT-department at Haukeland University Hospital. The software solutions are still under the responsibility of the registry.

3.3. Perforated peptic ulcer

Ulcer perforation had a high mortality before surgery was introduced around 1900 (Jennings 1940). The first patients operated by Miculitz died (Mikulicz 1885), but in 1896 Barker reported a series where three of seven patients operated on for ulcer perforation survived (Barker 1896). For patients treated during the years 1920-50, a lethality around 20 % was reported (Svanes et al. 1989). In reports of patients treated after 1950, lethality ranged from 5 to 24 % (Svanes et al. 1989). A study from Western Norway, covering the period 1935 to 1990, reported a decrease in lethality from 1935 to 1950. From this time on, lethality was stable until it increased slightly during the last decade (Svanes et al. 1989). Thus, surgery and treatment with antibiotics revolutionized the prognosis of ulcer perforation.

The outcome of ulcer perforation today, given surgical treatment including antibiotics, is determined by the patient's age, location of the perforation and delay in treatment (Svanes et al. 1994, Svanes et al. 1989). The last factor is influenced by the clinical practice, and is thus of particular interest. Postoperative death and complications are closely related to the duration of perforation in particular when the delay in treatment exceeds 12 hours (Svanes et al. 1994). Delays of more than 24 hours

increased lethality 7-8 times and complication rates three-fold in a study from western Norway (Svanes et al. 1994).

In the long run, subjects with a history of ulcer perforation have a lower survival rate than the general population (Svanes et al. 1996). Long-term survival in ulcer perforations patients compared to the general population was poorer in recent birth cohorts than in earlier birth cohorts (Svanes et al. 1996).

4. Aims of the study

The overall aim was to develop and adapt descriptive and analytic survival methods for a follow-up study of hip replacement patients. The specific aims were:

1. To study the long-term survival for patients with total hip replacements, accounting for population mortality rates. (Paper I)

2. To study possible risk factors for long-term survival of patients with total hip replacements, accounting for population mortality rates. (Paper I)

3. To assess the mortality in the early postoperative period after total hip replacements. (Paper II)

4. To evaluate causes of death for the early postoperative period after total hip replacements. (Paper II)

5. To survey the use of thromboprophylaxis in Norway. (Paper II)

6. To evaluate the influence of bilateral prostheses on the results from standard analysis for total hip replacements. (Paper III)

7. To study hip prostheses in both hips as a risk factor in the analyses of total hip replacements using modern tools for survival analysis. (Paper III)

8. Illustrate and discuss methods for calculating expected survival curves based on population mortality rates which are comparable with curves calculated by the Kaplan-Meier method. (Paper IV)

5. Material and methods

This thesis is based on patient-data from two main sources. In paper I, II, and III, the comprehensive data on total hip replacement patients from the Norwegian Arthroplasty Register was used. In paper IV data from 1098 perforated peptic ulcer patients, from the Bergen region, with up to 38 years of follow-up was used to illustrate the comparison of long-term estimated survival curves with calculated expected survival curves. Furthermore, data on mortality (from Statistics Norway) were used in all papers, and data on thromboprophylaxis and causes-of death were used in paper II.

5.1. The Norwegian Arthroplasty Register

The Norwegian Arthroplasty Register is a nationwide register for practically all types of joint replacement operations. Standard forms for the surgical procedure and detailed information on the prostheses are sent from all hospitals performing joint replacement operations in Norway (see appendix). The register started the registration of total hip prostheses operations in September 1987. In 1987 and 1988 two larger hospitals did not report. However, from 1989 practically all 68 hospitals sent in their forms. Since 1989 the reporting has covered 95 % –100 % of all operations. These reporting rates are based on comparisons with numbers from the Norwegian Patient Register in Trondheim (Havelin et al. 2000).

Based on the success for the THR-registry and a need for similar controls for all artificial joint replacements, the register for all joints started in January 1994 (Furnes et al. 1996).

The arthroplasty register is based on individual data for prosthesis operations from all patients even if some information, such as type of operation theatre and antibiotic prophylaxis, may be standard at the hospitals. The eleven-digit national identification number is used to link repeated operations from patients and time of death for deceased patients (obtained from Statistics Norway).

5.2. Additional data for hospital thromboprophylaxis policy

In paper II we studied the early postoperative mortality after total hip replacement surgery and what kind of thromboprophylaxis regimens that have been and are in use in Norway. The form for the joint replacement surgery does not include information on thromboprophylaxis data therefore a separate questionnaire was designed to collect this information. Although individual data would be ideal and desired for thromboprophylaxis, it would be impossible to obtain it in the present setting. If individual data for thromboprophylaxis were present, data on the risk-profile (previous heart attacks, thromboembolic events etc.) for the patients would be strongly desired since this obviously would be related to the thromboprophylaxis prescribed to the patient. The questionnaire was therefore designed to ask for the present policy of thromboprophylaxis at the hospital and former policies of prophylaxis used at the hospital, since this was the easiest to obtain (see appendix). The hospitals were asked to use all available sources to obtain this information. The vital information asked for on the questionnaire was the type(s) of thrombosiprophylaxis, including stockings, used at the hospital, but also the duration of the use.

5.3. Mortality data

The Norwegian Arthroplasty Register updates data on vital status for the joint replacement patients annually in order to obtain information on possibly deceased patients, with date of death. The mortality data is crucial with respect to the survival analyses of the prostheses. Survival time of unrevised prostheses in deceased patients are handled as censored observations with time of death as the last time the prosthesis was seen intact. The mortality data for the hip replacement patients formed the basis in the analysis of mortality for the total hip replacement patients in paper I and II.

In paper I, II and IV, national mortality tables from Statistics Norway were used to calculate expected number of deaths, expected intensity, and expected survival curves for the general population. The mortality tables were provided separately according to gender, in one-year intervals from age 0 to age 100, and for the years from 1960 to

1999. If there was a need for mortality rates for years outside the given intervals, linear extrapolation was used.

Information on causes of death in paper II were provided by Statistics Norway. For each deceased patient before 31st December 1995 a record consisting of one variable defining the source for the record (autopsy etc.), and four variables defining the causes of death according to the International Classification of Diseases (ICD-9) were provided.

5.4. Data on the perforated peptic ulcer patients

During the years 1935 through 1990, a total of 1483 patients with perforated peptic ulcer were admitted to hospitals in Bergen. Sixteen patients with malignant disease were not included. A total of 5 hospitals in Bergen contributed with patients to this data; Haukeland Hospital (1230 patients), Deaconess Hospital (151), Betanien Hospital (70), Red Cross Hospital (30), and Florida Hospital (2).

The patients were identified using several sources. Patients treated during the years 1935-1970 were identified through a card system based on diagnosis and through consecutive manual recordings of all patients operated on. For the period 1973-1990, the patients were identified through a computerized system. With an exception of missing data for the Red Cross Hospital during the war (1941-1944), these perforated peptic ulcer patients represent all patients with perforated peptic ulcer in the Bergen area for this period. The registration of deaths in Norway was computerized in 1952. To study the survival of the peptic ulcer patients, the data were therefore limited to 1097 patients observed after 1952.

5.5. Statistical methods

This thesis is based on data where time to some event is essential. Survival analyses hold therefore a central position. The methods used in paper I are extensively explained and advocated in section 5.6.

In paper II, on early postoperative mortality, we primarily use logistic regression, since we had a complete follow-up of all patients. Furthermore, generalized additive

logistic models (GAM) (Hastie and Tibshirani 1990) were used both to inspect the functional form of confounding factors used in the logistic regression and to visualize the relationship between year of operation and the early postoperative mortality.

Based on the mortality for each day in the early postoperative phase, the mortality curves were calculated. These mortality rates were thereafter smoothed using kernel-smoothing techniques (Wang 1998). The mortality curves are presented with point-wise score confidence limits (Vollset 1993).

5.6. Statistical methods used in paper I

In paper IV we argue for the use of a novel method for the calculation of expected survival curves. We suggest that presentation of the estimated patient survival curve (using the Kaplan-Meier calculation) together with the expected curve should be a standard in presentation of data on mortality for patients.

5.6.1.Quantifying differences between observed and expected mortality

Additionally, quantifying the differences in observed and expected survival may be considered for further analysis. (Notation used in this section is defined in section 3.1.1.). A commonly used method of comparing observed and expected mortality is the calculation of Standardized Mortality Ratios (SMR), which has a history back to the 18th century (Keiding 1987). This is the rate of observed number of deceased patients ($N(t)$), at time t, divided by the number of expected deaths in the population, with the same composition of matching variables (age, gender, etc.) as the patients ($E(t)$). The expected numbers are commonly based on national population mortality rates, $\lambda_i^*(t)$, matched to patient i, at time t. The SMR is typically calculated at the maximum time of observation (t),

$$SMR = \frac{N(t)}{E(t)}. \qquad (5.1)$$

There are in principle two ways for calculating the expected number of deaths ($E(t)$) using population mortality rates (Hartz et al. 1983, Keiding and Vaeth 1986, Smith 1984). The continuous time adjusted method, which calculates the expected number of deaths for each patient, i, (or patient category, i, for grouped data) up to time t, for each time-point that the patient (or group) is observed alive is,

$$E_2(t) = \sum_i \int_0^t l_i^*(u) \cdot Y_i(u) du \,. \tag{5.2}$$

Andersen and Væth (Andersen and Væth 1989) discussed simple methods for comparing observed and expected mortality. If the simple nonparametric multiplicative model,

$$l_i(t) = b(t) \cdot l_i^*(t) \,, \tag{5.3}$$

has a constant relative mortality ($b(t)=b, \forall t$) then the MLE estimate for b is,

$$\hat{b} = \frac{N(t)}{E_2(t)} \,, \tag{5.4}$$

which is the traditional (historical) SMR. This calculation of the SMR will typically be different from 1 even for long follow-ups (say 100 years), when both all patients and the related population should be dead. This is clear since it resembles the relative hazard, b. The relation between the observed and expected survival probabilities in the simple parametric multiplicative hazard model is,

$$S_i(t) = S_i^*(t)^b \,, \tag{5.5}$$

where $S_i^*(t)$ is the expected survival based on population mortality rates for individual *i*.

The second method for calculating the expected number of deaths is the direct method. This uses only the available population mortality rates and the information of follow-up (censoring) for the study-group for the calculation of the expected number of deaths. The expected number of deaths, up to time *t*, is hence,

$$E_1(t) = \sum_i \int_0^t l_i^*(u) \cdot S_i^*(u) \cdot C_i(u) du \,. \tag{5.6}$$

The later is obviously somewhat harder to calculate than $E_2(t)$. Furthermore, if we use $E_1(t)$ in the calculation, the SMR's will approach 1 when the follow-up time is large ($t \to \infty$, or in practice t=100, "In the long run we're all dead!"). There has been some discussions of different methods for calculating expected mortality and standardized mortality ratios (Hartz et al. 1983, Jones and Swerdlow 1998, Keiding and Vaeth 1986, Smith 1984, Tsai et al. 1992).

Other commonly used approaches for comparing observed and expected survival is to calculate relative survival rates as proposed by Ederer (Ederer and Axtell 1961),

$$R(t) = \frac{S(t)}{S^*(t)},$$

where $S^*(t)$ in principle can be calculated in two ways (Hakulinen 1982, Nielsen 1997, Verheul et al. 1993). The interpretation of the relative survival rate may be that it is a survival curve for patients if the standard mortality is removed. However the relative survival curve may, for certain patient materials (like total hip replacement patients), be increasing and even larger than 1 (Zahl and Aalen 1998), which is inaccurate for a conventional survival curve. The relative survival curve will be analogous to study a simple model for excess mortality, $l_i(t) = a(t) + l_i^*(t)$, where $a(t)$ is the excess mortality for the patients. The relationship between $a(t)$ and $R(t)$ is

$$R(t) = e^{-\int_0^t a(u)du}.$$

If the interpretation of $a(t)$ is an excess intensity it should be larger than 0, but, analogous to that $R(t)$ may be increasing, $a(t)$ may be less than 0. For the total hip replacement patients it will be negative. Checking the assumption of an excess intensity model can be done by inspecting a plot of the two survival curves “the direct calculated expected curve” and “the continuos time adjusted expected curve”. If the latter is lower, then individuals with low background mortality (e.g. young) have a higher excess mortality than others do. In the opposite case, individuals with high background mortality (e.g. old) have a higher excess mortality than others do.

The idea of calculating relative survival curves was presented by Ederer and colleagues (Ederer and Axtell 1961), and has later been discussed and developed by others (Estève et al. 1990, Hakulinen 1982, Hakulinen and Abeywickrama 1985)

5.6.2. Regression models including population mortality

The presentation of plots with observed and expected survival curves give easy understandable and interpretable results. Furthermore, the standardized mortality ratio with its long history and definition as a ratio of observed to expected deaths is easily presented. Both these simple approaches give however no direct option to account for possible confounding variables (except through stratification). It is thus desired to extend the analysis to some sort of regression model. One extension of the simple nonparametric multiplicative hazard model is an extended Cox proportional hazards

model including background mortality (with possible time dependent covariates) discussed by Andersen et al. (Andersen et al. 1985),

$$l_i(t) = l_i^*(t) \cdot v_o(t) \cdot e^{\underline{g}^T \cdot \underline{X}_i(t)}. \tag{5.7}$$

The interpretation of the parameter estimates, γ, in this model is given as log(relative hazard rate ratios). We use however the more intuitive term relative mortality ratios (RMR) for the proportion e^g. The model gives hence estimates for changes in the nonparametric multiplicative hazard,

$$\frac{l_i(t)}{l_i^*(t)} = v_o(t) \cdot e^{\underline{g}^T \cdot \underline{X}_i(t)}. \tag{5.8}$$

To exemplify this; consider the simplest situation with only one dichotomous (not time dependent) covariate X_i, which is 0 for individuals in group I and 1 for individuals in group J. If X_i is 0 then the model will reduce to,

$$X_i = 0: \ \frac{l_i(t)}{l_i^*(t)} = v_o(t) = b_I(t), \tag{5.9}$$

where $v_0(t)$, the baseline relative hazard, will be equal to the relative hazard $b_I(t)$ in the simple nonparametric multiplicative hazard model. For X_J equal to 1 the model is,

$$X_i = 1: \ \frac{l_i(t)}{l_i^*(t)} = v_o(t) \cdot e^g = b_J(t). \tag{5.10}$$

Hence the relative mortality for a patient j in patient group J should be proportional to the relative mortality for patient i in group I,

$$e^g = \frac{\dfrac{l_j(t)}{l_j^*(t)}}{\dfrac{l_i(t)}{l_i^*(t)}}. \tag{5.11}$$

The following approximations may therefore be applied;

$$e^g \approx \frac{b_J(t)}{b_I(t)} \approx \frac{SMR_J}{SMR_I}. \tag{5.12}$$

The first "≈" in this equation will be an equality if the proportional assumption in the regression model is fulfilled. The second "≈" will be an equality if $v_0(t)$ is constant as in (5.4).

This gives the option of checking model assumptions for proportionality. Plots of $\log(B(t))$'s, where

$$B(t) = \int_0^t b(u)du ,$$

hence mimics log-log survival plots for the standard Cox proportional hazards model. Thus the vertical distance between the curves should be constant over time *t*. See Figure 11.1 A-C for checking of model assumptions for some of the covariates used in paper I. The estimation of the integrated relative mortality has been shown in other reports (Andersen et al. 1993, Andersen and Væth 1989, Breslow and Langholz 1987, Breslow and Day 1985).

We have shown that results from the extended Cox model easily can be interpreted in terms of ratios of standardized mortality ratios (SMR's). Presentation of the well-known SMR's, results from the regression model, and the easily interpreted survival curves hence gives an attractive presentation of patient survival data, accounting for population mortality.

There are several alternatives for regression models for patient mortality including background mortality rates. The simplest alternative may be an extension of the standardized mortality ratio, which may be considered as a simplification of the extended Cox-model without the non-parametric baseline hazard, but only the population mortality rates (Breslow and Day 1985, Breslow et al. 1983, Hill et al. 1985, Knuiman et al. 1992). Furthermore, an alternative is a proportional model for the excess mortality (Bolard et al. 2001, Sasieni 1996, Zahl 1995). This model demands positive excess hazards, which sometimes can be a very strong assumption and is absolutely not satisfied for the total hip replacement patients. Furthermore, Aalens additive regression model can be extended to also incorporate background mortality rates (Zahl 1997, Zahl and Aalen 1998). Also Poisson regression models can easily be extended to include population mortality rates (Breslow and Day 1985). The ideas of the relative survival models has also been extended to regression models by Hakulinen and colleagues (Hakulinen and Abeywickrama 1985, Hakulinen and Tenkanen 1987). Others have also discussed some of these alternatives (Andersen and Væth 1989, Bolard et al. 2001, Buckley 1984, Estève et al. 1990).

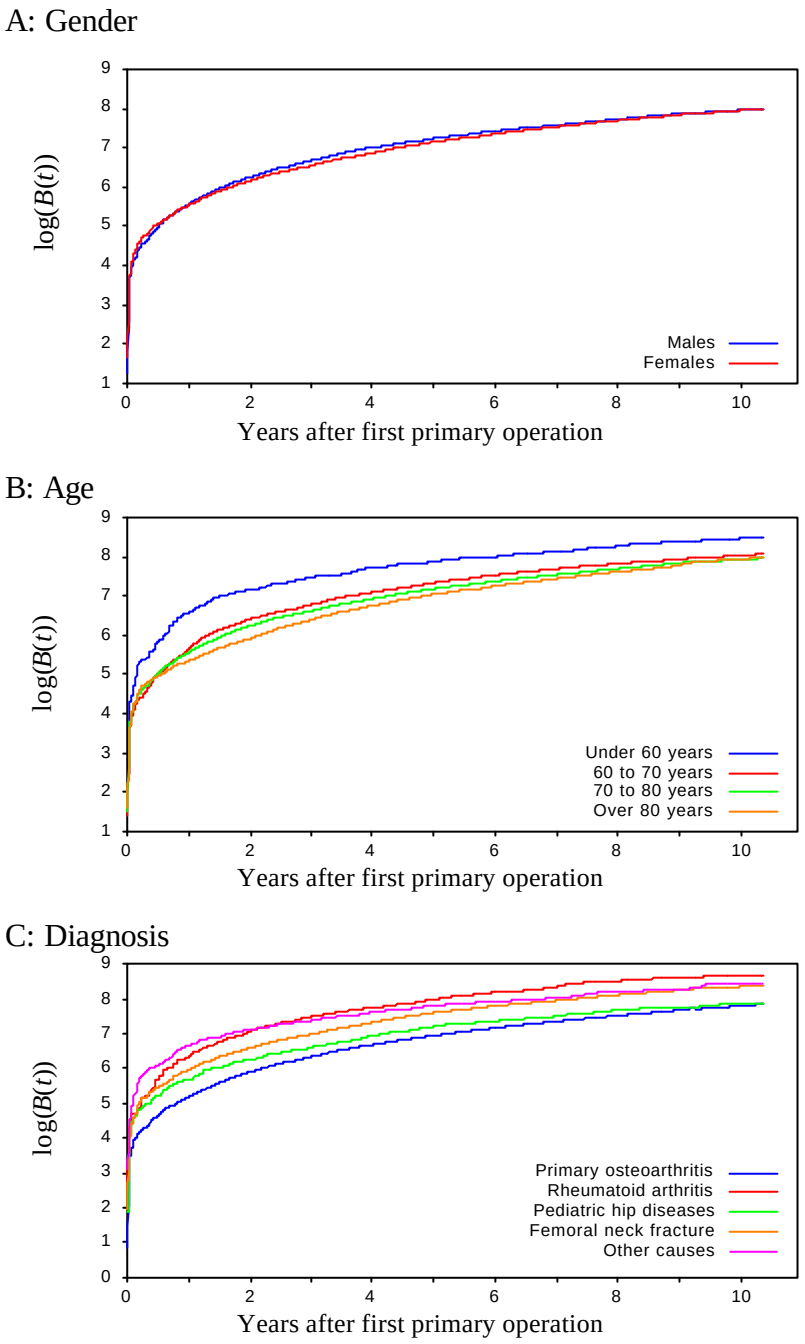


Figure 5.1. Plot of $\log(B(t))$ for gender, age and primary diagnosis. The model assumption of proportionality for the relative hazard in the extended Cox-model in paper I seems appropriate for gender (A) and age (B), but not for primary diagnosis (C). The primary diagnosis "other causes" has an increased relative mortality in the early postoperative period, which conflicts with the proportionality assumption. In paper I a time dependent covariate was used ($X(t)=I(t<60$ days)) to distinguish between effects the first 60 postoperative days and later.

6. Summary of papers

Paper I:

Mortality after total hip replacement, 0-10 years follow up of 39 543 patients in the Norwegian Arthroplasty Register.

Lie S.A., Havelin L., Engesæter L.B. Gjessing H.K., and Vollset, S.E.

Background: The long-term survival of patients with a total hip replacement is not well known. This study was done to examine the long-term survival for total hip replacement patients and to compare this survival with the survival for the general population, using the method from paper IV.

Material and methods: We followed 39 543 total hip replacement (THR) patients from insertion of their first primary hip prosthesis till time of death or until February 1st 1998. Kaplan-Meier curves for the patients were compared with expected survival curves. Furthermore, standardized mortality ratio's (SMR's) were used to compare the mortality between patients and the general population. Finally, an extended Cox regression model incorporating population mortality rates, and a time dependent covariate to identify secondary operations in the patients, was used to study differences in SMR's for explanatory variables and to control for confounding factors.

Results: The 8-year survival for THR patients was 75 %, while the expected number from the corresponding general population was 70 % (SMR=0.81). Patients under 50 years (SMR=2.50) and between 50 and 59 years (SMR=1.16) had an increased mortality compared to the general population. Further, patients with rheumatoid arthritis (SMR=1.48) or with femoral neck fracture (SMR=1.11) had an increased mortality. In the regression model we found that the SMR's decreased with increasing age and patients with two primary operations had a very low mortality. All patient catagories had an increased relative mortality the first 60 postoperative days (SMR=1.39).

Conclusion: THR patients have a reduced mortality compared to the standard population. This was however not the case for young patients (under 60 years) and patients with a diagnosis known to have high mortality. Patients with two primary total

hip operations had a further reduction in mortality compared to those with only one primary operation. For the first 60 postoperative days we found an increased relative mortality.

The statistical analysis of Kaplan-Meier curves compared to expected curves, standardized mortality ratios (SMR's), and the Cox-regression including population mortality rates, gives an attractive presentation of patient mortality data.

Paper II:

Early postoperative mortality after 67 548 total hip replacements - Causes of death and thrombosis prophylaxis in 68 Norwegian hospitals from 1987 to 1999.

Lie S.A., Havelin L., Engesæter L.B., Furnes O., and Vollset, S.E.

Background: In paper I an increased mortality for the first 60 postoperative days was found for patients with total hip replacements. In this paper we focused on this increased mortality and the use of thromboprophylaxis in Norway.

Material and methods: In this study we used data on 67 548 hip replacement patients reported until June 30th 1999. Data on mortality, until May 1st 2000, and data for causes of death, until December 31st 1995, was obtained. Information on the use of thromboprophylaxis at the different hospitals was collected using a separate questionnaire.

We used logistic regression, generalized additive logistic regression (GAM) models and calculated mortality curves (intensity/hazard) using Kernel smoothing techniques on the observed daily mortality.

Results: It was reported use of 24 different combinations of thromboprophylaxis during the 12-year study period. For the first postoperative week, the daily mortality was 2.5 deaths per 10 000 patients. At the 70th postoperative day it had decreased to 0.57 deaths per 10 000 patient.

Conclusion: There was a clear change in the types of thromboprophylaxis in use in Norway during this 12-year period. The last years *low molecular weight heparin*

(LMWH) completely dominated the marked (96 %). The mortality decreased rapid during the first postoperative weeks and after 3 weeks the mortality was less than for the general population (matched by age and gender). There was still a slight decrease in mortality between the 20^{th} and 70^{th} postoperative day. The most important risk factors for early postoperative mortality were high age, male gender, and an underlying diagnosis different from primary osteoarthrotis.

Paper III:

Dependency issues in survival analyses of 55 782 primary hip replacements from 47 355 patients

Lie S.A., Engesæter L.B., Havelin L.I., Gjessing H.K., and Vollset S.E.

Background: In analyses of time to revision for primary hip replacements, two prostheses from the same patient are most commonly considered to be two independent observations. Studies of the influence of having two prostheses for the risk of failure for each of the prosthesis and to what degree revision in the two hips are related, have rarely been presented.

Material and methods: We restricted the data to total hip replacements only from patients with available data on their first primary operation in the Norwegian Arthroplasty Register. Thus 47 355 patients first time operated between September 1987 and May 2000 were included. The total number of primary hip prostheses operations for these patients was 55 782.

Kaplan-Meier curves for all prostheses, ignoring that some patients had bilateral prostheses, were compared with Kaplan-Meier curves using only the first inserted prostheses, and with survival curves accounting for bilateral prostheses. Furthermore, was Cox regression analyses used to assess explanatory variables and to adjust for confounding factors. Results from standard Cox regression analyses were compared with results from a marginal model, a shared gamma frailty model, and a model using a time dependent covariate to condition on failures in the opposite hip.

Results: We found no practical difference between the three calculated survival curves for the hip replacement data. The standard Cox-model and the marginal model

gave equivalent results. In the shared gamma frailty model estimates for the risk factors were comparable with the former two approaches, even though the estimated frailty variance was high when all data were used. For the "homogeneous" data the estimated frailty variance was negligible. Using a time dependent covariate to condition on previous revisions in the opposite hip, we found a high risk of revision for the remaining hip if the opposite hip had been revised (RR=3.51, p<0.0001).

There was no difference in risk for revision between right and left hip prostheses. If the time interval between the two primary operations was more than two years the first hip prosthesis had an increased risk of revision compared to prostheses in patients with only one prosthesis (RR=1.26, p=0.0066), for the full data. While for the "homogeneous" data no statistically significant difference was found between unilateral and bilateral prostheses.

Conclusion: In analyses of risk factors and explanatory variables each hip can be used as the unit in analyses of time to revision. A failure of a hip prosthesis in one of the hips is, however, an important risk for a following revision in the opposite hip. This can be modeled using time dependent covariates.

Paper IV:

Expected survival compared with survival of peptic ulcer patients.

Lie S.A., Lie R.T. and Svanes C.

Background: In reports of patient survival, Kaplan-Meier survival curves are often presented. The patient survival curves are commonly presented with so-called expected survival curves. There are, however, different alternatives to calculate these curves and the interpretation of the curves may be problematic.

Material and methods: In this study, data from 1097 patients with perforated peptic ulcer, with a follow-up of 38 years, were used to illustrate the methods.

Results: If we use the Kaplan-Meier method to calculate $\hat{S}(t)$, it will estimate the expected survival, $S(t)$, for the patients. On the other hand, the hypothetical Kaplan-Meier calculation for random controls from the population, $\hat{S}_c(t)$, (matched for age,

gender and year of birth) would estimate the expected survival curve $S^*(t)$ for the controls.

It may therefore be sensible to compare $\hat{S}(t)$ with $S^*(t)$. Two alternatives for $S^*(t)$ are discussed and we advocate the direct adjusted curve as the expectation of a Kaplan-Meier curve for random population controls.

Schematic illustration of the estimated and expected survival curves for patients and controls:

	Patients	Controls
Estimated	$\hat{S}(t)$	$\hat{S}_c(t)$
Expected	$S(t)$	$S^*(t)$

Conclusion: In studies of patients survival Kaplan-Meier curves presented together with the expected survival curve presented in this article gives a satisfying presentation of the data. Presentation of survival curves should be done before more elaborate methods are used.

7. General discussion

This thesis has focus on applying appropriate analysis techniques for data on time to some event, either death or time to a revision surgery for prostheses. The data sources for the thesis was primarily the extensive database on total hip replacements from the Norwegian Arthroplasty Register. Furthermore, data with 38 years of follow-up for perforated peptic ulcer patients was also applied.

7.1. Methodological considerations

7.1.1. Study designs

Medical databases with a continuous follow-up of patients with a certain condition have become more and more common. Most of these data sources will represent observational or cross sectional studies. The motivation for the collection of the data can be several. Surveillance of differences or changes in the risk of specific conditions or diseases may be one.

Introduction of new drugs on the marked requires proof of efficacy using randomized clinical trials with specific requirements according to the FDA (Food and Drug administration, US) (Katz 1981). Such requirements are not present for the introduction of non-drug treatments, including orthopaedic procedures and products, but they should possibly be (Buchwald 1997). Concern has been raised to the small number of randomized trial in orthopaedics (Clark 1997, Laupacis et al. 1989, Rudicel and Esdaile 1985, Simon 1986, Surin 1989, van der Linden 1986). As a reply to this lack of studies, an effort has been made to present a system for a controlled introduction of new techniques and products (Malchau 1995). These systems include several stages in the introduction and investigation of new procedures. For instance; first sufficient laboratory tests should be present, then a small number of patients can be studied in a randomized trial, which could include RSA studies. This should be present before multi-center studies and the prostheses introduced on the open marked (Malchau 1995).

Moreover, comparison of randomized trials and register studies for total hip replacements have shown similar results (Garellick et al. 2000, Soderman et al. 2001, Soderman et al. 2000). The results from the national hip registry in Sweden have also shown that the overall revision rates for hip prostheses have decreased due to the results from the registry (Herberts et al. 1989, Herberts and Malchau 1997, Herberts and Malchau 2000).

Within orthopaedic surgery, randomized trials are rare. There are several reasons for this. The need to follow a sufficient number of patients for numerous years make such studies nearly impossible. Furthermore, large studies with a sufficient follow-up are not required before the products are allowed on the open market (Castro et al. 1997, Spencer 1996). Acceptable long-term results for good prostheses are 5 % re-operations before 10 years (95 % survival probability) and 2-3 % at 5 years. To detect a difference in risk for re-operation between two prostheses with 5-year failure rates of 2 and 5 % require 518 recruited patients per year if the level of significance is 5 % and the power is 80 %. Accumulated 2 590 patients are needed in this study (George and Desu 1974). If the 5 year failure rates were 2 and 3 %, a total of 15 543 patient would be needed.

The Norwegian Arthroplasty Register, and joint replacement registries in general, represents an observational study design with prospective registration of prostheses operations. This design will provide long-term results for the large variety of prostheses designs and techniques for the average orthopaedic surgeon. This type of study is a practical approach and not very resource demanding. It should, however, be kept in mind that potential confounders could influence results from such registries. If procedures or products are used only at few or single hospitals, with probably few or single surgeons, results for these procedures may reflect the skills of the surgeon rather than characteristics for the surgical procedure. Thus, it may be problematic to compare prostheses or procedures used at a limited number of hospitals since they may be heavily influenced by the skills of a limited number of surgeons.

The peptic ulcer patients data was retrospective collected for the Bergen area. For this type of patient material with a serious disease it may be sufficient to do a retrospective study, even with the long time-period, since all patients are admitted to a nearby hospital or other emergency unit. The occurrence of deaths before patients are

admitted to the hospital is low, since the perforated ulcer is not mortal itself, but conditions after the event is.

7.1.2. Outcome measures

The common outcome measure for total hip replacements in Arthroplasty Registers are a re-operation where there is a surgical removing or replacing of one or more components for the prosthesis. In paper I and II we focus on mortality/survival for the patients after total hip replacement operations. Paper III focus on the time from primary operation to a revision surgery, with special attention to patients with bilateral prostheses. In paper IV the long-term survival for perforated peptic ulcer patients.

7.1.2.1. Long term survival of patients

In studies of long-term survival it may be insufficient to draw conclusions and to compare different categories of patients without regarding the background mortality. An exception is if all patients are roughly the same age and of the same gender, comparing with background mortality in this setting will only result in referring all patients to the same reference. In analyses of patient mortality the data is linked to available information on data of death from Statistics Norway, using the individual population identification number in Norway. Mortality is hence a well-defined end point with a complete tracking of the Norwegian population. Survival times of patients still alive at the end of the follow-up or which has emigrated at a specific data are considered as censored observations at the time last seen. Hence studies of long-term all-cause mortality is relatively simple due to the complete information on date of death in Norway.

7.1.2.2. Short term mortality

Assessing short-term mortality is important in clinical materials related to an operation or other acute events. Usually it is possible to have complete information for such data due to the short observation time needed. Statistical methods used for ordinary survival data are hence not necessary for the present situation. Standard methods for binary data, e.g. logistic regression, are hence fully satisfactory.

It can also be argued both in favor for or against the implementation of background mortality rates in the analyses. Elderly patients will often have an increased mortality for the early postoperative period, due to the increased background mortality. However, when patients are in hospital-care it can be argued that the most important risk factors for mortality, age and gender, will not have the same importance due to the attention they receive under medical attention. An option in the analyses can be to analyze the early postoperative mortality without considering the background mortality, but to present the background mortality along with the patient mortality.

7.1.2.3. Prostheses revision

In analyses of prostheses survival in the Norwegian Arthroplasty Register, the outcome of most interest is failure of the prostheses reported as revision surgery. The reason for revision will often be a loosening of the prostheses, wear, osteolysis, infection, or a fracture (Lucht 2000, Puolakka et al. 2001). It can be argued against the use of this crude measure for the quality of the prostheses, while other possible more suitable measures are more difficult to obtain (Garellick et al. 2000). It may also be possible that the survival of the prostheses is related to the probability of dying and hence related to censoring. Patients with a high mortality (old patients) may therefore have a lower risk of re-operation of the prostheses. This may either be due to less activity for these patients or a higher threshold for the surgeons to operate these patients due to the higher mortality.

7.1.3. Completeness and quality of data

7.1.3.1. Total hip replacement data

Through the Norwegian Orthopaedic Association the Norwegian orthopaedic surgeons agreed to report their joint replacements to the Norwegian Arthroplasty Register. This enables the Norwegian Registry to track all joint replacements for a patient, regardless where in Norway the patient has been operated. A couple of surgeons are, however, not reporting their operations to the register, but these operations have minor influence. One of the surgeons has been the only using a particular prosthesis in Norway. Interpretation of results for this prosthesis would hence be problematic since it

reflects a single surgeon. It would be even more problematic should some surgeons underreport their re-operations.

The Norwegian Arthroplasty Register has been in regular contact with the Norwegian Patient Register, SINTEF/Unimed in Trondheim, and compares the number of registered prosthesis operations with them. Norwegian Patient Register has a mandatory registration based on summary reports from the hospitals in contrast to the Norwegian Arthroplasty Register with optional registration and individual data. Some minor hospitals have a low reporting rate, but the overall numbers showed that more than 95 % of the prostheses operations in Norway were reported to the registry.

7.1.3.2. Data on perforated peptic ulcer

The peptic ulcer data was collected in the city of Bergen in the county of Hordaland in western Norway. It represents all patients admitted to hospital during the years 1935 to 1990. Perforated ulcer is a condition, which always ends in a hospital stay. Therefore is the possibility for missing patients relatively small despite the long retrospective time for the study.

7.1.4 Statistics

7.1.4.1. Mortality rates

In studies of long-term survival the importance of comparing patient survival with some reference should be advocated. Possible choices of reference would be some sort of control group, possibly matched to the patients using some confounding variables or to use available mortality rates from relevant sources. Sources for these mortality rates may be previous similar studies (Nielsen 1997, Thomsen et al. 1991) or known mortality rates such as national mortality statistics.

To refer to the background mortality rates as national mortality rates for healthy individuals is not correct, since the national mortality rates consists of all individuals including all patients in any study. This can lead to an observed reduced mortality for a patient-material, which can be hard to interpret. On the other hand it may be impossible to compare patients with *healthy individuals* as these may be hard to define. Furthermore, healthy individuals should have a low mortality caused by accidents and

other unexpected sudden deaths. Thus, use of comparable control groups or background mortality rates may be preferable. Mortality rates from the complete population give an attractive comparison with almost any patient material. These rates are usually based on a large number of observations and can hence be thought of as being without uncertainty or variation.

One may argue that the mortality rates should be smoothed before they are used, but on the other hand the observed rate for one particular cell (e.g. for age, gender, and year of birth) reflect the specific death rate for that cell. Smoothing may therefore disturb the comparison of the particular patient with the accurate observed population mortality. Mortality-rates may sometimes be present from previous studies either through observed rates or maybe more preferable through rates from previous hazard regression models (e.g. the Cox-model)

7.1.4.2. Survival analyses

Analysis of survival data plays an important role in medical research (Altman et al. 1995). Presentation of survival probabilities for such follow-up data is commonly presented before more elaborate methods are considered. The Kaplan-Meier method for calculating survival probabilities has become a standard for calculating and graphical presentation of follow-up data. Presentation of the Kaplan-Meier curves with confidence limits (95 %) (Cantor 2001) and inference based on log-rank tests (Peto et al. 1977) gives an attractive initial presentation of the situation. The confidence limits can further be adjusted for the number of observations at risk (Dorey and Korn 1987) and the inverse Kaplan-Meier calculation can be used to calculate median follow-up for the study (Korn 1986, Schemper and Smith 1996). The simple interpretation of survival curves and the flexibility in the Kaplan-Meier method are important to keep in mind when introducing more elaborate methods.

The Cox proportional hazards model is with no doubt the most common regression technique for survival data. Its popularity may be explained by the simple and straightforward interpretation of the parameters for the explanatory variables (Tibshirani 1982). Estimation of the model parameters using the partial likelihood is relatively simple to implement and it is hence present in most commercial statistical packages for computers.

Frailty models for survival analyses of multiple failure data has become popular during the last decade (Liang et al. 1995, Wei and Glidden 1997). The term frailty was introduced by Vaupel et al. in 1979 (Vaupel et al. 1979). These models are the analogues to random effects models for normal distributed data (Hougaard 1995, Vaida and Xu 2000). There are several difficulties with frailty models. Interpretation of the parameters for the explanatory variables is not straightforward, especially for the proportional hazards model (Keiding et al. 1997). For the standard Cox model there are two interpretations of the parameters for the explanatory variables.

If all the other variables are fixed:

1. "The population effect of changing the value of a specific variable to another level"
2. "The effect for one individual (or item) of changing the value of a specific variable to another level."

For the frailty model only the second interpretation can be applied since the variable describing the individuals also must be fixed. Hence, even if the parameter estimates are equal in a standard Cox model and a frailty model, the interpretation of the effects in the frailty model can be absurd (e.g. for gender) or difficult, as it is for random effects models (Larsen et al. 2000). The proportional hazards frailty model,

$$l_{ji}(t) = v_j \, l_0(t) e^{\beta^T \mathbf{x}_{ji}}, \qquad (7.1)$$

has the term ϖ which describes the heterogeneity between each of the items (j=1,…,J). This term follows a distribution, often a gamma or a log-normal distribution (Aalen 1988), with mean 1 and variance θ. The interpretation of this model is that each item, individual has its own frailty for failure which will influence all observations from the item. Hence, an item with a high frailty component will have an increased risk of failure for all its observations. Observations from the same item will thus be correlated if there is a frailty effect. This interpretation makes it attractive to use frailty models for multivariate survival situations, where the idea is to model dependence between observations from the same patients. For the total hip replacement data, with 20 % bilateral prostheses, there may however be problems with the interpretation of the frailty as a possible dependence between the time to failure for the prostheses. The frailty will be dominated by the heterogeneity between patients with only one prosthesis, thus a possible dependence between bilateral prosthesis may vanish. The heterogeneity

between individuals, modeled by the frailty, may be interpreted as unobserved or missing important covariates, thus for the multivariate frailty situation it may be interpreted as unobserved common covariates for the cluster (Keiding et al. 1997). Effects of omitting important covariates in the Cox regression model has been studied by Scmoor and Schumacher (Schmoor and Schumacher 1997).

7.2. Discussion of results

7.2.1. Long term survival of patients

There are few studies of long-term mortality for total hip replacement patients (Lindberg et al. 1984, Schrøder and Erlandsen 1993, Surin and Sundholm 1983, Whittle et al. 1993) and total knee replacement patients (Schrøder et al. 1998). The database on total hip replacement patients from the Norwegian Arthroplasty Register is an almost complete registry on patients in Norway with total hip replacements. Together with the national mortality data from Statistics Norway, it forms an ideal data source for analysis of mortality. These data represent therefore a valuable and unique material for studies on long-term survival for joint replacement patients.

Patients with total hip replacements form a special data source in several ways. Total hip replacement operations are successful in terms of cost-effectiveness (Rorabeck et al. 1994) and usually improve function and quality of life for the patients. Furthermore, a total hip replacement operation is a major surgical procedure which may influence the mortality both directly, as for the early postoperative mortality, and possibly indirectly as for the long-term mortality. Mortality for total hip replacement patients was therefore of particular interest.

The overall long-term survival for total hip replacement patients was higher than in the corresponding Norwegian population. The most intuitive explanation for this is a selection of healthier individuals than the average citizen for this type of surgery. However, for different subsets of patients, there were different findings. If the indication for hip surgery was a disease with a known increased mortality, a high mortality was also found for total hip replacement patients within these diagnostic groups. Patients with rheumatoid arthritis are known to have an increased mortality (Vandenbroucke et

al. 1984, Wolfe et al. 1994) and this was also the case for rheumatoid arthritis patients with total hip replacement. We were not capable of assessing the difference in mortality for rheumatoid arthritis patients with or without prostheses, but it is plausible that there is a selection of healthier rheumatoid patients to total hip replacement surgery. The hypothesis of a selection mechanism for total hip replacement patients was strengthened by the finding that patients with bilateral primary total hip replacements had a further reduced mortality compared to unilateral patients. There was also no difference in mortality for patients with a revision surgery compared to patients with unilateral primary operations. For total hip replacements, we found no other study using repeated operations as risk factors for mortality. The reason might be that this is best implemented in the regression model for the mortality data using time dependent covariates, which may be technically demanding.

7.2.2. Early postoperative mortality

We found a higher long-term survival for total hip replacement patients compared to the general Norwegian population, with the exception of some patient categories. However for the early postoperative period there was an increased mortality for all patient categories. The increase in early postoperative mortality was only 1 % for the first 60 postoperative days. The daily mortality was 2,5 deaths per 10 000 patient for the first postoperative week. The increase in the daily mortality persists for as long as the 70^{th} postoperative day compared with the average mortality between day 200 and 300 for the patients. However, the main increase was for the first 20 postoperative days, while the increased mortality between day 20 and 70 was minor, compared with the average mortality between day 200 and 300. After day 20 the daily patient mortality was at the level of the corresponding Norwegian population, with a mortality of 0.95 deaths per 10 000 per day. However, to compare the early postoperative patient mortality with the background population is unfair due to the knowledge of an overall lower long-term mortality for the patients compared to the general population.

Our collected data for thromboprophylaxis, attached to the mortality information for the patients, can not be used as a guide for therapeutically practice, since this is not a randomized trial. Furthermore, the thromboprophylaxis data were summaries for the reporting hospitals and not on an individual basis and the potential hospital-confounders

for mortality are several. Some hospitals could have more low-risk patients than others, e.g. private hospitals. While other hospitals have more complicated and high-risk patients, e.g. university hospitals.

Thromboprophylaxis is most commonly used for 10-14 days postoperatively. In this period of time the mortality decreased most rapidly, and the mortality continued to decrease also after this period. This can not be taken into account for no effect of prolonging the use of thromboprophyalxis for a longer period, but there is no indication for an increase in mortality (rebound) after the period when most patients receive some sort of prophylaxis.

Due to the low mortality and therefore the need for large randomized trial to obtain statistically significant differences in mortality for different thromboprophylaxis regimens, surrogate measures are often used (Murray 2000). The most commonly used measure is deep venous thrombosis (DVT) obtained by venography. These measures are not necessarily clinical important (Murray 2000), but have a high occurrence and are therefore suitable in smaller randomized trials. However, to draw conclusions on mortality based on findings for DVT is problematic even though an association between DVT and mortality was shown already 25 years ago (Kakkar et al. 1975). Older studies may not be ideal to use as an argument for the association between DVT and mortality since newer methods for finding DVT is much more effective than the older methods.

7.2.3. Bilateral hip prostheses

The quality control of joint replacements is most commonly based on analyses where the joint represents the unit in the analyses ignoring that some 20 % of the hip replacements are bilateral (Morris 1993). According to our study, this will in be satisfactory most situations and also simplifies the analyses, as Kaplan-Meier survival probabilities and Cox regression models should be appropriate.

In studies of bivariate survival, the observations are often paired with the same follow-up time, e.g. for twins. For joint replacements, bilateral operations are relatively uncommon and are rarely performed at the same time in both hips (Alfaro-Adrian et al. 1999, Eggli et al. 1996, Husted et al. 1996, Laursen et al. 2000, Ritter et al. 1995). The argument for operating both sides at the same time may be a reduction in the overall hospital stay, overall operation risk, and a reduced total cost of the two operations

(Cammisa et al. 1988, Lorenze et al. 1998, Reuben et al. 1998). It must be taken into consideration, when the statistical analyses are planned, that individuals with a joint replacement on one side may have a second replacement later in the opposite side and that comparison of results from one side not can be directly compared with the opposite side (Knessl et al. 1989). How one hip prosthesis influence the outcome for a later prosthesis in the opposite hip is not straightforward to model (Madarasz and Zukor 1995).

The clinical reasons for why patients with a revision in one hip may have increased risk for a revision in the opposite hip are several. If the prosthesis in one of the hips is painful or loose, it can cause the patient to limp or to put more weight on the opposite hip. Furthermore, it can also be possible that some patients have characteristics which may influence both hips, e.g. a disease such as osteoporosis, allergy (Cancilleri et al. 1992, Gawkrodger 1993, Haddad et al. 1996, Rooker and Wilkinson 1980), or a higher risk for obtaining infections (Clementi et al. 1980, Nater et al. 1976, Waterman and Schrik 1985). Accordingly, some individuals might be more frail than others since the possible susceptibility will be equal for both hips in the patient, the concept of frailty models may be appropriate for analyses of total hip replacements (Vaupel and Yashin 1985, Aalen 1994).

7.2.4. Expected survival and survival of patients with peptic ulcer

The Kaplan-Meier curves estimating patient survival probabilities forms an important basis in analysis of survival data. The data from Bergen on perforated peptic ulcer patients with 38 years of follow-up illustrates that simple survival curves are an important first step before more elaborate methods are applied, but that they should be presented together with expected survival curves calculated from population mortality rates with a clear interpretation.

The S-Plus manual (S-Plus 2000) presents three methods for calculating expected survival curves and discusses the three methods as a more or less arbitrary choice between equivalent methods. The *exact* method (Ederer and Axtell 1961) calculated with a complete information of mortality rates from the reference population will be difficult or impossible to calculate and may depend on extrapolation of mortality rates. Comparison of this method with a Kaplan-Meier curve for patients with a censoring

pattern may then be unnatural. Furthermore, the *conditional* method, or *continous time adjusted* method, (Andersen and Væth 1989, Verheul et al. 1993), which is more simple to compute, is claimed to be related to the *direct* method (*Hakulinen* or *cohort* method). This is based on the term that $E(Y_i(t)) = S_i(t) \cdot C_i(t)$, where $Y_i(t)$ is 1 if patient *i* is observed at risk, $S_i(t)$ is the survival probability for patient *i*, and $C_i(t)$ is the censoring probability for patient *i*. This is not fully correct since $S_i(t)$ is not observable. In the direct method $S_i^*(t)$ is calculated from the population mortality rates, while $C_i(t)$ is 1 for the potential follow-up for patient *i*, and 0 otherwise, which usually will be until the end of study. Thus based on the idea that the expected curves are expected for random popualtion controls will $E(Y_i^c(t)) = S_i^*(t) \cdot C_i(t)$, where $Y_i^c(t)$ is 1 if the hypothetical control *i* is observed at risk.

In paper IV we advocate that the *direct* method for calculation of expected survival curves are easy interpretable, with a clear meaning, and that they therefore are preferred before other methods referred to as expected survival curves. Nielsen (Nielsen 1997) discusses consistency and asymptotic distribution properties for expected survival curves under the assumption of previous hazard rates from Cox-regression models.

8. Conclusions

1. The overall long-term survival for total hip replacement patients was higher than for the corresponding population.

2. Younger prosthesis patients and patients in diagnostic groups with a known increased mortality had, however, an increased long-term mortality. Patients with two hip prostheses had a further reduction in their long-term mortality compared to patients with one prosthesis.

3. During the early postoperative period there was an increased mortality for all patients. The main increase was for the first 20 postoperative days, while there still was a slight increase until the 70^{th} postoperative day.

4. For the early postoperative period were deaths categorized as thromboembolic events the most frequent causes.

5. There have been a large variety of different thromboprophylaxis regimens in use in Norway during the years 1987 to 1999. During the later years, almost all hospitals reported use of thromboprophylaxis including low molecular weight heparin (LMWH).

6. In analyses of time to failure of total hip prostheses it may be sufficient to consider two prostheses from the same individual as unrelated observations and dependency between them may be ignored.

7. Patients with a failure of a hip prosthesis on one side had an increased risk of failure of the prosthesis in the other hip.

8. We advocate that for studies of patient survival, the Kaplan-Meier estimator should be presented with expected survival curves based on population mortality tables.

These curves should reflect the expectation of hypothetical random selected population controls and should be presented before more elaborate methods are considered.

9. Future research

Until now, the Norwegian Arthroplasty Register has focused on primary prostheses in hip and knee. Data from the register may, however, also be used to study revision prostheses. Revision prostheses is a much more heterogeneous category and with poorer results than primary prostheses (Retpen et al. 1992, Stromberg et al. 1992). A simple study for the revision prostheses giving descriptive statistics and overall results will be of clinical interest and may form a basis for further research on revision prostheses.

There is an increasing focus on and need for analyses of repeated measures in medical research (Hougaard 1995, Kelly and Lim 2000, Aalen and Husebye 1991). In the Norwegian Arthroplasty Register about 20 % of the patients receive a second operation in the same hip (a revision surgery) and some patients have several operations in the same hip (there are patients registered with 8 operations in the same hip in the arthroplasty register). To evaluate characteristics for patients with repeated revisions will be of clinical relevance. Analyses of data for renewal processes are a methodological ongoing topic in statistics, where the hip replacement data can be illustrative (Ripatti and Palmgren 2000).

The Norwegian Arthroplasty Register has recorded joint replacement operations in practically all joints since 1994. Analyses of these data will play a more important role in the registry in the future. For prostheses in joints other than hips and knees, there are more patients with chronic diseases (e.g. rheumatoid arthritis). These patients may also have joint replacements in several joints (Gschwend 1995), which may be dependent in their time to failure. To study the data from several joints may be of particular interest for these patient categories. The relation between the joint replacements in the different joints should be incorporated in appropriate statistical methods.

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11. Appendix

11.1 Thromboprophylaxis questionnaire (Norwegian)

11.2 Total hip replacement-form used from 1993 (English translation)

11.3 Total hip replacement-form used until 1993 (Norwegian)

11.4 Total hip replacement-form used from 1993 (Norwegian)

11.1 Thromboprophylaxis questionnaire (Norwegian)

Nasjonalt Register for Leddproteser
Ortopedisk avdeling
Haukeland sykehus
5021 BERGEN

Spørreskjema om tromboseprofylakse ved innsetting av hofteprotese (Navn på sykehuset)

Periode dette regimet er benyttet: **Fra**: ____/____/____ **Til**: 30 / 04 / 99

☐ 1. Ingen tromboseprofylakse
☐ 2. Marevan: Varighet (antall dager): _____
☐ 3. Acetylsalisylsyre: Varighet (antall dager): _____
☐ 4. Lavmolykelært heparin:
☐ 4a. Klexane: Varighet (antall dager): _____
☐ 4b. Fragmin: Varighet (antall dager): _____
☐ 4c. Innohep: Varighet (antall dager): _____
☐ 4d. Clivarin: Varighet (antall dager): _____
☐ 5. Heparin: Varighet (antall dager): _____
☐ 6. Makrodex: Varighet (antall dager): _____
☐ 7. Annen type: Navn: _____
Varighet (antall dager): _____
☐ 8. Trombose strømpe: Varighet (antall dager): _____

(evt. flere kryss)

Kommentar:

Periode dette regimet er benyttet: **Fra**: ____/____/____ **Til**: ____/____/____

☐ 1. Ingen tromboseprofylakse
☐ 2. Marevan: Varighet (antall dager): _____
☐ 3. Acetylsalisylsyre: Varighet (antall dager): _____
☐ 4. Lavmolykelært heparin:
☐ 4a. Klexane: Varighet (antall dager): _____
☐ 4b. Fragmin: Varighet (antall dager): _____
☐ 4c. Innohep: Varighet (antall dager): _____
☐ 4d. Clivarin: Varighet (antall dager): _____
☐ 5. Heparin: Varighet (antall dager): _____
☐ 6. Makrodex: Varighet (antall dager): _____
☐ 7. Annen type: Navn: _____
Varighet (antall dager): _____
☐ 8. Trombose strømpe: Varighet (antall dager): _____

(evt. flere kryss)

Kommentar:

11.2 Total hip replacement-form used from 1993

(English translation)

THE NORWEGIAN ARTHROPLASTY REGISTER (TOTAL HIP REPLACEMENTS)

Patient: **Hospital:**

Previous operation in index hip:
0 No
1 Osteosynthesis for prox. femur fracture
2 Hemiprosthesis
3 Osteotomy
4 Arthrodesis
5 Total hip prosthesis
Type: .....
Year: .....
Number: .....
6 Other operation: .....

Date of operation: .....

Index operation is:
1 Primary operation
2 Revision

Hip:
1 Right
2 Left
3 Right, prosthesis in left hip
4 Left, prosthesis in right hip

Diagnosis (primary operation):
1 Idiophatic coxarthrosis
2 Rheumatoid arthritis
3 Sequelae after hip fracture
4 Sequelae after dysplasia
5 Sequelae after dysplasia with dislocation
6 Sequelae after slipped capital femoral epiphysis or Perthes disease
7 Ankylosing spondylitis
8 Other: .....

Reasons for revision (one or more):
1 Loosening of acetabular component
2 Loosening of femoral component
3 Dislocation
4 Deep infection
5 Fracture of femur
6 Pain
7 Other: .....
8 Osteolysis of acetabular component, no loosening
9 Osteolysis of femoral component, no loosening

Revision:
1 Change of femoral component
2 Change of acetabular component
3 Change of all components
4 Other:
- Removal of component (e.g. Girdlestone)
Which parts: .....
- Exchange of PE liner only
- Exchange of caput only
- Other: .....

Approach:
1 Anterior
2 Anterolateral
3 Lateral
4 Posterolateral

Osteotomy of trochanter:
1 Yes
2 No

Bone transplantation:
1 No
2 In acetabulum
3 In femur
4 In both

Acetabulum:
Name/type: .....
Catalogue number: .....
Hydroxyapatite coated: 1 Yes 2 No
1 Cement with antibiotic. Name: .....
2 Cement without antibiotic. Name: .....
3 Uncemented

Femur:
Name/type: .....
Catalogue number: .....
Hydroxyapatite coated: 1 Yes 2 No
1 Cement with antibiotic. Name: .....
2 Cement without antibiotic. Name: .....
3 Uncemented

Caput:
1 Fixed caput
2 Modular system.
Name/type: .....
Catalogue number: .....
Diameter (mm): .....

Systemic antibiotic prophylaxis:
1 No 2 Yes.
Name: .....
Dosage: .....
Duration (days): .....

Operating theatre:
1 'Green house'
2 With laminar air flow
3 Without laminar airflow

Duration of operation:
Skin to skin (min.):

Perioperative complication:
1 No
2 Yes. Name: .....

Surgeon (who has filled in the form)**:**

.....
(Surgeon name is not registered)

11.3 Total hip replacement-form used until 1993 (Norwegian)

NASJONALT REGISTER FOR TOTALPROTESER I HOFTELEDD
Ortopedisk avdeling
Haukeland sykehus,
5021 BERGEN

F.nr.:

Navn:

Sykehus:

ANAMNESE:

1. SMERTER (ett kryss):
☐1 Sterke spontane i hvile og om natten.
☐2 Sterke som hindrer all gangaktivitet.
☐3 Moderate, tillater begrenset gange.
☐4 Etter noe aktivitet, forsvinner i hvile.
☐5 Lette eller periodevise. Startsmerter.
☐6 Ingen smerter.

2. GANGEVNE (ett kryss):
☐1 Få meter med 2 krykker/stokker/sengeliggende.
☐2 Sterkt begrenset med eller uten stokker.
☐3 Begrenset med stokk (under en time). Kan stå lenge.
☐4 Kan gå lange avstander med en stokk.
☐5 Ingen stokk, men halter.
☐6 Normal gangevne.

3. FUNKSJONSGRUPPE (ett kryss):
☐1 Aktuelle hofte syk ellers frisk.
☐2 Begge hofter syke ellers frisk.
☐3 Annet som reduserer gangevnen.

4. TIDLIGERE OPERASJON(ER) I AKTUELLE HOFTE:
☐0 Nei
☐1 Osteosyntese pga. fraktur i prox.femurende.
☐2 Hemiprotese pga. fraktur
☐3 Osteotomi.
☐4 Artrodese.
☐5 Totalprotese(r) Type(r): . . . . . .
Årstall siste protese: ⌊__⌋⌊__⌋
☐6 Annet: . . . . . .

5. VARIGHET AV SYMPT. I AKT. HOFTE: ⌊__⌋⌊__⌋ år
(under 1 år = 0).

OPERASJONSOPPLYSNINGER:

6. OPERASJONSDATO: dag ⌊__⌋⌊__⌋ mnd ⌊__⌋⌊__⌋ år ⌊__⌋⌊__⌋

7. AKTUELLE OPERASJON ER (ett kryss).
☐1 Primær totalproteseoperasjon.
☐2 Reoperasjon.

8. AKTUELLE SIDE (ett kryss).
☐1 Høyre
☐2 Venstre
☐3 Høyre - venstre allerede protese.
☐4 Venstre - høyre allerede protese.

9. AKTUELLE HOFTEOPERASJON ER (ett kryss).
a) Primæroperasjon pga.:
☐1 Idiopatisk coxartrose
☐2 Rheumatoid artritt.
☐3 Seq.fr. colli fem.
☐4 Seq.dysplasi.
☐5 Seq.dysplasi med luksasjon.
☐6 Seq.Perthes/epifys.
☐7 Bechterew.
☐8 Annet: . . . . . .

b) Reoperasjon pga. (evt. flere kryss):
☐1 Løsning av acetabulardel.
☐2 Løsning av femurdel.
☐3 Luksasjon.
☐4 Dyp infeksjon.
☐5 Fraktur av femur.
☐6 Smerter.
☐7 Annet: . . . . . .

10. **HVIS** reoperasjon (ett kryss):
☐1 Reop. - bytte av femurdelen.
☐2 Reop. - bytte av acetabulardelen.
☐3 Reop. - bytte av hele protesen.
☐4 Reop. - annet: . . . . . .

11. TILGANG (ett kryss):
☐1 Fremre (Smith-Pettersen).
☐2 Anterolateral.
☐3 Lateral.
☐4 Posterolateral
☐5 Annen: . . . . . .

12. TROCHANTEROSTEOTOMI:
☐0 Nei
☐1 Ja

13. BENTRANSPLANTASJON:
☐0 Nei
☐1 I acetabulum.
☐2 I femur.

PROTESE. NAVN/TYPE **(Spesifiser nøyaktig):**
14. **Acetabulum:**
Navn/Type: . . . . . .
. . . . . .
☐1 Sement med antibiotika. Navn: . . . . . .
☐2 Sement uten antibiotika. Navn: . . . . . .
☐3 Ikke sementert.

15. **Femur:**
Navn/Type: . . . . . .
. . . . . .
☐1 Sement med antibiotika. Navn: . . . . . .
☐2 Sement uten antibiotika. Navn: . . . . . .
☐3 Ikke sementert.

16. **Caput:**
☐1 Fastsittende caput.
☐2 Separat caput. Navn/Type: . . . . . .
. . . . . Diam.: . . . . .

17. SYSTEMISK ANTIBIOTIKAPROFYLAKSE:
☐0 Nei
☐1 Ja. Hvilken: . . . . . .
Dose: . . . . . .
Varighet: . . . . . .

18. OPERASJONSSTUE:
☐1 "Green House"
☐2 Operasjonsstue med Allandertak.
☐3 Vanlig operasjonsstue.

19. OPERASJONSTID (hud til hud): ⌊__⌋⌊__⌋⌊__⌋min.

20. PEROPERATIVE KOMPLIKASJONER:
☐0 Nei.
☐1 Ja. Hvilken: . . . . . .

Lege : . . . . . .
(Legen som har fylt ut skjemaet)

11.4 Total hip replacement-form used from 1993 (Norwegian)

NASJONALT REGISTER FOR LEDDPROTESER
Ortopedisk avdeling
Haukeland Sykehus
5021 BERGEN
Tlf.: 55 97 27 63

1. F.nr. (11 sifre) .....
   Navn: .....
2. Sykehus: .....
   (Skriv tydelig!)

HOFTEPROTESER

ALLE TOTALPROTESER I HOFTELEDD REGISTRERES (ikke hemiproteser)
Innsetting, skifting eller fjerning av protese eller protesedeler.

4. TIDLIGERE OPERASJON I AKTUELLE HOFTE (evt. flere kryss)
- ❑ 0 Nei
- ❑ 1 Osteosyntese for fraktur i prox.femurende
- ❑ 2 Hemiprotese pga fraktur
- ❑ 3 Osteotomi
- ❑ 4 Artrodese
- ❑ 5 Totalprotese(r)
- ❑ 6 Annen operasjon .....

5. Hvis protese tidligere, TYPE(R): .....
Årstall siste protese: |_|_|
Antall proteser tidligere i aktuelle hofte: |_|_|

6. OPERASJONSDATO: dag |_|_| mnd |_|_| år |_|_|

7. AKTUELLE OPERASJON ER (ett kryss):
- ❑ 1 Primæroperasjon (Også hvis hemiprotese tidl.)
- ❑ 2 Reoperasjon (totalprotese tidligere)

8. AKTUELLE SIDE (ett kryss):
(Bilateral opr.= 2 skjema)
- ❑ 1 Hø
- ❑ 2 Ve
- ❑ 3 Hø - Venstre allerede protese
- ❑ 4 Ve - Høyre allerede protese

9. AKTUELLE OPERASJON ER:
(kryss av enten i 9A eller 9B)

A. Primæroperasjon pga. (ett kryss)
- ❑ 1 Idiopatisk coxartrose
- ❑ 2 Rheumatoid artritt
- ❑ 3 Seqvele etter frakt.colli fem.
- ❑ 4 Seqv. dysplasi
- ❑ 5 Seqv. dysplasi med total luksasjon
- ❑ 6 Seqv. Perthes/Epifysiolyse
- ❑ 7 Mb. Bechterew
- ❑ 8 Annet: .....
  (f.eks. caputnekrose, tidl.artrodese, akutt fraktur o.l.

B. Reoperasjon. pga. (evt. flere kryss)
- ❑ 1 Løs acetabular komponent
- ❑ 2 Løs femur komponent
- ❑ 3 Luksasjon
- ❑ 4 Dyp infeksjon
- ❑ 5 Fraktur (ved protesen)
- ❑ 6 Smerter
- ❑ 7 Annet .....
  (f.eks Girdlestone etter tidl. infisert protese, protesefraktur, utslitt plastforing osv.)
- ❑ 8 Osteolyse i acetab. uten løsning
- ❑ 9 Osteolyse i femur uten løsning

10. REOPERASJONSTYPE (evt. flere kryss)
- ❑ 1 Bytte av femur komponent
- ❑ 2 Bytte av acetabularkomponent
- ❑ 3 Bytte av hele protesen
- ❑ 4 Andre operasjoner:
  - ❑ Fjernet protese (f.eks Girdlestone).
    Angi hvilke deler som ble fjernet .....
    .....
  - ❑ Bytte av bare plastforing .....
  - ❑ Bytte av bare caput
  - ❑ Annet: .....
    .....

Hustrykkeriet H. S. 13.6.95 - 1/2

11. TILGANG
- ❑ 1 Fremre (Smith-Pettersen)
- ❑ 2 Anterolateral
- ❑ 3 Lateral
- ❑ 4 Posterolateral
- ❑ 5 Annen: .....

12. TROCHANTEROSTEOTOMI
- ❑ 0 Nei
- ❑ 1 Ja

13. BENTRANSPLANTASJON
- ❑ 0 Nei
- ❑ 1 I acetabulum
- ❑ 2 I femur
- ❑ 3 I acetabulum og femur
- ❑ 4 Benpakking i acetabulum (impaksjon)
- ❑ 5 Benpakking i femur (impaksjon a. m. Ling/Gie)

PROTESE: NAVN/DESIGN/"COATING"
Spesifiser nøyaktig eller bruk klistrelapp på baksida

14. Acetabulum
Navn/Type: .....
Evt. katalognummer: .....
- ❑ Med hydroksylapatitt ❑ Uten HA
- ❑ 1 Sement med antibiotika - Navn: .....
- ❑ 2 Sement uten antibiotika - Navn: .....
- ❑ 3 Usementert

15. Femur
Navn/Type: .....
Evt. katalognummer: .....
- ❑ Med hydroksylapatitt ❑ Uten HA
- ❑ 1 Sement med antibiotika - Navn: .....
- ❑ 2 Sement uten antibiotika - Navn: .....
- ❑ 3 Usementert

16. Caput
- ❑ 1 Fastsittende caput
- ❑ 2 Separat caput - NavnType: .....
  Evt. katalognummer: .....
  Diameter: |_|_| millimeter

17. SYSTEMISK ANTIBIOTIKAPROFYLAKSE:
- ❑ 0 Nei
- ❑ 1 Ja, hvilken .....
  Dose: .....
  Varighet (antall døgn): |_|_|

18. OPERASJONSSTUE
- ❑ 1 "Green house"
- ❑ 2 Operasjonsstue med laminær luftstrøm
- ❑ 3 Vanlig operasjonsstue

19. OPERASJONSTID (HUD TIL HUD): |_|_|_| MINUTTER

20. PEROPERATIV KOMPLIKASJON
- ❑ 0 Nei
- ❑ 1 Ja, hvilken: .....
  .....

Lege: .....
Legen som har fylt ut skjemaet, (navnet registreres ikke)

12 Papers I to IV