USING ENRICHED QUALITY REGISTER DATA FOR HEALTH CARE EVALUATION: EXAMPLES FROM RHEUMATOID ARTHRITIS

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Using Enriched Quality Register Data for Health Care Evaluation: Examples from Rheumatoid Arthritis

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ABSTRACT

Swedish registers have for decades successfully been used for medical research, enabling long-term follow-up of large patient cohorts using observational designs. With a tax funded health care system and the use of a personal identity number as a unique identifier, together with national health registers as well as national demographic registers, we have to a relatively low cost the possibility to answer an abundance of research questions in a real-world setting.

This thesis describes how the Swedish Rheumatology Quality register (SRQ) can be enriched with national register data for estimating disease occurrence, assessment of health care resource use and work loss, and for potentiating randomized controlled trials (RCTs) conducted within the register framework. More specifically, by using the SRQ that collects disease specific data on patients with rheumatic diseases in routine clinical care together with objectively assessed data from national registers we could in a large sample of patients with rheumatoid arthritis (RA) estimate the incidence and burden of RA. Furthermore, with a randomized pragmatic clinical trial included in the register framework, we could provide information on health economic outcomes regarding a common clinical question in early RA, whether to continue treatment by adding an expensive biologic alternative or to continue with a conventional combination treatment strategy after insufficient response to methotrexate.

We found an overall incidence of RA in Sweden on a par with previous local but detailed studies (41 per 100,000; paper I), with a substantial variation across age and sex. We observed that the incidence of RA peaked in the 7th decade in life in both sexes, and that the incidence in women was more than twice the incidence observed in men. Furthermore, we observed lower incidence estimates in individuals with higher education level and in densely population areas. With respect to burden of disease, we used general population comparators individually matched to register-identified subjects with RA and estimated the annual societal cost in prevalent as well as monthly societal cost in newly diagnosed patients to 2-3 times higher than in the general population (paper II).

The randomized Swefot trial compared the addition of the biologic drug infliximab versus conventional combination therapy in patients with early RA who had failed initial methotrexate monotherapy. With the Swefot trial included in the SRQ, we could for the first time in a randomized register trial setting analyze work loss and cost-effectiveness for a strategy adding a biologic alternative as compared to conventional combination therapy in methotrexate-refractory early RA.

We observed a substantial decrease in mean monthly work loss days in both treatment alternatives, with a reduction of 3 times to double that in the general population from randomization to 21 months of follow-up, but no difference between the strategies could be detected (paper III). This remaining gap to the general population indicates a need for earlier diagnosis as well as for more effective treatment strategies of RA. In the cost-effectiveness analysis we observed similar effects between the strategies over 21 months, while the infliximab strategy incurred higher costs (paper IV), suggesting that an attempt with conventional combination therapy appears reasonable before starting infliximab treatment in methotrexate-refractory early RA, both from a clinical and economic perspective.
LIST OF SCIENTIFIC PAPERS

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II. **Eriksson JK**, Johansson K, Askling J, Neovius M.
    Costs for hospital care, drugs and lost work days in incident and prevalent rheumatoid arthritis: how large, and how are they distributed?

III. **Eriksson JK**, Neovius M, Bratt J, Petersson IF, van Vollenhoven RF, Geborek P, Ernestam S. Biological vs conventional combination treatment and work loss in early rheumatoid arthritis: a randomized trial.

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<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>ARTIS</td>
<td>Anti-Rheumatic Therapies in Sweden</td>
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<td>AS</td>
<td>Ankylosing spondylitis</td>
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<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Chemical classification system</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>DAS</td>
<td>Disease activity score</td>
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<td>DMARD</td>
<td>Disease modifying anti-rheumatic drug</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>EQ-5D</td>
<td>Euroqol 5-dimensions</td>
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<td>EULAR</td>
<td>European League Against Rheumatism</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>ICD</td>
<td>International Classification of Disease</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<td>ITT</td>
<td>Intention-to-treat</td>
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<td>JIA</td>
<td>Juvenile idiopathic arthritis</td>
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<tr>
<td>mITT</td>
<td>modified intention-to-treat</td>
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<td>NPR</td>
<td>National Patient Register</td>
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<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
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<td>PDR</td>
<td>Prescribed Drug Register</td>
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<tr>
<td>PsA</td>
<td>Psoriatic arthritis</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted life-year</td>
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<td>RA</td>
<td>Rheumatoid arthritis</td>
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<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>SCB</td>
<td>Statistics Sweden</td>
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<td>SRQ</td>
<td>Swedish Rheumatology Quality Register</td>
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<td>Swefot</td>
<td>Swedish farmacotherapy</td>
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<tr>
<td>TNFi</td>
<td>Tumor necrosis factor inhibitor</td>
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<tr>
<td>TTO</td>
<td>Time trade-off</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1 INTRODUCTION

For decades, Swedish registers have successfully been used for medical research, enabling long-term follow-up of large patient cohorts using observational designs. For example, the early established Swedish Cancer register has frequently been used to study cancer-related research questions, and has, through the personal identity number, been enriched with data on hospital admissions for studying the risk of cancer among patients with a specific medical condition. Other early examples of using register-based designs in health-related research are found from the Scandinavian Simvastatin Survival Study and the prospective-controlled Swedish Obese Subjects study linked to national register data for studies on mortality, cancer, and hospitalizations.

More recently, research databases have been established including several data sources using clinical quality registers enriched through register linkage with outcomes such as mortality, cancer, and work loss from national registers. Hereby a high granularity regarding clinical information can be obtained from the quality registers, while still exploiting the strengths associated with national registers. Moreover, while quality registers can provide much valuable data on their own, the true potential for both research and health care improvement may be in the combination through register-linkage and extensions where randomization occurs within the quality register framework. However, enriched quality register data create both new possibilities and potential problems for evaluation of effectiveness, safety, and health economic outcomes.

The four studies included in this thesis provide examples of how register-linkage can be used for estimating disease incidence, testing the robustness of register-based identification of disease, assessment of health care resource use and work loss, and for potentiating randomized controlled trials (RCTs) conducted within clinical quality registers.

Apart from being examples of how to use and enrich quality registers, the studies are also of scientific interest in their own regard, providing information regarding disease incidence and the burden of disease on an unprecedented scale within the field of rheumatoid arthritis (RA) (papers I and II). The register-enriched RCT enables analysis on whether differences in radiological outcomes translate into actual changes in work loss (paper III), something that is commonly claimed and used as motivation for the high cost of biologic drugs in RA. Finally, the register-enriched RCT can also be used for cost-effectiveness analysis of biologic versus conventional combination treatment (paper IV), adding important data to the ongoing discussion whether expensive biologic alternatives are good value for money as second line treatment compared to considerably cheaper non-biologic alternatives.

The introduction section is aimed to introduce the concepts needed for interpretation of the studies included in this thesis, and starts with a brief overview of the register linkage procedure and the personal identity number, followed by an introduction to epidemiological concepts of study designs and analyses, concepts of health economic analysis, description of RA and how the register-based methodology in this thesis add to the existing knowledge, and ends with ethical considerations.
1.1 REGISTER-BASED RESEARCH IN SWEDEN

The setting in Sweden, with a tax funded health care system and drugs that are provided free of charge above a threshold (2200 SEK in year 2014; www.tlv.se), and most importantly from a data linkage perspective, a personal identity number for all Swedish residents, makes Sweden an attractive environment for register-based research. With the virtually complete inpatient register of hospital discharges, together with the non-primary outpatient part of the National Patient Register, disease conditions and events of many study subjects are accessible, while dispensed prescription drugs for any indication are available from the Prescribed Drug Register. These national health registers, held at the National Board of Health and Welfare, are important data sources in health-related research in Sweden.

In addition to the national health registers, there are several quality of care registers in Sweden that collect data on a specific disease or intervention. These registers are usually established within the medical profession, and historically by enthusiasts, since it usually requires a huge effort in the start-up phase. The purpose of these registers is to monitor and improve health care, in some cases to provide the treating physician with individual decision support, and to conduct research. In 2014, 81 registers were qualified, by the National Board of Quality of Care Registers in Sweden, to be of sufficient quality to receive a certificate of quality register and to receive funding from the government for improvement and to further increase the quality of the register (http://www.kvalitetsregister.se/).

The Swedish Rheumatology Quality Register (SRQ), including the biologics register ARTIS (Anti-Rheumatic Therapies in Sweden), is a quality of care register that collects disease specific data on patients with rheumatic diseases in daily clinical practice.6 For the data used in this thesis, we have, through the personal identity number, linked the SRQ to national health registers as well as to other quality of care registers, and to the registers at the Social Insurance Agency. By the data enrichment procedure of the SRQ we have at a low cost established a powerful enriched clinical care register database where we have the possibility to answer an abundance of research questions, over a long time period with virtually complete follow-up, and in a real-world setting.

1.2 THE SWEDISH PERSONAL IDENTITY NUMBER

All persons who are registered in Sweden are assigned a 10 digit personal identity number administrated by the Swedish Tax Agency.21 The structure of the personal identity number includes data on birth and sex, where the first six numbers describes date of birth (YYMMDD), and is followed by a three-digit birth number, where the third digit specifies the sex of the individual (odd number indicating male and even number indicating female). The tenth and final digit is a control number indicating if the date of birth and the three digit number are correct. From this structure, the total number of possible unique personal identity numbers are 500 male and 499 female combinations for the same date.22

The system of personal identity number was established in 1947, with the control number added in 1967.21 This system is fundamental in the Swedish society where many of the rights and obligations as a Swedish resident hinge upon identification in registers and by authorities, and is also of great importance in medical research. Although the personal identity number is unique, there are situations where numbers have been reused or have been corrected, resulting in that the same personal identity
number has been assigned to more than one person, or that more than one number have been assigned to the same person, respectively. Reuse of personal identity numbers is rare, but may be necessary due to the limited number of unique combinations for the same date. In the 1950s and 1960s, Sweden had many immigrants that received 1st of January or 1st of July as date of birth, and this explains why reuse of numbers during this period is more common. The most common reasons for changing the personal identity number is incorrect date of birth or incorrect sex among immigrants or newborns. Other more uncommon situations for changing the personal identity number is adults changing sex, and in individuals requiring protected identity.

An estimated 13,500,000 personal identity numbers have been provided from 1969 until January 2008, whereof 15,887 numbers were reused, and 75,638 individuals had received a new personal identity number, including 26,265 out of 7,938,077 individuals born in Sweden (0.33%). Although the number of reused and changed personal identity numbers are few compared to the total number assigned, the researcher has to be aware of the potential problem and take this into consideration when working with register data linkages.

### 1.3 OCCURRENCE OF DISEASE

In epidemiology, there are two fundamental measures to describe the occurrence of disease, incidence (proportion or rate) and prevalence (proportion). The incidence proportion, or sometimes just incidence, is a measure of risk for developing a condition within a period of time, while incidence rate includes the time at risk for the individual study subjects. The incidence proportion is defined as the number of new cases during a time period, divided by the total number of study participants initially at risk. In contrast, the denominator in the incidence rate measure is the sum of person-years, or any other time unit, which the total number of study participants initially at risk contribute to the cohort study. If all study subjects can be followed throughout the study period, the incidence proportion is equal to the incidence rate. Unlike the prevalence measure, which describes the spread of a disease as a proportion of cases in the population at a given point in time (or during a given period in time), the incidence describes the occurrence of new cases.

### 1.4 COHORT STUDIES

A cohort study is a type of observational study design where study subjects are divided into groups based on exposure and are followed over time, with an aim of measuring the occurrence of one or several outcomes during the follow-up period, and to compare these occurrence rates between groups. Compared to RCTs, cohort studies typically have long follow-up time and high generalizability by including a representative sample of the source population. However, they may suffer from methodological issues, which make it difficult to estimate causal effects for a specific intervention or other exposure. A major methodological problem is that patients may be selected by certain known or unknown characteristics to a specific treatment, resulting in selection bias. Other problems may be challenges to define exposure status, and the high cost associated with collecting all data needed to have enough statistical power. However, the latter is not much of an issue when using national population-based registers available for example in Sweden.
1.4.1 Analysis

Cohort studies often involve research questions with time to a specific event, such as time to death, time to a specific disease, or time to treatment discontinuation, and study subjects may drop out of the study before the end of follow-up. With different time at risk for study subjects, occurrence of disease can be measured by the incidence rate. To include time at risk in the analysis, the association between exposure status and the outcome or event is usually evaluated using survival analysis, where the Cox proportional hazard regression often is used, enabling adjustment for potential confounders and investigate effect modification.

1.4.2 Matching

Matching of unexposed comparator subjects to exposed study subjects on certain characteristics that may affect both the exposure and the outcome is one way to deal with confounding in cohort studies, since the potential association between exposure status and matching factors at baseline are prevented. One advantage for matching on a set of characteristics compared to adjusting for the same characteristics in a cohort study design without matching, is that potential interactions among the matching factors are also included in the matched design. This allows for estimation of an overall effect, whereas controlling for several interactions may complicate the interpretation of results. In contrast, results from a matched design of unexposed to exposed study subjects may be easily presented, since the cohorts are followed side by side over time. However, although potential confounding for matching factors at start of follow-up are reduced in a matched cohort design, these characteristics may still need to be controlled for in the analysis if the exposure and the matching factors affect the time at risk, or if there are additional confounders, even when adjusting for the additional confounders.

1.5 RANDOMIZED CONTROLLED TRIALS

The randomized controlled trial is the gold standard design for measuring causal effects, meaning that since everything else is equal, there is a causal effect of the intervention if the outcome differs between groups to which subjects have been allocated at random. Subjects are randomly allocated to receive an intervention (or placebo), and are thereafter followed over time. With the randomization procedure, both known and unknown confounders are ideally spread out and balanced in the treatment groups, with reduced potential for biased estimates from patient characteristics that may have an effect on the outcome. Limitations of RCTs, with its experimental nature of the design, are that trials commonly include a selected group of participants due to strict inclusion and exclusion criteria, have a limited follow-up time, and are expensive to conduct. Thus, RCTs typically have high internal validity (unbiased and valid estimates of the treatment effect on the outcome), while the external validity (the generalizability) of the estimated effect might be limited.

There are different approaches to analyze RCT data, where the intention-to-treat (ITT) principle is the dominant strategy in the interpretation of RCTs. Under the ITT, all patients allocated to a treatment are followed in that treatment group regardless of protocol breach. For example, in the analysis subjects remain in the treatment group to which they were allocated regardless whether the patient never received the allocated treatment, mistakenly received the alternative intervention, or did not adhere to the intended treatment. Using the ITT approach, characteristics other than the pure
biological effect that may influence the efficacy of the intervention are included in the analysis. Such characteristics may be the ability to administer the drug, drug adherence of the patients, as well as other measured or unmeasured characteristics among the patients.

Other approaches to analyze RCT data are per-protocol analysis, where study subjects that completed the trial according to protocol are included, and modified ITT,\textsuperscript{29} where study subjects with some deviations from the study protocol are excluded.

In Figure 1 the rationale behind the ITT approach is presented in a directed acyclic graph.\textsuperscript{30} If data from an RCT is analyzed by the ITT method, the effect of the allocated treatment \( R \) on the outcome \( Y \) is measured, and the path from \( A \to Y \) through the unmeasured confounding \( U \) is blocked according to graph theory in directed acyclic graph (\( A \) is a collider). If instead using per-protocol analysis, the treatment effect of drug \( A \) on the outcome \( Y \) is measured, which may be biased by the potential unmeasured confounding \( U \) since the path \( A \leftarrow U \to Y \) is unblocked.

If no confounding, selection bias or measurement bias for the randomly assigned treatment \( R \) exists, the association between \( R \) and the outcome \( Y \) can be interpreted as the causal effect of \( R \) on \( Y \). However, using the ITT approach and, as in most situations in randomized trials, with patients not adherent to the allocated treatment, potential misclassification bias is introduced. While, as noted, in per-protocol analysis potential unmeasured confounding may instead result in a biased estimate of the treatment effect.

![Directed acyclic graph of a randomized trial](image)

\textbf{Figure 1} Directed acyclic graph of a randomized trial

\( R \): Randomly allocated treatment; \( A \): Adherence to the assigned treatment; \\
\( U \): Unmeasured confounding; \( Y \): The outcome of interest

\subsection*{1.6 REGISTER-ENRICHED RANDOMIZED CONTROLLED TRIALS}

The combination of randomization and observational register data, with an RCT conducted within the register-enriched framework, has the potential of using the generalizability of “real world data” that has been recorded in daily clinical practice along with properties of randomization such as a reduced risk of selection bias.

In more detail, by combining real-world data with a randomization procedure in the quality of care register, the long follow-up, many different outcomes, and clinically relevant comparisons between treatments from the register data are combined with the possibilities of estimating causal effects from the RCT. The features of including clinically relevant interventions, inclusion of a diverse population of participants recruited in a real-world clinical setting, and data collection on several different outcomes, refer to the term pragmatic clinical trial or practical trials.\textsuperscript{31} Finally, since the clinical data are entered
into the quality of care register in routine practice, this design allows for long-term follow-up at a low cost.

1.7 COST AND COST-EFFECTIVENESS STUDIES

Economic assessments of the treatment of disease evaluate the economic value of therapeutic interventions with an overall aim to maximize health. A common study design in economic assessments captures self-reported data on costs from questionnaires. While this design enables data collection on a detailed level, questionnaires are commonly associated with both non-response and recall bias. By instead using a register-enriched database with objectively assessed data on health care and work loss, the weaknesses inherent in using questionnaires may be avoided, but with the loss of collecting all potential cost components.

While studies of burden of disease, or cost of illness, assess the health care use and/or work loss, cost-effectiveness studies combine the costs incurred by the new intervention and the health related quality of life gained from it, compared to another intervention. The comparison intervention may for example be standard of care or no intervention at all. The results are presented as incremental costs and effects between the treatment groups, and usually in an incremental cost-effectiveness ratio (ICER), which is defined as the difference in costs divided by the difference in effects between treatment alternatives.

1.7.1 Costs

Costs are generally divided into three categories, health care costs, productivity losses, and intangible cost.

Health care costs, sometimes referred to as direct costs, are all costs associated with the health care used for having the intervention in question. For valuing productivity losses, sometimes referred to as indirect costs, two methods are often used, the human capital approach and the friction cost method, where the former is heavily dominating cost of illness studies in RA. Finally, intangible costs refer to the suffering incurred by the disease and the interventions needed, and may be more difficult to quantify than direct and indirect costs.

1.7.1.1 Human capital approach

The human capital approach values productivity losses by using the value of an individual’s future earnings. The market value of lost productivity associated with illness is therefore an individual’s reduced production as compared with if the same individual would continue to be in full health. The reduced production is estimated using gross earnings with taxes included, and hence, valued to the actual amount the employer pays for the production delivered.32

There are a number of limitations using the human capital approach. Criticisms have been raised against the assumption that, even if the unemployment rate would be high, a worker cannot be replaced. Further, the value of future production may not reflect the gross earnings (e.g. housewives), and leisure time is not valued as it would be in general welfare economics.32
1.7.1.2 Friction cost method

The friction cost method uses the same underlying assumption as the human capital method, that future production is valued using the individual’s future earnings. The difference compared to the human capital approach is the assumption that the worker can be replaced after a period of time, referred to as the friction time, until the absent worker returns or is replaced.\(^{33}\)

In the short-term, the human capital and the friction cost method result in similar estimates of productivity losses. However, in the long-term, lower cost estimates would be obtained with the friction cost method.

One concern with the friction cost method is that illness and premature death would result in reduced unemployment rates in the overall society. Furthermore, it has been argued that, for consistency, the friction cost method should also be used to estimate direct costs, resulting in unrealistic health care cost estimates.\(^{34}\) After the friction period, the price of labor is set to close to zero, which implies a substantially reduced health care cost since the labor cost is a major part of the value added in a health care program.\(^{34}\) Finally, estimating the length of a friction period may be challenging, as it is likely to differ according to characteristics such as employment position, educational level, and the situation on the labor market.\(^{35}\)

1.7.2 Perspectives

Costs and benefits that are relevant to include in the analysis depend on which perspective being used. Common perspectives used in cost-effectiveness analysis are the individual, health care, and societal perspectives. For example, from the health care perspective, costs of drugs and resource use in the therapy delivered would be relevant, while productivity losses are not borne by the hospital and should not be included. However, to identify the most efficient use of health care, and since productivity losses are part of the social resources and paid for by taxes, it has strongly been recommended to include productivity losses and to use the societal perspective in cost-effectiveness analysis.\(^{36,37}\)

1.7.3 Health-related quality of life

Cost-utility analysis is one type of cost-effectiveness analysis where the effect is measured as quality adjusted life-years (QALY) gained. Utility is a valuation of health-related quality of life in states where 0 indicates dead and 1 indicates full health. A QALY is the product of the utility value of a specific health state and the time spent in the health state. One common instrument to measure utility in cost-utility analysis of RA is the EuroQol 5-Dimensions (EQ-5D) instrument.\(^{20,38,39}\) The EQ-5D comprises five questions regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with three alternative responses for each (an updated version with five alternatives is under development; http://www.euroqol.org/).

The 243 different health states in the three-level EQ-5D questionnaire (\(3^5=243\) possible combinations) may be converted to a single country specific index value.\(^{40}\) Cost-utility analyses on Swedish data often use index values from the UK, and sometimes from the US. However, experience-based value sets for EQ-5D health states in Sweden have recently been published, but may be investigated in more detail before implementation.\(^{41}\)
As with the Swedish preference set, both the UK and the US preference sets have used the time trade-off (TTO) method in deriving index values to each health state. The TTO method compares the time in a specific health state to the time with full health. Time in the current health state is varied until the respondent is indifferent between the alternatives. The utility score for the current health state is then the time with full health divided by the time in the current health state. For example, a patient indicates that ten years of living would be required in his or her current health state to be equivalent of three years of living with full health. The utility in this health state would then be 0.3 (3/10).

In longitudinal data where several measurements over time are available, accumulated QALYs during follow-up are often used. Accumulated QALYs are calculated as the area under the utility curve, with utility on the y-axis and time on the x-axis.

Major advantages of the QALY approach, in contrast to many other effect measures, are that the QALY measure captures changes both in morbidity and mortality, and may be compared among all patients and between different diseases, interventions and health care programs.

One limitation with the QALY measure is that all QALYs are considered to have the same value. For example, few patients with a large increase in health-related quality of life may result in similar estimates as when many patients have a small increase. Some argue that a high QALY change among few patients that may be life-saving, should be given more weight as compared to a small increase among many patients, as may often be the case in chronic inflammatory diseases such as RA. Furthermore, QALYs do not take into account when in life the change of health-related quality of life takes place.

### 1.7.4 Discounting

Discounting in health economic assessment is a method used to adjust for future costs and benefits to the present value. The concept of discounting is that receiving something with a value today has a greater value than to receive the same thing in the future.

National pricing and reimbursement agencies usually recommend discounting of cost and health effects at an annual rate of 3% or 5% in the main analysis, and up to 10% in sensitivity analysis, and also without discounting of health effects. While there is an agreement among health economists that future costs should be discounted, there is some disagreement regarding which discount rate to use for future benefits, or whether to discount future benefits at all. Some have argued that a year of life is the same whenever it occurs in time, and health effects should for that reason not be discounted. However, much of the literature indicates that individuals place greater weight on benefits that occur soon in time, as compared to delayed benefits, suggesting that future benefits should be discounted in the analysis. The Swedish national reimbursement agency, the Dental and Pharmaceutical Benefits Board (www.tlv.se), recommends discounting of both costs and effects to an annual rate of 3%, and to conduct sensitivity analysis with discount rates of 0% and 5%.

### 1.7.5 Incremental cost-effectiveness ratio (ICER)

The ICER combines the costs and effects for one intervention compared to another intervention (often the standard care) and is used in health economics for supporting decision making regarding health interventions. The ICER can be presented in the cost-effectiveness plane consisting of four quadrants,
quadrants I-IV in a clockwise order starting in the upper right quadrant, with the plotted difference in costs (y-axis) against the difference in effects (x-axis) between treatment groups (Figure 2). In quadrant I the new treatment is more effective but also more costly, in quadrant II the new treatment dominates with lower costs and better effect, results in quadrant III indicates that the new treatment is less costly but also less effective, and in quadrant IV the standard treatment dominates as the new treatment is more costly and less effective. The willingness to pay threshold, the monetary value per unit of effect that would be acceptable and considered cost-effective, is also easily presented in the cost-effectiveness plane through a line with where the slope represents the threshold.

Figure 2 The cost-effectiveness plane with an imagined willingness to pay threshold (dotted line). The white area illustrates acceptance of new treatment, where increased costs for the gained effect may be acceptable (upper right quadrant), new treatment dominates (less costly and more effective; lower right quadrant), or may be acceptable (less effective but also less costly; lower left quadrant).

1.8 RHEUMATOID ARTHRITIS (RA)

RA is a chronic disease characterized by systemic inflammation, joint destruction, and presence of autoantibodies, and if not controlled, results in disability, reduced quality of life, and higher risk of cardiovascular as well as other comorbidities.45

1.8.1 Epidemiology

Around 0.5-1% of the western population are living with RA,46 and around 50,000 individuals have RA in Sweden.47 The annual rate of new cases is 20-50 per 100,000, but prevalence and incidence estimates differ considerably depending on age and sex, since RA onset is more common in older individuals and 2-3 times more common in women than men.48 Other risk factors for RA includes genetic factors, with a 3-fold increase risk when family history of RA is present,49 and smoking, the strongest environmental factor with approximately a 2-fold increased risk for RA.50,51

With respect to previous incidence estimates of RA, reports have suggested that the incidence has declined during the second half of the 20th century, while more recent studies report an increase in the last decade. With exception of nationwide incidence studies of RA from Finland,52,53 previous reports have based their estimates on up to a few hundred individuals with RA diagnosis verified using standard RA classification criteria. Such a study design may provide good incidence estimates of
defined RA in that specific study area, but may not be generalizable to physician-diagnosed RA on a national level, which would be the “real-life” occurrence of RA. Subgroup analysis in small sample studies may also be limited or impossible, and it is unclear whether the incidence of RA varies with factors other than age and sex, such as demographic factors and geography.

1.8.2 Definitions and outcome measurements

RA is a classification disease where no single clinical test alone can be used to verify a diagnosis. To be classified as having RA, the patient has to fulfill a number of different criteria. An often used classification tool is the American College of Rheumatology (ACR) criteria from 1987, with good features to verify established RA, but with limitations in identifying patients early in the disease course. An updated version has therefore been developed by the ACR and the European League Against Rheumatism (EULAR) organizations, the 2010 ACR/EULAR criteria. It has been estimated that the updated version identifies similar number of incident RA cases at start of follow-up, as the 1987 ACR criteria would have identified after five years of follow-up.

Severity of RA is usually categorized based on disease activity with the 28-joint count disease activity score (DAS28), ranging from 0 to 10 (higher number indicates more disease activity), and is often used for treat-to-target approaches in clinical practice (Table 1). The DAS28 measure consists of 4 components: number of swollen joints (0-28), number of tender joints (0-28), erythrocyte sedimentation rate (ESR), and the patient-reported general health assessment on a visual analogue scale (0-100).

Other measures of disease severity are the health assessment questionnaire (HAQ), which is a patient-reported questionnaire, ranging from 0 to 3, assessing the physical function and disability in patients with RA. Measures of radiological progression of joint destruction using radiographs of patients’ hands and feet are also used. One such scoring system when comparing the radiographs is the Van der Heijde modification of the Sharp score, ranging from 0 to 448.

<table>
<thead>
<tr>
<th>Disease activity score</th>
<th>Disease activity category</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 &lt; 2.6</td>
<td>Remission</td>
</tr>
<tr>
<td>DAS28 &lt; 3.2</td>
<td>Low disease activity</td>
</tr>
<tr>
<td>3.2 ≤ DAS28 ≤ 5.1</td>
<td>Moderate disease activity</td>
</tr>
<tr>
<td>DAS28 &gt; 5.1</td>
<td>High disease activity</td>
</tr>
</tbody>
</table>

1.8.3 Management and treatment

Since the late 1990s the treatment of RA has changed dramatically with the introduction of biologic drugs, with superior efficacy in treating disease activity compared to non-biologic alternatives. Biologic drugs for treatment of RA refers to large complex protein molecules that, instead of passing the cell-membrane as smaller molecules, act outside the cell by blocking components of the immune system that have an important role in the inflammation process. A common mechanism for biologics in RA is blocking of a chemical activator of inflammation, the tumor necrosis factor (TNF), and such drugs are usually referred to as TNF inhibitors (TNFi). In addition to an increased number of new
therapeutic options, treat-to-target approaches, early identification of RA onset, and careful monitoring of the disease course have improved the management and treatment of RA.\textsuperscript{61}

The standard recommendation in RA is to initiate non-biological disease-modifying anti-rheumatic (DMARD) therapy as early as possible in the disease course. At this stage, adding low dose glucocorticoids may also be considered.\textsuperscript{62} One common strategy is to initiate treatment with methotrexate monotherapy. However, only around one third of the patients reach low disease activity after 3 months using methotrexate alone.\textsuperscript{63-65} In patients who do not respond to the first DMARD strategy, current recommendations are to consider an alternative or a combination DMARD therapy in those patients with absence of poor prognostic factors (such as rheumatoid factor or anti-citrullinated protein antibodies, radiographic progression, or high disease activity), and to consider adding a biologic drug in those who have poor prognostic factors present.\textsuperscript{62}

The randomized Swefot trial aimed to answer this common clinical question in early RA, that is, which strategy, adding a TNFi or further conventional DMARDs, is preferable in patients not achieving low disease activity after 3-4 months of methotrexate monotherapy.\textsuperscript{65,66} The clinical results showed superiority of the TNFi strategy after 1 year,\textsuperscript{65} but with no difference in DAS28 between the strategies after 2 years, although a statistically significant difference in radiographic progression was detected favoring the TNFi treatment strategy.\textsuperscript{66} Similar results have been confirmed from other randomized trials using a similar study design,\textsuperscript{64,67} and also in patients with established RA.\textsuperscript{68}

However, no health economic analysis regarding which strategy to choose has been reported in this patient group, neither regarding work loss outcomes nor in a complete cost-effectiveness analysis.

1.8.4 Consequences and costs

With the chronic inflammatory and destructive nature of RA, high health care use, work loss, and reduced quality of life have been reported in these patients.\textsuperscript{69-72} Reduced employment alternatives and increased productivity losses imply that evaluations of the burden of disease, not only from a health care perspective, but from a societal perspective, are crucial in understanding the value of interventions in RA.

Two recent reviews have compiled data from several burden of disease studies in RA, in an attempt to compare existing studies despite the different methodological approaches and differences in disease severity and comorbidity in study subjects. The most recent review reported a weighted mean annual cost per patient with established RA to €4170 in health care costs and €8452 in productivity losses.\textsuperscript{70} The other systematic review found that the cost per patient was €21,069 in the US, €13,463 in Europe, and €12,893 in Sweden, and that productivity losses constituted less than 50% of the total costs.\textsuperscript{73} The higher cost in the US compared to Europe was due to higher use of biologics. Already in the beginning of the biological era, biologic drugs appeared to considerably increase the treatment costs of RA, with health care costs mainly driven by drug use instead of hospitalization costs as before the introduction of biologics.\textsuperscript{74}

Cost data often display a skewed distribution where few patients contribute a large proportion of the total cost. As a result, in cost of illness analyses, it is important to also understand the underlying cost distribution. However, previous cost of illness studies in RA have not based their estimates on
nationwide individual level data, and no study has compared these cost estimates to the general population in order to understand the additional costs in RA.

1.9 ETHICAL CONSIDERATIONS

Ethical approval for the data linkage and for all included studies in this thesis was granted by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden. The Swefot study was approved by the regional ethics committees of all 15 participating rheumatology units in the trial, and written informed consent was given by the participants before inclusion.

For registration in the SRQ there is a routine of informed consent, and patients have the choice to withdraw the consent at any time and for any reason, and all observations would be removed from the SRQ.

Informed consent from study subjects not included in the SRQ is impossible, as these data are anonymized and some subjects may already be deceased. In addition, with more than 500,000 included study subjects in the data linkage, it would also be practically impossible to inform all study participants.

Our opinion that the possibilities of this research project using the SRQ enriched by data from national registers outweigh the risk of perceived violation of personal integrity for study subjects, was shared by the ethical review board. As further safeguards, the research group only had access to anonymized data, and results are only presented on an aggregated level so that individual patients cannot be identified.

This project demonstrates effective research methods at a relatively low cost, methods that could be replicated to disease areas other than rheumatology, and on a national level to monitor incidence, prevalence, and burden of disease in a way that has not been previously possible, as some of the used registers were only recently established. In addition, we hope that the results from this project could lead to improvements in health care delivery, and thus, in the future, patients with RA could benefit from the study results.
2 OBJECTIVES

The overall aim of this thesis was to describe different ways of using Swedish register data to inform evaluations of health care interventions and epidemiologic inquiries, exemplified by using the SRQ linked to national registers.

The specific objectives were:

1. To combine quality register, national health register, and demographic register data to determine the incidence of RA in Sweden (paper I)
2. To combine quality register, national health register, demographic register, and Social Insurance Agency register data to assess the disease burden measured by cost of work loss, hospital care, and drug use in prevalent and incident RA (paper II)
3. To combine randomized controlled trial, quality register, national health register, demographic register, and Social Insurance Agency register data to
   a. evaluate the effect on sick leave and disability pension of TNFi+methotrexate versus conventional combination treatment in early RA patients not responding to methotrexate monotherapy (paper III)
   b. conduct a cost-effectiveness analysis of TNFi+methotrexate versus conventional combination therapy from the societal perspective (paper IV)
3 MATERIAL AND METHODS

3.1 SETTINGS

All Swedish residents have a 10-digit unique personal identity number, administered by the Swedish Tax Agency, used to identify residents at authorities and in registers. Using this unique key it is possible to merge registers on an individual level to establish a research database which include data from different sources.

In Sweden the health care system is tax funded and offers universal access to all residents, and prescription drugs are provided free of charge above a threshold (1800 SEK during the study period, 2200 SEK in 2014; www.tlv.se). In the case of RA and other inflammatory diseases, patients are typically diagnosed and treated by rheumatologists at non-primary outpatient and inpatient care facilities, rather than by general practitioners. Care for RA represents a mix of combined outpatient and inpatient facilities, with the vast majority of rheumatologists working at hospitals (>90%) rather than as private practitioners.75

3.2 DATA ENRICHMENT OF THE SRQ

In the data enrichment procedure of the SRQ, the first step was identification of all patients with RA in the SRQ, while the National Board of Health and Welfare identified all patients from the National Patient Register listing at least one main or contributory diagnosis of RA according to the ICD (International Classification of Disease) coding system (Figure 3). For analysis of biologic drug use, patients with any biologic drug prescription in the Prescribed Drug Register were also identified. In addition, general population comparators were sampled from the demographic registers held at Statistics Sweden. Five comparators per RA patient were sampled on an individual level based on age, sex, residence, and year. Patients with any RA diagnosis together with their general population comparators constituted the study cohort.

Data on patients in the randomized Swefot trial65 were also collected in the SRQ, as any data collected in routine daily clinical care at the rheumatology clinic. The enrolled Swefot patients were thus also included in the register-enriched database as subjects in the study cohort, and were also matched to general population comparators.

The study cohort was thereafter merged to the national health registers held by the National Board of Health and Welfare, registers at the Social Insurance Agency, as well as other quality of care registers. Not all data sources outlined in Figure 3 were included in this thesis. Included data sources are described in the next section.
Figure 3 The data enrichment procedure of the SRQ. Patients with RA were identified from the SRQ and the NPR. In addition, for analyses of biologic drug use, all individuals with prescribed biologics were identified from the PDR. After sampling of general population comparators from the Register of Total Population, the study cohort was defined. The study cohort was thereafter linked to national registers and to other quality of care registers. The SRQ may also be linked to medical files for validation studies and to biobank sample repositories.

SRQ: Swedish Rheumatology Quality Register; NPR: National Patient Register; PDR: Prescribed Drug Register

3.3 DATA SOURCES

All data sources used for the included studies are described in this section, and summarized in Table 2.

Table 2 Data used from the different data sources included in the register-enriched database

<table>
<thead>
<tr>
<th>Register holder and data source</th>
<th>Identification of subjects</th>
<th>Data used (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Swedish Rheumatism Association</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRQ/ARTIS (including Swefot)</td>
<td>Patients with RA</td>
<td>Clinical data related to RA, HAQ, EQ-5D, treatment information (1999-2012)</td>
</tr>
<tr>
<td>National Board of Health and Welfare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Patient Register</td>
<td>Patients with main or contributory diagnosis for RA</td>
<td>Health care use (not primary care; inpatient: 1971-2012; outpatient: 2001-2012)</td>
</tr>
<tr>
<td>Prescribed Drug Register</td>
<td>-</td>
<td>Drug prescriptions (not in-hospital drug use; July 2005 - 2012)</td>
</tr>
<tr>
<td>Cause of Death Register</td>
<td>-</td>
<td>Deaths (1956-2012)</td>
</tr>
<tr>
<td>Statistics Sweden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Register of the Total Population</td>
<td>Sampling of comparators on age, sex, place of residence, and year</td>
<td>Birth, death, civil status, country of birth, migration (1968-2012)</td>
</tr>
<tr>
<td>LISA</td>
<td>-</td>
<td>Level of education (1990-2012)</td>
</tr>
<tr>
<td>Social Insurance Agency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social insurance compensations</td>
<td>-</td>
<td>Compensated days for sick leave and disability pension (1994-2012)</td>
</tr>
</tbody>
</table>
3.3.1 The Swedish Rheumatology Quality Register (SRQ)

The SRQ was started in 1995 by the Swedish Rheumatology Society. It followed on regional register initiatives, and developed over time into a harmonized national register. The primary purpose of SRQ was to improve the health care and treatment for patients with RA, but with time patients with other rheumatic diseases, e.g. ankylosing spondylitis (AS) and psoriatic arthritis (PsA), have also been included. In the late 1990’s, when the first biologic drug was approved for the treatment of RA in Sweden, the Swedish Biologics Register ARTIS started in collaboration with the Swedish Medical Products Agency with the primary aim to evaluate the safety of these drugs.

The SRQ together with complementary regional initiatives have since provided clinicians and patients in Sweden as well as internationally with a large amount of clinically useful information. Major strategic advantages of these registers are that they are fully integrated in health care, and used to continuously improve care, i.e. they are designed to be useful in daily clinical practice. This design also enables patients to have access to their particular information in the register and to provide their own patient-derived information, for example from own computers at home or from touch pads in the waiting rooms. These features distinguish the Swedish registers from many other registers internationally, which are often designed to answer one specific research question, rather than being a multipurpose and continuously growing source of information. Among other variables, SRQ includes date and type of diagnosis, the ACR criteria at the time of diagnosis, and data on disease activity, disability and treatment. Today SRQ includes data from more than 60 clinics, and covers a high proportion (87-95%) of the patients with RA treated with biologics.

3.3.2 The randomized Swefot trial

The aim of the Swefot (SWEdish FarmacOTherapy) trial was to compare the intensive treatment alternatives of adding conventional DMARDs or a TNFi (infliximab) in the common clinical situation of patients with early RA that have failed their initial treatment with methotrexate monotherapy (Figure 4). The Swefot study was investigator initiated and was funded by the Swedish Rheumatism Association and Schering-Plough/Merck Sharp and Dohme.

Adult patients (aged ≥18 years) with a diagnosis of early RA (symptom duration <1 year) were recruited from 15 rheumatology units in Sweden from 2002 through 2005. Key inclusion criteria were fulfilment of the 1987 revised ACR criteria, a disease-activity score based on DAS28 >3.2, no previous DMARD treatment, and no or stably dosed oral glucocorticoid therapy for at least 4 weeks, using at most 10 mg daily prednisolone (or equivalent). Due to the different route of administration of the two treatment alternatives, where infliximab is given as an infusion and conventional combination therapy is given orally, the use of blinded assessors in the trial was considered but deemed unfeasible owing to the limited personnel at smaller participating units. For this reason, the Swefot study was an open-label trial, where both doctors and patients were aware of the treatment allocation (addition of two oral drugs versus one infusion).
3.3.2.1 Procedure

An overview of the trial procedure is presented in Figure 4. At inclusion patients started methotrexate monotherapy to be taken every week at an initial dose of 10 mg. The dose was increased every 2 weeks by 5 mg to 20 mg weekly. After a run-in period of 3-4 months on methotrexate, the DAS28 was assessed. Patients with low disease activity (DAS28 <3.2) left the trial, while those with moderate to high disease activity (DAS28 ≥3.2) were randomized to receive additional treatment with infliximab (3 mg/kg body weight, rounded up to the nearest 100 mg increment, given intravenously at weeks 0, 2, and 6 and every 8 weeks thereafter) or conventional combination therapy with sulfasalazine and hydroxychloroquine (400 mg/day given orally). Patients were scheduled for a visit at the rheumatology clinic every 3 months the first year, and thereafter at 18 and 24 months after inclusion to the trial. Included subjects could discontinue the assigned treatment at any time for lack of effectiveness, adverse effects, or by their own choice.

3.3.2.2 Treatment adjustments

In case of adverse events and within the protocol, sulfasalazine and hydroxychloroquine could be dose-reduced or withdrawn (while continuing the other), or alternatively, replaced by ciclosporin A (2.5 mg/kg/day; increase up to 5 mg/kg/day allowed). Infliximab could be discontinued and replaced by etanercept (50 mg subcutaneously/week).

3.3.2.3 Study outcome

The primary outcome of the Swefot trial was achievement of a good response in disease activity according to the EULAR criteria after 1 year of follow-up, which has been reported previously. In the study protocol, secondary analysis of health economic outcomes were prespecified. In paper III, we compared the compensated days of sick leave and disability pension between the treatment arms over 21 months, while in paper IV the difference between the arms in both costs and health-related quality of life were analyzed by calculating the ICER.

![Figure 4 Procedure of the Swefot trial](image)

RA: Rheumatoid arthritis; DAS28: disease activity score based on 28 joint count; EULAR: European League Against Rheumatism
3.3.3 National health registers

The national health registers are kept by the National Board of Health and Welfare, and the national health register sources used in this thesis are described here.

3.3.3.1 The National Patient Register

The National Patient Register contains inpatient discharges and non-primary outpatient care. The inpatient register, also known as the Hospital Discharge Register, started in 1964 and became nationwide in 1987 when introducing the ninth revision of the International Classification of Disease (ICD) coding system in Sweden. The ICD10 coding system has been used since 1997 (with the exception of the county of Skåne where ICD9 was used throughout 1997). Data on every discharge are collected, including main and contributory diagnoses from inpatient care. The coverage in terms of registered discharges are virtually complete, with close to 100% of all inpatient care reported to the register. The outpatient component started in 2001 and diagnoses are coded according to the ICD10 coding system. The coverage is nationwide, but varies with year and specialty. The proportion of outpatient visits reported are constantly increasing, and in 2013 87% of all non-primary outpatient care visits in somatic care were reported in the register. Most of the non-reported visits were at private practitioners.

In both the inpatient and the outpatient component, visits are categorized by diagnoses according to classification of diagnostic related groups (DRG). Medically similar hospitalizations or non-primary outpatient care visits, also with similar resource use, are grouped together based on the main diagnosis for the hospital discharge or outpatient visit. This system was initially developed at Yale University in the US in the 1960s for quality control in health care, but in Sweden a version adapted for Nordic conditions is currently in use (NordDRG). The NordDRG version includes around 580 groups in inpatient care and 400 groups in the non-primary outpatient care, and is used for describing the case-mix at the hospital, planning, monitoring performance, and for reimbursement of the health care delivered. When using DRG for reimbursement purposes, the price per DRG is a fixed price for a specific year, and is a weighted average for all the health care delivered in that group and year.

The accuracy of the RA diagnosis in the National Patient Register has been validated in a total of 200 subjects, including 100 prevalent and 100 incident register-identified patients with RA, as defined in paper I and paper II. In this validation study, 90 patients (90%) in both the prevalent and incident group fulfilled either the 1987 ACR or the 2010 ACR/EULAR classification criteria. Of these 90 patients in the incident group, 90% had a register identification date <2 years from date of symptom onset, indicating a high validity also in incident patients.

3.3.3.2 The Prescribed Drug Register

The Prescribed Drug Register started in July 2005 and includes data on all dispensed prescription drugs in ambulatory care in Sweden, while in-hospital drug use is not recorded on a patient level. Among other variables, the register includes the Anatomic Therapeutic Chemical (ATC) code and name of the prescribed drug, as well as dosage, route of administration, and price.
3.3.3.3 The Cause of Death Register

The Cause of Death Register started to collect data on deaths and causes of deaths in Sweden in 1961. Unlike the National Patient Register where the Swedish version of the ICD coding system is used, the causes of death are coded according to the international ICD coding system (www.who.int).

3.3.4 Demographic registers

Statistics Sweden (www.scb.se) keeps registers of demographic data. The following register sources were used in this thesis.

3.3.4.1 The Register of the Total Population

The Register of the Total Population is kept at Statistics Sweden since 1968 and is a subset of the population register held at the Swedish Tax Agency (Skatteverket) for tax administration. This register includes for example information on birth, sex, residence, civil status, death, country of birth, and migration. We used the Register of the Total Population for sampling general population comparators to the patients with RA.

3.3.4.2 Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

This database includes aggregated data by calendar year since 1990 from both Statistics Sweden, the Social Insurance Agency, and the Swedish Agency for Innovative Systems. The focus of the register is on the individual but also variables connected to family, companies, and places of employment are included. The individual section includes for example data on gainful employment, income, compensation from social insurances, and years of education (≤9, 10-12, and ≥12 years).

From the LISA database and for the included studies, we used only the level of education. The annually aggregated data on compensation for sickness or disability could not be used in the analyses including sick leave and disability pension (paper II-IV), since these analyses are in relation to a specific date (RA onset in paper II, and date of randomization in the Swefot trial in paper III and paper IV). Instead, we used data on a daily level directly from registers kept at the Social Insurance Agency.

3.3.5 Registers at the Social Insurance Agency

In the registers at the Social Insurance Agency, among other social insurance compensations sick leave and disability pension episodes as well as economic compensation are recorded. The sick leave (sjukpenning in Swedish) compensation of the first time period is covered by the employer, except the 1st unpaid day, and during the study period this has been day 2-14. Hence, from day 15 the sick leave is registered by the Social Insurance Agency (as 15 days and not as 1 day). Both sick leave and disability pension (in Swedish sjukersättning in individuals 30-64y, and aktivitetsersättning in individuals 19-29y) can be part-time or full-time (25%, 50%, 75%, or 100%).

The Social Insurance Agency has established a database for this register where the researcher may request data on different perspectives (on an individual level or by benefit), and types of compensations. Depending on data source used, and in comparison to the annually summarized data of sick leave and disability pension in LISA, the analysis may not be straight forward. In our case, where we analyzed the total days of work loss adding sick leave and disability pension together (paper II-IV),
it could result in that the total compensation in individuals that have had overlapping periods of sick leave and disability pension accumulate more than 100% work loss. The reason for this is that sick leave is registered as the percentage of the time left after reducing the time on disability pension. For example, an individual with 50% disability pension and 100% sick leave during the same period, would have a net of half time disability pension and half time sick leave.
3.4 STUDY POPULATION AND OUTCOMES

In this section the study population and the outcomes of each study are described.

3.4.1 Paper I – Incidence of RA

In paper I the nationwide register-assessed incidence of RA in Sweden was estimated. We also analyzed how the incidence varied across age, sex, geography and demography. In order to describe the sensitivity of the register-based definition of incident RA, from a register-based research perspective, the robustness of different RA case definitions was tested.

The overall mean annual incidence during 2006-2008 was estimated, which means that the numerator was the number of new cases with RA, also referred to as incident RA, in 2006, 2007, and 2008. The denominator was the number of adult residents in Sweden in 2006, 2007, and 2008, respectively (population at risk). The cut-off age of 18 years was used as patients in the Swedish health care system are not treated in adult care until they turn 18.

The coverage of patients with new onset RA in the SRQ is high, but not complete (estimated coverage 78% in 2012). To estimate the incidence we therefore also identified patients with RA in the National Patient Register. We used both the inpatient and the outpatient component of the register as well as both main and contributory diagnoses, and identified patients by using ICD8-10 codes (Table 3).

<table>
<thead>
<tr>
<th>ICD version</th>
<th>ICD codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD10</td>
<td>M05, M06.0, M06.2, M06.3, M06.8, M06.9, M12.3</td>
</tr>
<tr>
<td>ICD9</td>
<td>714A/B/C/W, 719D</td>
</tr>
<tr>
<td>ICD8</td>
<td>712.10/20/38/39</td>
</tr>
</tbody>
</table>

The base case register-based definition of incident RA required fulfillment of 3 criteria:

1. **Primary identification**: Patients ≥18 years with a first ever inpatient or non-primary outpatient care visit listing a main or contributory diagnosis for RA, or registered in the SRQ with an incident RA diagnosis in 2006-2008.
2. **Follow-up visit**: A second discharge or non-primary outpatient care visit for RA within 1 year after the first visit.
3. **Exclusion of potential prevalent cases**: Patients with any registered DMARD treatment >6 months before the first visit with RA were excluded.

A more liberal as well as a more strict definition were tested. In the liberal definition, we used the same definition as in the base case, but without criterion 3. In the strict definition, the criterion of at least one of the visits should be at a rheumatology or internal medicine department was added.

We estimated crude incidence rates as well as standardized to age, sex, and/or level of education of the Swedish population in 2008.

In this study we also assessed the anti-rheumatic treatment penetration of biologic and non-biologic DMARDs, and glucocorticoids by collecting data on prescriptions of non-infusion drugs from the
Prescribed Drug Register according to ATC codes (Table 4), while infusion biologic drug use was collected from the SRQ (abatacept, infliximab, rituximab, and tocilizumab).

Table 4 ATC codes used for identifying prescriptions of DMARDS and glucocorticoids

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Drug</th>
<th>ATC codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-biologic DMARDS</td>
<td>Auranofin</td>
<td>M01CB03</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td>L04AX01</td>
</tr>
<tr>
<td></td>
<td>Ciclosporin</td>
<td>L04AD01</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine</td>
<td>P01BA02</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
<td>P01BA01</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>L04AX03</td>
</tr>
<tr>
<td></td>
<td>Sodium aurothiomalate</td>
<td>M01CB01</td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine</td>
<td>A07EC01</td>
</tr>
<tr>
<td>Biologic DMARDS</td>
<td>Abatacept</td>
<td>L04AA24</td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
<td>L04AB04</td>
</tr>
<tr>
<td></td>
<td>Anakinra</td>
<td>L04AC03</td>
</tr>
<tr>
<td></td>
<td>Certolizumab pegol</td>
<td>L04AB05</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>L04AB01</td>
</tr>
<tr>
<td></td>
<td>Golimumab</td>
<td>L04AB06</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>L04AB02</td>
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<td></td>
<td>Rituximab</td>
<td>L01XC02</td>
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<tr>
<td></td>
<td>Tocilizumab</td>
<td>L04AC07</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Prednisolone</td>
<td>H02AB06</td>
</tr>
</tbody>
</table>

3.4.2 Paper II – Costs for hospital care, drugs and lost work days in RA

In this study the annual costs for health care and lost work days in patients with prevalent and incident RA were assessed. Incident cases were defined as the base case definition in paper I, but using 2009 as the primary identification year instead of 2006-2008. Prevalent cases were defined as alive and living in Sweden on 1 January 2010, with ≥2 visits listing RA from the National Patient Register and/or included with a diagnosis of RA in the SRQ. All costs for the patients with RA were compared to their comparators matched 5:1 on age, sex, education level, residence, and year, in order to obtain a benchmark for the cost attributable to the RA disease.

Costs for hospital care, drugs, and lost work days were assessed during 2010 in prevalent patients, while for incident patients these cost components were collected during 1 year of follow-up from the register identification date (1st ever visit listing RA in 2009). In the analysis costs were estimated in SEK, but converted to 2010 euros (€1 = 9.54 SEK in 2010) in the presented results.

3.4.2.1 Health care costs

To estimate the cost for hospital admissions and visits in non-primary outpatient care the price per DRG was used. This is a weighted average of costs per diagnostic related group, and is supposed to cover the expenses for the hospital of the health care delivered.

Costs for drugs, except for infusion drugs, were collected directly from the Prescribed Drug Register, while data on in-hospital drug use given by infusion (abatacept, infliximab, rituximab, and tocilizumab)
were collected from the SRQ and turned into costs by using the 2010 drug costs in Sweden (www.tlv.se).

### 3.4.2.2 Productivity losses

In the main analysis the value of work days lost was estimated by using the human capital approach, including all days on sick leave and disability pension during follow-up. To estimate the productivity losses, we multiplied the accumulated days of work loss with the average Swedish salary, including social fees (31%), in 2010 (www.scb.se). In order to simplify comparisons to some previous cost studies of RA, we also valued the work loss by using the friction cost method in sensitivity analysis, with a friction time of 6 months for individuals to be replaced.

### 3.4.3 Paper III – Infliximab versus conventional combination treatment and work loss in early RA

Patients not responding to initial methotrexate monotherapy were randomly assigned to the addition of either infliximab (also referred to as biological treatment group) or sulfasalazine and hydroxychloroquine (conventional treatment group, also referred to as triple therapy; Figure 4). Days of sick leave and disability pension, with a maximum of 30 compensated days/month, were analyzed in all patients <63y (retirement age was 65y during the study period) who had undergone randomization. In the main analysis, all randomized patients were included using the ITT approach, and the sum of monthly sick leave and disability pension days was compared between the treatment arms at 12 and 21 months after randomization. A few patients never received their allocated treatment, and were removed in a modified intention-to-treat analysis. In addition, we also conducted a per protocol analysis in all patients that completed the treatment 1 and/or 2 years according to the protocol. Finally, to describe the work loss development in comparison to the general population, we also computed the sick leave and disability pension days in matched general population comparators included in the register-enriched database.

### 3.4.4 Paper IV – Cost-effectiveness of infliximab versus conventional combination treatment in early RA

All randomized patients, both working age as well as retired, in the Swefot study were included in this cost-effectiveness analysis. We analyzed both the accumulated societal costs and health-related quality of life during 21 months of follow-up (from randomization to end of trial) by computing the ICER.

#### 3.4.4.1 Estimation of costs

We performed the cost-effectiveness analysis both from the health care and the societal perspective. Included cost components were anti-rheumatic drugs, inpatient care, non-primary outpatient care, sick leave, and disability pension. As in paper II, we assessed costs for hospital admissions and visits in non-primary outpatient care using the weighted average price per DRG.

Anti-rheumatic drug use was collected from the SRQ, where anti-rheumatic treatment information were recorded during the Swefot trial. Data on drug prescriptions from the Prescribed Drug Register, which started in July 2005, was not available for all patients during their follow-up. Drug doses and
frequencies for biologics, conventional DMARDs, glucocorticoids, and non-steroidal anti-inflammatory drugs was turned into costs by using the 2011 drug prices in Sweden (www.tlv.se).

Productivity losses were estimated similarly as in paper II. Complete and objectively assessed day level data on sick leave and disability pension were available from the registers at the Social Insurance Agency. We used the human capital approach for estimating the productivity losses in the main analysis, and the friction cost method, with a friction period of 6 months for individuals to be replaced, in sensitivity analysis.

All costs were converted to 2011 euros (€1 = 9.03 SEK in 2011).

3.4.4.2 *Estimation of quality adjusted life years (QALYs)*

EQ-5D utility was collected quarterly in the Swefot trial. We calculated the area under the curve for the utility scores plotted against time using the trapezoid method, where the area under the curve represents the accumulated QALYs during follow-up. The UK EQ-5D preference set was used in the main analysis. We also conducted a sensitivity analysis with the EQ-5D US tariff.

3.4.4.3 *Discounting*

In cost-effectiveness analysis the general recommendation is to apply an annual discount rate on both costs and effects. In this study, given the short follow-up time with only 9 months beyond the first year considered for discounting, the results are presented undiscounted.

3.4.4.4 *ICER*

The ICER was calculated by taking the difference in cost divided by the difference in QALYs between the infliximab arm and the conventional treatment arm.
3.5 STATISTICAL ANALYSIS

All statistical methods for analyzing the data included in this thesis are presented here.

3.5.1 Poisson distribution

The Poisson distribution was used to describe the uncertainty around the incidence rate in paper I, by assuming that the number of incident cases followed this distribution.

The Poisson distribution is a discrete probability distribution that is used to describe the variability around a known average rate of occurrence. If an average rate is known, and the events occur independently of the time since the last event, the Poisson distribution describes the probability that a given number of events will occur.26

3.5.2 Kaplan-Meier estimator

In paper III the time to discontinuation by the randomly allocated treatments (infliximab versus conventional treatment group) are presented in a Kaplan-Meier survival curve.

The Kaplan-Meier estimator measures, over time, the fraction of subjects that have not had the event of interest, i.e. the probability of each event at the time it occurs.86 This method is widely used in survival analysis, due to its efficient use of the available information in censored data.

3.5.3 Cox regression

A Cox regression model was fitted in paper III, and presented together with the Kaplan-Meier survival curve, to assess the between-group differences in time to discontinuation by the randomly allocated drug (infliximab versus conventional treatment group).

Cox regression, or Cox proportional hazard regression, is widely used in survival analysis where the time, which may be associated to any characteristics included in the model, to any event is analyzed.25 The hazard ratio is computed between the exposed and unexposed group for a certain characteristic, and is defined as the ratio of new cases per population at risk per unit time between the groups that are compared. As noted in the name, the hazards are assumed to be proportional over time. Therefore no assumptions need to be made about the shape of the underlying risk distribution since the baseline hazard is canceled out in the regression formula. For this reason Cox regression is usually considered to be a semi-parametric model.

3.5.4 Analysis of covariance

In paper III we used analysis of covariance (ANCOVA) to estimate the differences at 12 and 21 months after randomization in compensated days of sick leave and disability pension between the treatment arms (infliximab versus conventional treatment group). The analysis was adjusted for days of work loss during the 30 days before randomization.

ANCOVA is a general linear model that mixes analysis of variance (ANOVA) and regression. When comparing two groups using a continuous outcome, two parallel straight lines are obtained relating outcome to any covariates in the model. Advantages of using ANCOVA with baseline and follow-up measurements are that it generally has greater statistical power to detect a treatment effect.
compared to other methods, such as change score analysis, but foremost, it is a powerful method to measure change from baseline to follow-up by adjusting for potential baseline imbalances between groups.87

In our example, we estimate the difference between the treatment groups and adjust this difference in work loss to what it would be if everyone had the same number of days of work loss before randomization.

The ANCOVA in paper III can be expressed as a single regression equation:

\[
WorkDaysLost_{12/21\text{months}} = \beta_0 + \beta_1 \text{Group} + \beta_2 \text{WorkDaysLost}_\text{baseline} + \varepsilon
\]

where \( \beta_0 \) is a constant (intercept), \( \beta_1 \) is the effect of interest (i.e. the difference between the treatment arms), and \( \beta_2 \) the effect of baseline adjustment.

Since the estimated difference between two groups is the vertical distance between the regression lines, one assumption using ANCOVA is that the slopes of the regression lines for the groups should be equal, i.e. they should be parallel. Other assumptions include linear relation between the dependent variable and covariates, and normal distribution of the error terms (but not necessarily for the dependent variable or covariates).

### 3.5.5 A note on statistical power in the Swefot trial

Aiming for enrollment of 600 patients, the Swefot trial was initially designed to detect a difference of 15% in the treatment effect, based on disease activity using the EULAR criteria,81 between the infliximab and the conventional treatment arm with a statistical power of 90% (\( \alpha=0.05 \)). With slower recruitment of patients to the trial than anticipated, in the end, a total of 487 patients were enrolled to the study, resulting in a reduced estimated statistical power to 75%.

In paper III, 105 and 99 patients of working age were included in the infliximab and the conventional treatment group, respectively, for comparison of monthly days of sick leave and disability pension between the treatment arms. The number of patients needed at a given power to detect a difference of 2-6 work loss days per month is presented in Figure 5. For example, with 100 patients in each group, a mean difference of 5 days/month between the treatment arms can be detected at a power of 85%.
3.5.6 Incremental cost-effectiveness ratio (ICER)

In paper IV we computed the ICER between the two treatment strategies of the Swefot trial as the difference in the accumulated costs divided by the difference in accumulated effects between the infliximab and the conventional treatment arm.

$$ICER = \frac{Cost_{\text{Infliximab}} - Cost_{\text{Conventional treatment}}}{Effect_{\text{Infliximab}} - Effect_{\text{Conventional treatment}}}$$

Since the ICER is a ratio it is not straightforward to compute the uncertainty of the ICER point estimate. However, one method for estimating the uncertainty around the ICER point estimate is to use non-parametric bootstrapping, and present the result in a scatterplot in the cost-effectiveness plane, or as a probability of the ICER point estimate to be below a certain willingness-to-pay per QALY ratio in a cost-effectiveness acceptability curve.

3.5.7 Seemingly unrelated regression

We used a seemingly unrelated regression equation for computing the ICER for the infliximab compared to the conventional treatment group in paper IV. The analysis was adjusted for potential baseline imbalances in age, sex, EQ-5D, DAS28 and health assessment questionnaire (HAQ) scores at randomization, as well as accumulated costs during 60 days before randomization. It was also repeated unadjusted for other covariates.

Compared to ordinary least square regression, the seemingly unrelated regression method has the advantage of capturing correlation between costs and effects and might result in higher efficiency.
3.5.8 Bootstrapping

The uncertainty around the mean estimates of costs, effects, and the ICER in paper IV was assessed using non-parametric bootstrapping with 1000 iterations. In paper II we used bias-corrected and accelerated bootstrapping\textsuperscript{90} to estimate the between-group difference in days of work loss with 95% confidence intervals.

Bootstrapping is a technique where sampling is performed on the existing data. Since no assumptions on the underlying distribution is made, bootstrapping is useful in situations where the variable of interest is skewed. A number of iterations of sampling with replacement (usually $\geq$1000) are applied, and for each of the iterations statistics are computed.\textsuperscript{91}
4 RESULTS

In this section the results from each study is presented.

4.1 PAPER I

In 2006 to 2008, 8826 individuals were identified as incident RA according to the base case definition, which corresponded to an overall incidence of 40.6 per 100,000 (95% CI 39.7 to 41.4). The overall incidence in women (55.7 per 100,000; 95% CI 54.3 to 57.1) was more than twice the incidence observed in men (25.0 per 100,000; 95% CI 24.0 to 25.9).

In age and sex specific analysis we observed an increasing incidence with age until the 70-79 years age group, with 102 per 100,000 for women and 67 per 100,000 for men, and thereafter the incidence decreased in the oldest (Figure 6).

When using the liberal definition of incident RA, the overall incidence estimate increased to 46.4 per 100,000 (+14%), while when using the strict definition the incidence estimate decreased to 36.8 per 100,000 (-9%; Figure 6). We also noted a high biologic and non-biologic DMARD penetration from 6 months before until 2 years after first RA diagnosis across all definitions (>90%) as well as across age groups (>90% in all age groups except patients ≥80 years old).

Although no geographic gradient was found, we found a clear gradient across population density and level of education, with lower standardized estimates in population dense areas and among individuals with higher education level (51 to 44 to 33 per 100,000 in individuals ≥9 years, 10-12 years, and >12 years, respectively).

Figure 6 Mean annual register-based incidence of rheumatoid arthritis (RA) per 100,000 by sex and age for the liberal, base case and strict definition of RA. The overall incidence by case definition is indicated in parentheses.
4.2 PAPER II

Of 49,829 patients identified as prevalent RA, the mean annual cost per patient in the 18-64 years group was €23,147 (versus €8364 in matched general population comparators), where 75% was accounted for by productivity losses, and only 25% by health care costs (Figure 7). In the ≥65 years group the mean health care cost was €6438 (versus €2773 in comparators).

Among the prevalent patients with RA using biologics the mean annual total cost in 18-64 years was €32,626, and in the ≥65 years group €15,235, which was 4 and 6-7 times the cost in their matched general population comparators, respectively. In non-biologic users the mean total cost was €19,628 in the 18-64 years group and €5275 in the ≥65 years group.

Among the patients with incident RA (n=2695), the mean monthly cost increased from a level close to the matched general population comparators 12 months before the register identification, peaked the month following the identification date, and decreased to twice the cost of the comparators 1 year thereafter (Figure 8). One year after the register identification, the monthly societal cost in the 18-64 years group was €1252 versus €628 in the comparators (mean difference €624; 95% CI 517 to 740). Among the older patients the monthly health care cost was €487 versus €230 in the comparators (mean difference €258; 95% CI 181 to 350).

The cost distributions were heavily right skewed in both the incident and the prevalent patients with RA, with approximately 13% of the patients accounted for 50% of the annual total cost.

Figure 7 Mean (bars) and median (black dots) annual costs in patients with prevalent rheumatoid arthritis (RA), prevalent RA treated with biologics, and matched general population comparators

RA treated with biologics: patients with RA, with any dispensed non-infusion biologics in 2009, or with an ongoing treatment of infusion biologics on 1 January 2010; Comparators: general population comparators matched 5:1 by age, sex, education level, place of residence, and year.
Figure 8 Mean (bars) and median (black dots) monthly costs in patients with incident rheumatoid arthritis (RA) 18-64 years (upper panel) and ≥65 years (lower panel), and mean monthly cost in comparators (white diamonds), in relation to register identification date.

Comparators: general population comparators matched 5:1 by age, sex, education level, place of residence, and year.
4.3  PAPER III

Out of 493 patients that were screened for inclusion to the Swefot trial from October 2002 through December 2005, 487 were enrolled in the study. Of 258 randomized patients, with DAS28 >3.2 after 3-4 months of methotrexate monotherapy, 204 were <63 years at randomization, whereof 105 were randomly allocated to infliximab and 99 to conventional combination treatment. Seven patients in the infliximab and 4 in the conventional treatment group never received the study drug. In the infliximab arm 69% (n=72) followed the study per protocol for 21 months, while 53% (n=52) in the conventional treatment arm completed the study according to protocol. The hazard ratio for the difference in time to discontinuation in the infliximab compared to the conventional treatment group at 21 months after randomization was 0.51 (95% CI 0.31 to 0.82).

Mean sick leave and disability pension days at randomization were 17 days/month in both groups (mean difference 0.6; 95% CI -3.0 to 3.9). Using the ITT approach, the mean changes in sick leave and disability pension at 21 months after randomization were -4.9 days/month in the infliximab and -6.2 days/month in the conventional treatment group (adjusted mean difference 1.6; 95% CI -1.2 to 4.4).

Excluding patients that never received the study drug in a modified ITT analysis, the adjusted mean difference was 1.5 days/month (95% CI -1.5 to 4.4), and in per-protocol analysis the adjusted mean difference was 0.3 days/month (95% CI -2.8 to 3.8).

Similar to the results at 21 months after randomization, no significant differences were observed in ITT, modified ITT, or per-protocol analyses at 12 months after randomization.

Work loss in relation to general population comparators

At 1 year before randomization, the overall mean monthly days of sick leave and disability pension started to increase from the same level as in the general population (5 days/month), and increased to 20 and 18 days/month in the (future) infliximab and the conventional treatment groups, respectively, at the start of the run-in period (Figure 9). Compared to the general population, the randomized patients reduced their monthly days of sick leave and disability pension from a level 3 times greater at randomization to twice the days at 21 months after randomization, with most of the observed reduction already present after 6 months.

Work loss in non-randomized patients

Patients of working age who after the run-in period did not undergo randomization, most of whom responded to the methotrexate monotherapy (defined as a DAS28 ≤3.2; n=135), started from a lower level at the time of methotrexate monotherapy initiation as compared to the randomized patients. The non-randomized group decreased their monthly work loss days from 12 to 8 days/month during the run-in period, and further decreased their work loss days to the level of the general population 7 months thereafter (6 days/month; Figure 9).
Figure 9 Mean monthly days on sick leave and disability pension in relation to date of randomization (maximum 30 days)

Run-in period: Methotrexate monotherapy; Controls: General population comparators matched 5:1 by age, sex, education level, place of residence, and year; error bars: SEs; Infliximab: Infliximab plus methotrexate; Conventional treatment: Sulfasalazine and hydroxychloroquine plus methotrexate; Non-randomized: Non-randomized patients of whom a majority had a favorable DAS28 response after the run-in period.
4.4 PAPER IV

Out of the 258 randomized patients in the Swefot trial, 128 were randomized to infliximab and 130 to conventional combination treatment. A few patients never received the randomly allocated drug (8 patients in the infliximab group and 5 patients in the conventional treatment group). A higher proportion of patients in the infliximab arm completed 2 years of follow-up compared to the conventional treatment arm, 70% (n=90) versus 57% (n=74), respectively.

**Costs**

With the high cost of infliximab, the patients in the infliximab arm incurred higher health care costs compared to the conventional treatment arm (€19,215 versus €4710; adjusted mean difference €14,280; 95% CI 12,269 to 16,101; Figure 10). Furthermore, the patients in the infliximab group had more rheumatology clinic visits, resulting in higher costs of health care use than the conventional treatment group (€8272 versus €5653; adjusted mean difference €2676; 95% CI 1425 to 4058).

In the main analysis using the human capital approach, no difference in productivity losses was detected between the infliximab and the conventional treatment group (€33,804 versus €29,220; adjusted mean difference €3961; 95% CI -3986 to 11,850). A similar result was obtained in sensitivity analysis when instead the friction cost method was applied for valuation of productivity losses.

The higher health care costs in the infliximab arm resulted in higher total costs from both the societal (€61,291 versus €39,584; adjusted mean difference €20,916; 95% CI 12,800 to 28,660) and the health care perspective (€27,487 versus €10,364; adjusted mean difference €16,956; 95% CI 14,647 to 19,162).

**QALYs**

During the 21 months of follow-up from randomization, the infliximab group accumulated on average 1.10 QALYs while the conventional treatment group accumulated on average 1.12 QALYs (adjusted mean difference favoring the infliximab arm 0.01; 95% CI -0.07 to 0.08).

**Incremental cost-effectiveness ratio (ICER)**

Including productivity losses the ICER from the societal perspective between the infliximab and the conventional treatment group was €2,404,197 per QALY, while only including health care costs the ICER from the health care perspective was €1,948,919 per QALY (Figure 11). As Figure 11 indicates, no bootstrap sample was cost saving for the infliximab compared to the conventional treatment group, and 60% of the bootstrap samples displayed a higher accumulated QALY in the infliximab arm and thus presented in quadrant I.
Figure 10 Specific and total costs from the health care and societal perspective for the infliximab versus the conventional treatment strategy

Infliximab: Infliximab plus methotrexate;
Conventional treatment: Sulfasalazine and hydroxychloroquine plus methotrexate.

Figure 11 The point estimate and bootstrapped incremental cost-effectiveness ratio plotted in the cost-effectiveness plane by societal and health care perspective for the infliximab versus the conventional treatment strategy

WTP: willingness to pay
5 DISCUSSION

5.1 MAIN FINDINGS

This thesis describes how register-enriched quality of care register data can be used in studying the occurrence and burden of disease, including considerations of possible limitations with register-identification of cases. Furthermore, with a randomized pragmatic clinical trial included in the register framework, we have provided information on health economic outcomes to a common clinical question in early RA, namely whether to continue treatment by adding a biologic alternative or to continue with a conventional combination treatment strategy after insufficient response to methotrexate.

More specifically, by enriching the SRQ with data from Swedish national health registers, demographic registers, and the registers at the Social Insurance Agency, the aims of this thesis were to (i) estimate the nationwide incidence of RA in Sweden overall and across subgroups of age, sex, demography, and geography, (ii) estimate the annual burden in terms of costs of hospital care, drugs, and lost work days in incident and prevalent RA, (iii) compare the effect on work loss in a treatment strategy of adding infliximab versus adding further conventional DMARDs in patients with methotrexate-refractory early RA, and (iv) to estimate the incremental cost-effectiveness of the infliximab versus the conventional treatment strategy.

5.1.1 Incidence of RA

We estimated the nationwide incidence of RA in Sweden to 41 per 100,000. The incidence in women and men was 56 and 25 per 100,000, respectively, and increased considerably with age with a peak in the 70-79 years age group in both sexes. Using age- and sex standardized estimates, lower incidences were observed in densely populated areas and in individuals with high education level, but no geographic trends were detected. Changing the register-based case definition of RA to a more liberal and a more strict definition, respectively, altered the incidence estimates by less than 15%.

5.1.2 Costs for hospital care, drugs, and lost work days in RA

In 22,000 prevalent working age patients with RA the mean annual societal cost was €23,000, of which one quarter was attributed health care costs and three quarters to productivity losses. This cost was 2-3 times higher than the corresponding costs in general population comparators, resulting in an estimated annual cost of €15,000 attributable to RA. The corresponding mean annual incremental cost in retirement age prevalent patients with RA (n=28,000) was €4000, with inpatient care as the largest cost component.

In new onset RA, the mean monthly cost increased from a level close to that of the general population 12 months before the first registered RA diagnosis. A peak in mean monthly costs was observed one month after the identification date of RA diagnosis, and then decreased to twice the cost as compared to the general population 12 months thereafter.

The cost distributions were heavily skewed, with less than 15% of the patients contributed with more than half of the total annual cost.
5.1.3 Infliximab versus conventional combination treatment and work loss in early RA

In patients with early RA and an insufficient response to methotrexate monotherapy who were randomly allocated to receive infliximab or conventional combination therapy in addition to methotrexate, the monthly days of sick leave and disability pension were significantly reduced over 21 months. However, no difference in work loss days could be detected when comparing the strategies of adding infliximab or adding further conventional DMARDs after methotrexate failure. At 12 months before randomization, the monthly work loss days started to increase from the same level as the general population. At randomization, the observed level of 17 days/month in both treatment arms was 3 times the days in the general population, and at 21 months after the randomization the work loss days were double that in the general population.

Even though the randomized patients did not have a favorable DAS28 response at 3 months, they reduced their work loss days over this run-in-period. However, the observed improvement was much greater in the non-randomized patients, most of whom had a favorable DAS28 response (Figure 9).

5.1.4 Cost-effectiveness of infliximab versus conventional combination treatment in early RA

Over 21 months we observed higher drug and health care costs in patients with methotrexate-refractory early RA who were randomly allocated to infliximab, as compared to those who were randomized to receive conventional combination therapy, while no differences in productivity losses or QALYs between the treatment strategies could be detected. The incremental cost-effectiveness ratios for the infliximab versus the conventional treatment strategy were €2,400,000/QALY from the societal perspective and €1,900,000/QALY from the health care perspective. Given willingness to pay levels that are generally considered to be acceptable (US$50,000-100,000 or £20,000-30,000 per QALY), the infliximab strategy, as compared to the conventional alternative, was not found to be cost-effective over 21 months in this trial.
5.2 PREVIOUS RESEARCH

5.2.1 Incidence of RA

Previous estimates of RA incidence in Sweden have been reported from regional studies from southern Sweden that found more than a 2-fold variation, with 24 versus 50 cases per 100,000.96,97 The larger and most recent study by Englund and colleagues reported a higher overall incidence estimate in 2008 as compared to our estimate (50 versus 41 per 100,000). With the exception of their regional and our national study approach, the discrepancy between their study and ours may be due to our better possibilities of excluding prevalent RA patients through both a longer washout period and access to prescription drug data.

An incidence study from the US based on 466 cases between 1995-2007 from Minnesota has been reported by Myasoedova and colleagues.98 Although we used a different study design and case ascertainment technique, the overall (their 41 versus our 41 per 100,000) and age as well as sex-specific incidence estimates were remarkably similar to our estimates.

As for European countries, incidence estimates have been reported from Finland (45 per 100,000),53 Denmark (31 per 100,000),99 the UK (25 per 100,000),100 and Italy (35 per 100,000).101 In the reports from Italy, Denmark, and Minnesota, as in our study, the incidence of RA was found to peak in the 6th-7th decade of life in both women and men, while the studies from Finland and the UK reported a more widespread peak before age 60 years. However, another study using the same cohort from Norfolk in the UK,100 but with longer follow-up time (5 years) for estimating the incidence of RA, still found a widespread peak in women, but with an incidence of 54 per 100,000 in women and 24 per 100,000 in men,102 which is more comparable to our estimates. Furthermore, in that study, applying the 2010 ACR/EULAR classification criteria at baseline was similar to the estimates using the 1987 ACR classification criteria cumulatively over 5 years.56

5.2.2 Costs for hospital care, drugs, and lost work days in RA

A recent review compiled data on cost of illness studies in RA with a comprehensive discussion about difficulties in comparisons between studies due to different methodological approaches, health care settings, and study objectives of the reviewed reports.103

Despite these difficulties, another review tried to estimate a weighted mean annual cost based on data from 26 cost of illness studies in RA.104 They reported a mean annual cost per prevalent RA patient of €4170 in health care costs and €8452 in productivity losses. Our total cost estimates accumulated over 1 year were substantially higher with €6352 in health care costs and €16,907 in productivity losses. More comparable estimates resulted when subtracting the cost of the general population comparators (€4228 in excess health care cost and €9816 in productivity losses). However, our estimates were still higher. One reason for the discrepancy may be that the weighted mean annual cost estimates in the review were partly based on studies before or very early in the biologic era (8 studies published before 2003).

As with previous estimates of the incidence of RA, cost estimates have also been reported based on questionnaire data from southern Sweden in patients with established RA.72 The mean annual cost per patient was estimated to approximately €12,000 (ours €13,665), with productivity losses accounting
for 55% of the total cost (73% in our study). Although this study was conducted in a regional sample in the early biological era, the estimates are largely in keeping with ours. However, this study also included cost components that we did not have access to, i.e. costs associated to primary care visits, community services and transportation, patient costs, and informal care, which together accounted for 18% of the estimated total cost in the study.

With respect to productivity losses during the first year in newly diagnosed patients with RA, an overall cost estimate in the working age population of the FIN-RACo trial from Finland,\textsuperscript{105} was reported to be \( \text{€8320} \) in 2002.\textsuperscript{106} In their study, RA-related disability pension and sick leave for any reason were included in the analysis. Reducing our estimate of productivity losses with the corresponding costs in the general population comparators resulted in an estimated work loss cost attributable to RA of \( \text{€6560} \). With the exception of the sick leave estimates due to any reason in their study, the discrepancy may also be explained by more aggressive treatment alternatives in our study as well as stricter regulations in the welfare system in Sweden during recent years, with decreasing days of both sick leave and disability pension during the recent decade in patients with RA.\textsuperscript{8,107}

5.2.3  **Infliximab versus conventional combination treatment and work loss in early RA**

Data from RCTs including patients with early RA have shown that the most used TNF inhibitors in RA (infliximab, etanercept, and adalimumab) in combination with methotrexate are clinically and radiologically superior to methotrexate alone.\textsuperscript{15,108,109} However, the recent double-blind randomized controlled TEAR (Treatment of Early Aggressive Rheumatoid Arthritis) trial showed similar results in disease activity and small differences in radiographic progression after 2 years, as was found from the Swefot trial,\textsuperscript{66} in treatment strategies of patients randomly allocated to methotrexate plus etanercept or triple therapy, regardless of immediate initiation or following insufficient response to methotrexate monotherapy.\textsuperscript{64} From the same trial, similar estimates in disease activity and small differences in radiographic progression were observed after 2 years between groups of subjects who were randomized to immediate methotrexate monotherapy who thereafter had a sufficient response after 24 weeks (DAS28 <3.2), to immediate methotrexate with step-up combination therapy at 24 weeks due to insufficient response (DAS28 \( \geq 3.2 \)), and to immediate methotrexate in combination with sulfasalazine and hydroxychloroquine or to methotrexate plus etanercept.\textsuperscript{110}

In studies based on self-reported data, early treatment initiation after diagnosis, as compared to starting treatment later in the disease course, has been shown to have a stronger effect on work loss.\textsuperscript{111,112} Several studies have reported the impact of biological agents on work participation,\textsuperscript{113} where only four identified studies have used an RCT design.\textsuperscript{13-16} All four studies compared TNFi plus methotrexate with methotrexate alone, and found a significant improvement favoring the TNFi therapy. However, none of the studies compared TNFi plus methotrexate to combination DMARD therapy, analyzed the effect in methotrexate refractory early RA, and all used self-reported work loss data. These study characteristics compounded with the addition to different approaches to assess work loss and different follow-up periods complicate comparisons between these studies and ours. The FIN-RACo trial reported that a strategy of starting combination DMARD therapy is superior to single DMARD therapy in early RA.\textsuperscript{105} Rather than using single DMARD therapy as comparison, it appears therefore more reasonable to compare a biologic combination alternative to a combination DMARD therapy.
5.2.4 Cost-effectiveness of infliximab versus conventional combination treatment in early RA

To the best of our knowledge, no previous study from a randomized trial has presented cost-effectiveness results based on directly observed costs and quality of life in methotrexate-refractory early RA.

The BeSt trial compared four different treatment strategies in patients with early RA, and found that a strategy of initial infliximab plus methotrexate therapy resulted in more QALYs and less productivity losses, as compared to initial combination therapy with methotrexate, sulfasalazine, and prednisone. However, the analysis has been criticized for not adjusting for potential imbalances in baseline productivity, with the argument that substantial differences in incremental costs were observed when assessing productivity losses using the human capital or the friction cost method. Comparisons with our results to the results from the BeSt study may be difficult. The BeSt study did not include a strategy starting with triple therapy and patients had not previously failed methotrexate, while work loss and utility were improved already during the run-in period of methotrexate monotherapy in the Swefot trial.

As discussed, the randomized double-blind TEAR trial showed similar clinical outcomes and small although statistically significant radiographic differences between four treatment strategies after 2 years in early RA patients. In this trial, patients were randomly allocated to immediate etanercept plus methotrexate, immediate triple therapy, or to two different step-up strategies with the same treatment alternatives but with immediate methotrexate monotherapy as first-line treatment. Preliminary results presented in abstract form in a life-time horizon cost-effectiveness modelling study based on the TEAR trial indicate that the strategy of immediate etanercept plus methotrexate, as compared to the immediate triple therapy strategy, was not found to be cost-effective in relation to what most health care settings consider to be acceptable (ICER = $837 100). Similar clinical and radiographic outcomes have also been reported after 5 years of follow-up in the NEO-RACo trial, where patients with early RA were randomly allocated to receive immediate therapy with infliximab or placebo, in addition to combination therapy with methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone. Finally, in patients with established RA included in the double-blind randomized noninferiority RACAT (Comparison of Active Therapies) trial, triple therapy was also found to be noninferior to methotrexate plus etanercept after 48 weeks of follow-up regarding disease activity and radiographic progression. Although no health economic analysis has been presented from either the NEO-RACo or the RACAT study, the higher drug cost in the TNFi arm would likely favor the conventional treatment strategy.

5.3 IMPLICATIONS

Using a register-enriched quality of care register methodology enables a strong observational study design with long-term follow-up of real-world patients for many different outcomes and to an affordable cost. In contrast, while the RCT is one of the most powerful tools available in medical research, randomized trials are often very expensive to conduct leading to a limited number of patients enrolled, or that the intended trial may not be conducted at all, with potential power issues and concerns relating to representativeness of the results. By combining the randomization procedure
in a pragmatic clinical trial setting with the observational register-enriched platform, the study design becomes far more powerful enabling safety, effectiveness, and cost-effectiveness assessments of treatment alternatives in a large sample and to a low additional cost, while at the same time accounting for unmeasured confounders and selection bias. With the improvement and enormous opportunities to conduct effective medical research in relation to cost when combining strengths from randomized trial and prospectively recorded register data,\textsuperscript{10,118,119} and given that over 80 Swedish registers are of sufficient quality to be certified as quality of care registers, efforts should be prioritized to enable randomized register trials to a higher extent in medical research in Sweden.

With respect to methotrexate-refractory patients with early RA in the Swefot trial, over 21 months, work loss and quality of life improved similarly in a treatment strategy of adding infliximab as compared to adding further conventional DMARDs to methotrexate, while higher costs were observed in the infliximab arm. Based on these results, an attempt with conventional combination therapy appears reasonable before starting infliximab treatment, both from a clinical and economic perspective. However, less radiographic progression was observed in those patients starting infliximab therapy after methotrexate failure, why larger studies and longer follow-up may be warranted to confirm the study conclusion.

In addition to the non-responders of methotrexate monotherapy who were randomized to a combination therapy in the Swefot trial, we also analyzed work loss outcomes in the non-randomized group, and observed a substantial decline in monthly work loss days after methotrexate monotherapy initiation. In less than a year after the month of run-in, the average number of monthly work loss days was at the same level as the general population, a finding that supports the notion that it is acceptable to delay a more aggressive treatment alternative for a few months in favor of methotrexate monotherapy. This finding has been supported by data from the recent TEAR trial including poor prognosis early RA, as well as previous reports from the Swefot study, where patients who had a favorable response to methotrexate monotherapy within 6 months continued to do well both clinically and radiographically.\textsuperscript{110,120} However, no analysis using work loss as an outcome has been reported from the TEAR trial.

With an immediate aggressive combination therapy, rather than a step-up treatment strategy, the risk of over-treating in the approximately one third of patients with early RA who respond to the initial methotrexate therapy would be reduced, with reduced risks of adverse consequences. However, immediate initiation of aggressive therapy may be warranted in some patients, and predictors of achieving EULAR good response at the time of initiation with methotrexate monotherapy has previously been investigated in the participants of the Swefot trial.\textsuperscript{121}

\section*{5.4 STRENGTHS}

In this population-based matched cohort study design, detailed clinical data from the SRQ was used as a foundation, with patients enrolled in the randomized Swefot trial included, and were linked to nationwide register data. This design enabled follow-up of patients with RA alongside general population comparators, both backward and forward in time from the date of RA diagnosis, and date of randomization for patients in the Swefot trial. The matched comparators served as a benchmark of mean annual cost of health care, drugs, and productivity losses (paper II; Figure 7 and 8), as well as a
benchmark for mean monthly days of sick leave and disability pension (paper III; Figure 9) in the general population as compared to newly diagnosed patients with RA. Thus, the overall cost, including loss of work days, associated with the RA disease could be estimated.

Non-response and recall bias, associated with questionnaires, were avoided by access to nationwide health care data from inpatient and non-primary outpatient care, prescription drugs, and objectively assessed sick leave and disability pension. All these data were on an individual level and on a daily basis, and were available for all study subjects, including those patients who discontinued the Swefot trial, as well as for general population comparators. The use of national data sources also resulted in a large sample size of incident patients, with the possibility of robust subgroup estimates and of testing different case definitions of register-based incident RA. The methodology used in the incidence study of RA (paper I), as in register-based methodology in general, is relatively easy to reproduce with the same setting and may be used in time-trend analysis in future data linkages. Moreover, the detailed clinical data of quality of life from the SRQ combined with cost components captured from national registers, enabled, to the best of our knowledge, the first cost-effectiveness analysis of a register-enriched randomized controlled trial (paper IV).

Finally, with respect to the register-based methodology, the data linkage procedure used in this thesis maximizes data use from national health register sources routinely collected in clinical care and from drug prescriptions given in ambulatory care, while the clinical variables entered into the SRQ can be minimized, an important feature to lower the work load for rheumatologists entering data into SRQ.

5.5 LIMITATIONS

The register-based approach also has limitations. One limitation with a register-based study design is that identification of subjects may be sensitive to the case definition of disease based on clinical criteria, such as RA. To qualify as having RA in the SRQ the ACR criteria are used at inclusion, while this may not be the case for patients listing a diagnosis of RA in the National Patient Register with visits at non-rheumatology departments. In the study of RA incidence (paper I) we assessed the risk of misclassification by testing the sensitivity of the register-identification of incident RA and estimated the treatment penetration in the identified RA cases, given that close to all patients in Sweden with new onset RA are initiating DMARD therapy. Furthermore, a validation study of the RA diagnosis in the National Patient Register showed a high validity, with 90% of prevalent RA fulfilled either of the ACR or the ACR/EULAR classification criteria.

Another limitation is that using a register-based approach may introduce selection bias due to missing individuals who have problems with accessing care, for example older people and people with severe diseases. This may potentially result in an underestimation of the true number of individuals with RA.

From the registers we did not have access to all possible cost components, for example costs related to primary care, physiotherapist visits, stays in rehabilitation units, transportation, presenteeism, unpaid work, and out-of-pocket patient and family costs. With the absence of these cost components the true cost was probably underestimated. A recent review estimated cost associated with patient and family to €2284, which was 18% of the total societal cost based on pooled health care costs and productivity losses from different cost of illness studies, and where productivity losses was valued with the human capital approach. A recent study from Norway reported costs associated with visits to
primary care and physiotherapists, and stays in rehabilitation units in patients with RA, who had initiated first-line DMARD therapy, to compose 4.1% of the total cost. However, while the total societal costs in prevalent and incident RA are likely to be underestimated in our study (paper II), we had access to the major cost components, i.e. health care use, drugs, and productivity losses. Moreover, with the similar improvement in quality of life between the infliximab versus the conventional combination therapy, and the large drug cost difference, it would be unlikely that any potential cost differences in missing cost components would change the study conclusion of the cost-effectiveness analysis.

A further limitation was that we did not have access to sick leave periods shorter than 15 days, which is the time period that was covered by the employer during the study period (except the unpaid 1st day of sick leave). Given the chronic inflammatory and destructive nature of the RA disease, sick leave periods for RA are usually not short. In a study from Finland, with a similar social security system as compared to Sweden, sick leave periods of 10 days or less were found to constitute only 0.2% of total sick leave days in recent onset RA during 5 years of follow-up. This finding indicates that the potential underestimation of sick leave days due to missing short sick leave periods in our data may be limited.

The unblinded design is probably the most important concern with the Swefot trial, i.e. both patients and physicians were aware of the treatment allocation. Single-blinding of the trial was considered, which would be blinding of the treatment allocation when assessing disease activity, but was deemed unfeasible due to limited personnel resources at smaller participating units. However, the work loss outcome (paper III) and cost outcomes (paper IV) were objectively assessed using registers, and the radiological results were assessed by readers masked to the allocated treatment.

With the unblinded design it is not unreasonable to believe that patients allocated to conventional treatment may have been more willing to abandon the allocated therapy for perceived lack of effectiveness, while patients allocated to TNFi therapy may have continued with the regimen knowing that no superior alternative was available. However, findings from the one-year data argue against this hypothesis, with indeed high disease activity, and at a similar level at the time of discontinuation between the two groups of those who discontinued the allocated treatment.

Other limitations of the work loss (paper III) and the cost-effectiveness (paper IV) studies based on data from the Swefot trial were the short time horizon and the limited number of included study subjects. Rather than diverging, however, the average monthly days of work loss followed a similar trajectory between the infliximab and the conventional combination strategy over 21 months. With no difference in disease activity over 2 years, and with a similar trajectory in health related quality of life, it is difficult to consider that the two strategies may start to diverge in the future owing to the small difference in radiographic progression. Data on work loss and health care use will be possible to analyze over longer time horizons, as these outcomes are collected via register-linkage.

With 204 working age patients included in the work loss study (paper III), 258 randomized individuals in the cost-effectiveness analysis (paper IV), and a power analysis in the study-design phase based on disease activity measured after 1 year and not based on work loss days, costs, or QALYs after 21 months, there may be a risk of type II error. From Figure 5 it can be concluded that more than 500
patients per group would be needed to detect a difference in mean lost work days of 1.6 days/month to a power of 75%. An RCT including more than 1000 patients, even enrolling patients included in the SRQ, would be expensive and rather unrealistic to conduct. This together with the possibly unexpected result of a non-significant point estimate (1.6 days/month) not favoring the infliximab treatment indicate that the potential problem with a type II error for detecting a statistical difference may not be a major concern for the conclusion of the study. Again, the quality of life and work loss development showed similar trajectories between the treatment strategies over 21 months of follow-up, while the drug cost was considerably higher in the infliximab arm.

5.6 CONCLUSIONS

Register-enriched quality of care register data in Sweden can be used to study nationwide real-life occurrence and burden of disease with the possibilities of robust subgroup estimates and time-trend analysis by establishing a database that is easy to reproduce and update within the same setting.

By using the SRQ linked to national registers we could estimate the overall incidence of RA in Sweden on a par with previous local but detailed studies, and importantly, beyond estimates across age and sex, describe the variation in age- and sex adjusted incidence according to region, population density, and level of education. With general population comparators individually matched to register-identified subjects with RA we could also estimate the annual societal cost in prevalent as well as monthly societal cost in newly diagnosed patients with RA to 2-3 times higher relative to the general population. With the individual level data we could further describe the cost distribution. The distribution was found to be heavily right-skewed, with a minority of the patients with RA contributed the majority of the total cost. This emphasizes the notion that predicting and intervening for reducing costs in RA may be very different in different patients segments.

The register-enriched quality of care register data with the observational nature is by itself an important and highly useful database with possibilities to answer an abundance of research questions by using many different outcomes over long time periods and in a real-world setting. However, the true potential is when combining such a framework with a pragmatic randomized controlled trial included in the quality register platform.

The randomized Swefot trial investigated a common clinical situation in early RA, whether to intensify treatment by adding an expensive biologic drug or further conventional DMARDs to patients with insufficient response to methotrexate. Data from enrolled patients were collected in the SRQ, and thus allowed for investigating this research question using different outcomes in a register-enriched randomized controlled trial setting.

With respect to work loss, the decrease in mean monthly work loss days was substantial in both treatment alternatives, with a reduction of 3 times to double that in the general population from randomization to 21 months of follow-up, but no difference between the strategies could be detected at 12 or 21 months after randomization. The remaining gap to the general population indicates a need for earlier diagnosis as well as for more effective treatment strategies of RA.

Finally, by combining quality of life data from the randomized Swefot trial with costs captured from the national registers, similar effects were observed over 21 months, while the infliximab strategy
incurred higher costs, as compared to the conventional treatment. These findings indicate that the infliximab strategy is not cost-effective as second line treatment at willingness-to-pay levels generally considered acceptable.

5.7 FUTURE RESEARCH

The register-based methodology used in this thesis is an effective approach to research that can be conducted to a relatively low cost, and is comparatively easy to replicate in other disease areas. With the many quality of care registers in Sweden that collect data on different diseases and interventions, there is great potential for conducting effective research using similar study designs.

Since the introduction of biologic drugs the research field of RA has attracted more attention and is today an intense and highly active field of medical research. However, many research questions still remain unanswered. In relation to the studies in this thesis the following questions would be of interest

- Incidence of RA:
  To understand how future estimates from similar register-based designs with similar register-identification definitions relate to changes in the classification criteria of RA.

- Need for earlier diagnosis of RA:
  To identify patients earlier in the disease course of RA may have the potential of improving patients’s clinical outcomes as well as reducing sick leave and disability pension days due to RA.

- Treatment in early RA:
  The overall question is which therapy to initiate in whom, and which therapy to continue with, and in whom, of those not responding to the first-line treatment. That is, how can therapy need be predicted on an individual level?

- Long-term follow-up of register-based outcomes in the Swefot trial:
  The radiologically superior outcomes in the infliximab strategy, as compared to the triple therapy strategy, after methotrexate failure may have an effect in the longer term. With the work loss and cost data collected from registers, these outcomes could be investigated over several years by an update of the register linkage with more recent data.
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8 SAMMANFATTNING PÅ SVENSKA

8.1 BAKGRUND

8.1.1 Registerforskning i Sverige


Utöver nationella hälsoregister har även kliniska kvalitetsregister för specifika diagnoser och interventioner etablerats, där data insamlas i klinikens dagliga verksamhet. Syftet med kvalitetsregistret är att följa upp och förbättra vården, i vissa fall bidra med beslutsstöd till den ansvariga läkaren, och att bedriva forskning. De första kvalitetsregistren startade redan på 70-talet med knäplastikregistret och höftplastikregistret, och därefter har fler och fler kvalitetsregister startats. År 2014 fanns 81 olika kvalitetsregister med varierande kvalitetsgrad certifierade i Sverige.

Svensk reumatologis kvalitetsregister (SRQ) startade i mitten av 90-talet med det primära syftet att förbättra vård och behandling av patienter med reumatoid artrit (RA), men började senare också att inkludera patienter med andra reumatiska sjukdomar. I slutet av 90-talet, när de första biologiska läkemedlen för RA blev godkända i Sverige, startades det biologiska behandlingsregistret ARTIS som en del av SRQ.

8.1.2 Reumatoid artrit (RA)

RA, även kallad ledgångsreumatism, är den vanligast förekommande kroniskt inflammatoriska ledsjukdomen. Ungefär 0.7% av Sveriges vuxna befolkning (ca 50,000 personer) lever med diagnosen RA, med större förekomst hos kvinnor än hos män och ökad förekomst med ökad ålder. Den mest betydelsefulla faktorn för RA-sjukdomens utveckling hos drabbade personer är behandling. Sedan introduktionen av biologiska preparat i slutet av 90-talet har behandling av RA förändrats radikalt, men till en betydligt högre kostnad än tidigare tillgängliga behandlingsalternativ. De biologiska läkemedlen påverkar immunsystemet och har visat sig vara mer effektiva än konventionell standardbehandling för reducering av sjukdomsaktivitet och minskad radiologisk förändring (strukturella förändringar i leder), men är associerade med vissa biverkningar.

Till följd av den stora utbredningen av RA och till följd av det lidande som RA medför är samhällskostnaderna stora. Effektivare behandling i form av biologiska läkemedel har givit förhoppningar om att produktionsbortfall i form av sjuksskrivning och förtidspension, som utgör den största delen av den totala kostnaden för samhället, minskas i högre utsträckning och på så sätt ekonomiskt försvara dessa läkemedel.
8.1.3 Swefot – en randomiserad kontrollerad studie


8.2 SYFTE

Syftet med denna avhandling var att beskriva hur svensk registerdata kan användas vid epidemiologiska frågeställningar och vid utvärdering av sjukvård genom att använda SRQ länkat till nationella register och register vid Försäkringskassan. Det specifika syftet med de enskilda studierna var att

1. Beräkna incidensen (nyinsjuknandet) av RA i Sverige totalt, samt uppdelat på kön, ålder, utbildningsnivå, och hemvist (studie I)
2. Beräkna sjukdomsbördan av RA med avseende på kostnad för sjukvård, läkemedel, och produktionsbortfall i relation till allmänbefolkningen (studie II)
3. Beräkna effekten på sjukkrivning och förtidspension av biologisk behandling med infliximab jämfört med konventionell kombinationsbehandling bland patienter med nydebuterad RA (studie III)
4. Genomföra en kostnadseffektivitetsanalys av infliximab jämfört med konventionell kombinationsbehandling (studie IV)

8.3 METOD

Genom att använda personnummer har vi länkat ihop SRQ och nationella hälsoregister, samt även information om sjukkrivning och förtidspension (sjukersättning/aktivitetsersättning) från Försäkringskassan. Till en relativt låg kostnad skapades därigenom en kraftfull forskningsdatabas. Med klinisk detaljerad data från SRQ tillsammans med observationella data av lång och praktiskt taget fullständig uppföljning från framförallt klinisk daglig verksamhet samt data på utskrivna receptläkemedel, men också uppgifter om arbetsoförmåga, kan flera olika frågeställningar i ett stort urval av patienter med RA studeras. I databasen ingår även fem jämförelseindivider från allmänbefolkningen utan RA som har matchats per RA-patient på ålder, kön, utbildningslängd, bostadslänn, och år.

I tillägg har data från den randomiserade studien Swefot registrerats i SRQ. Tillsammans med de fördelar som observationella data ger av lång och nära nog komplett uppföljning av många olika och objektivt bedömda utfall, kunde vi bland randomiserade patienter jämföra hälsoekonomiska utfall som arbetsoförmåga och kostnadseffektivitet. Den randomiserade designen resulterar i en minskad
risk av att andra faktorer påverkar behandlingen och utfallet (confounders), vilket kan leda till felaktiga resultat.

8.4 RESULTAT

8.4.1 Studie I – Incidens av RA
Med en registerbaserad definition identifierades 8826 individer som nyinsjuknade i RA under 2006-2008 i Sverige, vilket motsvarar en incidens av 41 per 100,000 individer. Incidensen var 56 per 100,000 för kvinnor och 25 per 100,000 för män, och ökade med ålder till 70-79 år bland både kvinnor och män (Figur 6). Vidare noterade vi en lägre incidens av RA i tätbefolkade områden och bland personer med högre utbildning, men ingen geografisk trend kunde urskiljas. Genom att ändra vår identifierings-algoritme testade vi den registerbaserade definitionen av nydebuterad RA till en mer strikt och mer liberal definition, vilket resulterade i att det totala incidensestimatet ändrades med mindre än 15%.

8.4.2 Studie II – Kostnader för sjukvård, läkemedel och arbetsoförmåga bland patienter med RA
Medelkostnaden per patient med RA i arbetsför ålder uppgick till €23,000 per år, av vilket en fjärdedel var sjukvårdskostnader och tre fjärdedelar utgjorde produktionsförluster (Figur 7). Bland pensionärer med RA var medelkostnaden per patient €4000 per år, med slutenvård som den största kostnaden. Jämfört med allmänbefolkningen var dessa kostnader 2-3 gånger större, medan medelkostnaden bland patienter med RA som använder biologiska läkemedel var 4 gånger större i den arbetsföra åldern, och 6-7 gånger större bland pensionärer.

Jämfört med allmänbefolkningen, ökade medelkostnaderna per patient med nydebuterad RA från samma nivå 12 månader före diagnos, toppade med 3 gånger kostnaden månaden efter diagnos, för att minska till den dubbla kostnaden jämfört med allmänbefolkningen 12 månader därefter (Figur 8).

8.4.3 Studie III – Infliximab jämfört med konventionell kombinationsbehandling och arbetsoförmåga bland patienter med nydebuterad RA
Patienter med nydebuterad RA som inte svarade på sin initiala metotrexatbehandling randomiserades till att behandlas med infliximab eller med konventionell kombinationsterapi i tillägg till metotrexat. Båda behandlingsgrupperna minskade avsevärt antal medeldagar per månad av sjukskrivning och förtidspension under 21 månaders uppföljning, men ingen skillnad mellan behandlingsgrupperna kunde påvisas.

Vid 12 månader före randomisering ökade antal medeldagar per patient från samma nivå som allmänbefolkningen, för att vara som högst vid månaden före randomisering med 17 dagar i båda grupperna, vilket var 3 gånger så mycket som allmänbefolkningen. Vid 21 månader efter randomisering hade antal medeldagar per månad reducerats till den dubbla jämfört med allmänbefolkningen (Figur 9).

Patienter som inte randomiserats, av vilka de allra flesta hade ett tillräckligt bra svar på sin initiala metotrexatbehandling, startade från färre dagar av sjukskrivning och förtidspension jämfört med de randomiserade patienterna och minskade antal medeldagar per månad till samma nivå som allmänbefolkningen inom 1 år efter behandlingsstart (Figur 9).
8.4.4 Studie IV – Kostnadseffektivitet av infliximab jämfört med konventionell kombinationsbehandling bland patienter med nydebuterad RA

Under 21 månader observerade vi högre läkemedel och sjukvårdskostnader bland patienter med nydebuterad RA som slumpmässigt tilldelats behandling med infliximab, jämfört med de patienter som slumpmässigt tilldelats behandling med konventionell kombinationsterapi efter ett otillräckligt svar av metotrexatbehandling. Däremot kunde ej någon skillnad i hälsorelaterad livskvalitet med kvalitetsjusterade levnadsår (QALY) påvisas. Den ökade kostnaden per QALY för behandlingsstrategin med infliximab jämfört med konventionell kombinationsterapi blev därför mycket hög, med €2,4 miljoner per QALY från ett samhällsperspektiv (inklusive produktionsbortfall) och €1,9 miljoner per QALY från ett sjukvårdsperspektiv (exklusive produktionsbortfall). Dessa kostnader per QALY är högre än vad som vanligtvis anses vara acceptabla nivåer för kostnadseffektivitet.

8.5 SLUTSATS

Registerberikade kvalitetsregister kan användas för att på nationell nivå studera sjukdomsförekomst och sjukdomsbördan med goda möjligheter till subgrupps- och tidsserieanalyser. Detta är möjligt genom att tillfälligt upprätta en forskningsdatabas som är relativt lätt att återskapa med uppdaterad data.

Genom att data från den randomiserade Swefot-studien registrerades i SRQ, kunde vi i en registerberikad randomiserad studie undersöka hälsoekonominss utfall i en klinisk vanlig behandlingssituation för patienter med nydebuterad RA, nämligen huruvida fortsatt behandling med ett biologiskt läkemedel (infliximab) är bättre än fortsatt behandling med konventionella läkemedel bland patienter som misslyckats med en initial metotrexatbehandling.

Båda behandlingsgrupperna i Swefot-studien minskade väsentligt antal medeldagar av sjukskrivning och förtidspension under 21 månader, men ingen skillnad mellan grupperna kunde påvisas. Antal dagar vid 21 månader efter randomisering var fortfarande det dubbla jämfört med allmänbefolkningen, vilket indikerar ett behov av effektivare behandlingsalternativ och att tidigare kunna diagnostisera nydebuterad RA.

Slutligen, genom att kombinera data av livskvalitet från den randomiserade Swefot-studien med kostnader inhämtade från nationella register observerades under 21 månader en liknande utveckling av behandlingseffekt mellan infliximab och trippelterapigruppen, medan patienter i infliximabgruppen ackumulerade betydligt högre kostnader. En mindre radiologisk progress observerades dock bland patienter i behandlingsstrategin med infliximab, vilket innebär att framtida studier med längre uppföljning eventuellt behöver bekräfta dessa studieresultat.