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**EXPLORING A NATIONAL PRACTICE-
BASED REGISTER FOR THE
MANAGEMENT OF RHEUMATOID
ARTHRITIS**

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The bottom line is that

–we, as physicians, owe it to society to assess and reduce the under-care and over-care and medical errors that are contributing to the healthcare cost crisis

– we, as physicians, owe it to our patients to provide more effective, cost-efficient care by making optimal use of current information and technology,

and

– we, as rheumatologists, are best positioned to chart the course and guide improvement in the care of rheumatic and musculoskeletal diseases

LG Anderson

ABSTRACT

Rheumatoid arthritis (RA) is a chronic, inflammatory, auto-immune disease with an unpredictable and debilitating course. From diagnosis and onward, RA patients who need treatment with anti-rheumatic drugs will require on-going contact with health care professionals to ensure adequate management of their disease. A national quality register for RA, established in Sweden in 1995, aims to support efforts by both rheumatologists and patients to optimise patients' future health. The large amounts of data in the register enable investigation of the utility of the register to further the development of the management of RA.

The aim of this thesis was to increase our knowledge about aspects of the clinical management of RA as determined by the rheumatologist. Data from the Swedish Rheumatology Quality Register (SRQ) were used to analyse factors influencing prescription in incident RA and to study the relationship between clinical rheumatologists' assessments of disease activity and standardised outcome measures, in particular the disease activity score based on 28 joints counts (DAS28).

The decision to prescribe a disease modifying anti-rheumatic drug (DMARD) in incident RA was associated with the patient's age, disease activity as measured by DAS28, and the calendar year of the patient's first consultation (year), with some variation by hospital type. On the whole, DMARD prescription increased over the five year period with DMARDs being prescribed more frequently in university and county hospitals compared with district hospitals. Although increasing disease activity would more likely elicit a DMARD prescription in all hospital types, this influence was greater in district hospitals than in either university or county hospitals. When the association of year with increasing DMARD prescription was analysed using Statistical Process Control, the increase was accounted for by a single upward step in July 1998, which could well be related to the promulgation of treatment recommendations that same year.

The relationship between the physician's assessment of disease activity and the DAS28 showed that when the rheumatologist deems disease activity to be "none" in patients treated with biologics, this is not far removed from the DAS28-based definition of remission but is most closely concordant with the recently proposed definition of "minimal disease activity". It is likely that DAS28 will remain useful for monitoring quality on a group level but it cannot replace the rheumatologist's global assessment to justify treatment decisions at the individual patient level. In a cross-section of unselected RA patients, both the standard DAS28 based on the erythrocyte sedimentation rate and DAS28 using high sensitive C-reactive protein (DAS28-CRP) were benchmarked against the rheumatologist's global assessment of disease activity. Both DAS28 and DAS28-CRP tend to overestimate disease activity compared with the physician's global assessment of disease activity. New cut-offs for DAS28-CRP disease activity states are proposed.

In summary, the existence of a national practice-based register for RA has enabled the identification of factors driving prescription of DMARDs in the treatment of incident RA during a period of change in rheumatological practice. The study has also generated knowledge about the utility of the different versions of DAS28 in populations typical for Swedish clinical practice.

LIST OF PUBLICATIONS

- I. Carli C, Ehlin AG, Klareskog L, Lindblad S, Montgomery SM. **Trends in disease modifying anti-rheumatic drug prescription in early rheumatoid arthritis are influenced more by hospital setting than patient or disease characteristics.** *Ann Rheum Dis.* 2006;65:1102-5.
- II. Carli C, Bridges JFP, Ask J, Lindblad S. **Charting the impact of guidelines on the management of early rheumatoid arthritis.** *Scandinavian Journal of Rheumatology.* 2008;37:188-193.
- III. van Vollenhoven RF*, Carli C*, Augustsson J, Nilsson J-Å, Klareskog L, Lindblad S. **Physician-defined disease activity “none” in RA: relationship with DAS28 and with core-set variables.** *Submitted.*
- IV. Carli C, Ask J, van Vollenhoven RF, Fored M, Lindblad S. **Adjusting cut-offs for DAS28-CRP based on the rheumatologist’s global assessment of disease activity.** *Submitted*

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AMA	Anti-malarial drugs
Anti-CCP	Anti-cyclic citrullinated protein
CRP	C-reactive protein
DAS28	Disease Activity Score based on 28 joints
DAS28-CRP	DAS28 using CRP
DMARD	Disease modifying anti-rheumatic drug
ESR	Erythrocyte sedimentation rate
GC	Glucocorticosteroids
HAQ	Health Assessment Questionnaire (Swedish modified version)
MCP	Metacarpal phalanges
MTP	Metatarsal phalanges
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drugs
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PGH	Patient global health
PhGA	Rheumatologist's global assessment of disease activity
PIP	Proximal Interphalangeal (joint)
RA	Rheumatoid arthritis
RF	Rheumatoid factor
ROC	Receiver operating characteristics
SJC	Swollen joint count
SPC	Statistical Process Control
SRQ	Swedish Rheumatology Quality Register
SSR	Swedish Society for Rheumatology
SSZ	Sulphasalazine
TJC	Tender joint count
VAS	Visual analogue scale

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune, systemic, inflammatory disease with an unknown aetiology. It is characterised by persistent synovial inflammation leading to destruction of cartilage and bone erosion which in part can be explained by the over-expression of pro-inflammatory cytokines.¹ RA afflicts contra-lateral joints of the body, typically affecting the hands and feet but not exclusively so. Characteristic symptoms include painful and swollen joints, morning stiffness, fatigue, weight loss, malaise and fever. Other organs such as the skin, lungs, heart and kidneys can be affected.² The suffering that patients with RA endure is compounded by an increased risk of morbidity and mortality from cardiovascular diseases, infections and respiratory diseases and survival for these patients has not improved to the same degree as in the general population over recent decades.³ The costs related to RA are considerable for society in terms of lost working capacity, sickness benefits, and medical care. In Sweden, these costs have been estimated to 770 million Euros during 2006.⁴

Although it is now known that RA has been around for millennia, it was first recognized and described as a separate disease in 1800.⁵ Until some decades ago there were few effective treatments and patients suffered devastating disability as a result. Since then, clinical trials have provided convincing evidence for early intervention with disease modifying anti-rheumatic drugs (DMARD) to reduce radiological progression of joint damage and for maintaining physical function.⁶⁻⁹ The prescription of DMARD has increased since the 1980s,¹⁰⁻¹⁶ but their use in daily clinical practice varies considerably.^{15 17-19}

Rheumatologists' understanding of the concept of early RA and the treatment modalities employed have been investigated using questionnaires¹⁴ but little is known about the factors that influence DMARD prescription in clinical care. Presumably disease activity and severity will exert a major influence on the rheumatologist's decision to prescribe anti-rheumatic pharmacotherapy. However, it is unlikely that all rheumatologists will understand these terms in exactly the same way, just as rheumatologists do not always understand well-defined classification criteria for RA in the same way.²⁰ Especially the understanding of disease activity and how to measure it in clinical trials has been problematic.²¹ For this reason disease activity indices have been developed for use in clinical trials where the effect of a single drug or intervention is under study. The value of these indices in routine clinical care is unclear.²²⁻²⁹

1.1 INCIDENCE AND PREVALENCE

Studies of the incidence and prevalence of RA over the last fifteen years have produced varying rates world-wide.³⁰ Incidence rates for RA in northern Europe range between 20-50 cases per 100,000 in the adult population.³¹ Wiles et al aptly described estimating incidence rates as trying to hit a moving target, as the slow development of disease manifestations in some cases delayed diagnosis up to 5 years, increasing incidence rates for any particular year by up to 35% compared with initial estimations. For patients who had sought care for RA within a year of symptom debut, the incidence rate was 21.8 per 100,000.³² At the same time, there are indications that RA is on the decline across the world,³³⁻³⁷ which may complicate attempts at accurate estimations still

further. A Swedish study from 1999 placed the incidence of RA in southern Sweden to 24 per 100,000; 29 women and 18 men per 100,000, respectively.³⁸ When considering only those patients who were diagnosed within a year of symptom debut, the incidence rate was 20.5 per 100,000 of the adult population.

The prevalence of RA in the Swedish population was estimated in 1995 to 0.51%.³⁹ In that study a modified version of the 1987 American College of Rheumatology (ACR) revised classification criteria was used that excluded the requirement of 6 weeks disease duration, and allowed cumulative documented evidence of criteria. Twenty patients (11 males and 9 females) were identified in the population illustrating the difficulty of estimating RA's true prevalence, considering that the proportion of women to men in RA is usually reported to be in the range of 2-3:1.² In Norway, the prevalence of RA has been calculated to 0.44% (Oslo)⁴⁰ and 0.47% (Troms).⁴¹ In general, the prevalence of RA appears to be greater in the United States and northern Europe (other than in Sweden and Norway) than in other parts of the world.^{30 31}

1.2 CLASSIFICATION CRITERIA FOR RA

RA can be difficult to diagnose and in order to differentiate RA from other inflammatory arthritides the American Rheumatism Association (now ACR) developed classification criteria for RA.⁴² The 1987 revised criteria are used in the SRQ for incident cases of RA (Table 1).²⁰ Patients must satisfy at least four of the seven criteria.

Table 1. The 1987 revised criteria for the classification of rheumatoid arthritis

Criterion	Definition
1. Morning stiffness*	Morning stiffness in and around the joints, lasting at least one hour before maximal improvement
2. Arthritis of 3 or more joint areas*	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hands*	At least one area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis*	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on postero-anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

* Criteria must have been present for at least 6 weeks

1.3 CHANGING APPROACHES TO THERAPY FOR RA

Quite possibly due to the unknown aetiology of RA and its relentless course, there have been a number of creative, if not seemingly desperate, attempts to treat RA as late as the 1950s. Some of these, such as using cafestol, an extract from the coffee bean which is now known to be the most cholesterol-elevating compound in the human diet,⁴³ would most probably be contra-indicated today on medical grounds. Other methods to contain the symptoms of RA, such as lobotomy⁴⁴, would probably be shunned on ethical grounds. An impressive array of animal venoms, nutritional supplements, surgical interventions, fever-inducing physical therapies and hormone therapies, including insulin, has been described.⁴⁵ The discovery of cortisone in 1948 and its subsequent use in RA, however, signalled the beginning of a new era in the treatment of RA.²

1.3.1 Contemporary Therapeutic Strategies

The traditional approach to therapy RA in the decades prior to the 1990's was dominated by the therapeutic pyramid. The therapeutic pyramid involved treating symptoms with non-steroid anti-inflammatory drugs (NSAID), progressing to more potent drugs, i.e., cortisone and DMARD, when NSAIDs no longer had any effect. Recognising that the traditional pyramid approach did not prevent joint damage in RA, a step-down approach was proposed whereby a combination of drugs was used to control inflammation early in the disease before joints damage occurred.⁴⁶⁻⁴⁸ It is now generally accepted that early and aggressive treatment is essential to minimise future incapacity.^{49 50}

1.4 DISEASE ACTIVITY IN RA

In RA, there is no one measure which is directly related to diagnosis, prognosis or outcome, analogous to HbA_{1c} in diabetes⁵¹. The concept, "disease activity", provides rheumatologists with a common and practical approach to understanding and representing the underlying processes that characterise RA. Defining what constitutes disease activity makes it possible to develop measures for it. Disease activity, in contrast to disease severity, is characterised by the reversible manifestations of RA at a given time, although some of these manifestations such as joint swelling can be difficult to differentiate from joint destruction. Disease severity, of which persistent disease activity is only one aspect, encompasses even the progression and long-term outcomes of the disease such as impairment, extra-articular manifestations and RA-induced co-morbidity.⁵² The acute phase response and the degree of disease activity are surrogate markers of inflammation⁵³ but are closely related to joint destruction and thus severity.⁵⁴⁻⁵⁶ Controlling the major expression of disease activity is central to the management in RA, a finding that has been borne out in a number of studies.^{57 58}

1.4.1 Measures of Disease Activity

Realising that a common set of measures for clinical trials would be to great advantage when comparing results between trials, ACR/OMERACT proposed a core set of disease activity measures.⁵⁹ About the same time, Dutch rheumatologists were developing a composite index of disease activity, the Disease Activity Score (DAS).⁶⁰ ⁶¹ Composite indices have the advantage of being able to detect clinically important effects where individual measures fail, provided they are computed from at least 2 relevant clinical outcome measures that have low correlation with each other.^{62 63} The DAS is based on the Ritchie articular index, the 44 tender joint count, the erythrocyte sedimentation rate (ESR) and the patient's global health (PGH). DAS28, which is

derived from the DAS, uses 28 joint counts, those being the joints of the hands, wrists, elbows, shoulders and knees.⁶⁴

A DAS28 which uses high sensitive C-reactive protein (CRP) instead of the ESR has been developed in recent years⁶⁵ and validated retrospectively using data from two randomized controlled trials (RCT). Patients in these two trials had active, persistent disease were treated with abatacept or placebo.⁶⁶ In both RCTs patients had a disease duration of at least 1 year and insufficient response to treatment with methotrexate⁶⁷ or anti-TNF α .⁶⁸

DAS-CRP may be preferable to DAS28 which uses the ESR since CRP correlates more closely with disease activity than the ESR,^{69 70} is a predictor of functional outcome⁷¹ and joint damage,⁷²⁻⁷⁴ and is an important predictor of subsequent death from cardiovascular disease.^{75 76} A substantial proportion of variability in the ESR is explained by the effects other than the acute phase response, e.g., age, sex, serum immunoglobulins, rheumatoid factor (RF), and haemoglobin.⁷⁷ DAS28-CRP may also be preferable for practical reasons as CRP is the standard measure of inflammation in many clinics and results can be obtained more quickly than for the ESR. The way in which these two disease activity scores are derived is shown in Table 2.

Table 2. Indices are calculated using weighted tender and swollen joint counts, acute phase reactants and the patient’s assessment of general health.

Index	Formula
DAS28	$0.56 * \sqrt{(TJC28)} + 0.28 * \sqrt{(SJC28)} + 0.70 * \ln(ESR) + 0.014 * GH$
DAS28-CRP	$0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.36*\ln(CRP+1) + 0.014*GH + 0.96$

TJC: tender joint count of 28 joints; SJC: swollen joint counts of 28 joints; ln: the natural log; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GH: general health as assessed by the patient.

Several simpler composite measures of disease activity, such as the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI) have been developed and tested in clinical settings.^{65 78-82}

1.4.2 Response Criteria and Disease Activity States

For clinical and trial purposes it is interesting to know if disease activity in individual patients has improved in response to prescribed treatments. Response criteria based on both the ACR core set of outcomes,⁸³ the DAS28⁸⁴ and the less widely accepted SDAI and CDAI⁸⁵ have been developed. The definition of improvement using the ACR core set requires a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining core set measures, i.e., patient and physician global assessments, pain, disability, and an acute-phase reactant.⁸³ The DAS28-based European League Against Rheumatism (EULAR) response criteria classify individual patients as non-, moderate, or good responders, dependent on the extent of change and the level of disease activity reached.⁸⁴ Cut-offs for disease activity states based on DAS28 are shown in Table 3.

Table 3.

Activity state	DAS28
Remission	<2.6
Low activity	2.6-<3.2
Moderate activity	3.2-5.1
High activity	>5.1

1.5 APPROACHES TO MEASURING QUALITY IN RHEUMATOLOGY

The science behind quality measurement in arthritis care and management is still in the early phases⁸⁶ and American College of Rheumatologists (ACR) has begun to develop quality measures for rheumatic diseases in recent years.⁸⁷ ACR has endorsed a starter set of three quality measures for RA⁸⁸ which can be summarised as follows:

- ACR core set criteria should be documented within 3 months of diagnosis and at least annually thereafter;
- DMARD should be prescribed unless contraindicated, or the disease is inactive or there is documentation of patient refusal;
- treatment should be intensified in the case of ongoing active disease or upon evidence of progressive bony erosion over six months.

The European League Against Rheumatism has included “quality of care” in its mission statement and although it is not directly involved in the evaluation of the quality of care, it supports initiatives by others in this area.⁸⁹

The Swedish Society for Rheumatology (SSR) has had a more pragmatic approach to the question of quality measurement. Although no formal agenda or mission statement has been issued, SSR has been integral in the development of Swedish Rheumatology Quality Register (SRQ), which can be described as a tool to capture data which rheumatologists believe to represent meaningful measures of outcomes and processes in rheumatological care.

1.6 THE SWEDISH RHEUMATOLOGY QUALITY REGISTER

The SQR, formerly known as the Swedish RA Register, was established in 1995 and is run by SSR. A register can be defined as a continuously updated file of individuals with symptoms, health status, diseases or of events in a defined population.⁹⁰ The idea of a register addressing the quality of clinical management in RA on a national level evolved during the 1993 annual conference for Swedish physicians. It was inspired by the Better Anti-Rheumatic Pharmacotherapy (BARFOT) study group, which had six participating centres at that time. The SRQ is the result of the combined efforts and enthusiasm a number of Swedish rheumatologists backed by the SSR.

Broadly speaking, the aim of the Register is to support participating clinics in their efforts to continually improve treatment results for arthritis patients. The Register was partially funded by the National Board of Health and Welfare and later, by the Swedish

Association of Local Authorities and Regions contingent upon the provision of annual reports for early RA and biological DMARD treatment.

In 1995, the Register had five participating centres providing a total of 208 patients. The numbers increased to 460 patients from 14 centres by the end of 1996, after including some of the patients from BARFOT. As of September 2008, the Register has over 19,800 patients with RA and about 5,000 patients with other forms of arthritis such as ankylosing spondylitis, spondarthritis or psoriatic arthritis. The name of the Swedish RA Register changed to the Swedish Rheumatology Quality (SRQ) Register in January 2008 to better reflect its content.

SRQ is best described as an umbrella register and regional registers in rheumatology, such as the Stockholm’s Biologics Register (STURE), use the SRQ to compile and store data. Each centre owns its data and a national SRQ committee administers and oversees the development of the Register.

1.6.1 Content and Structure

SRQ collects clinically relevant data from patients with chronic arthritis who are over 16 years of age, and who have agreed to be included in the Register. At inclusion, each patient is assigned a code to allow data abstraction without revealing the patient’s identity. In addition to the ACR classification criteria for RA (section 1.1), a set of disease activity measures adapted from the ACR core set criteria are collected for patients with RA.⁵⁹ The adapted criteria differ in that joint counts are based on 28 tender and swollen joints not 66/68 joint counts. These measures are summarised in Table 4.

Table 4. Adapted core set criteria for RA in the SRQ and method of assessment.

Disease activity measure	Method of assessment
Tender joint count *	Tender-not tender dichotomy for 28 joints
Swollen joint count *	Swollen-not swollen dichotomy for 28 joints
Patient’s assessment of pain	Visual analogue scale 100mm
Patient’s global assessment of disease activity	Visual analogue scale 100mm
Global assessment of disease activity *	5 point scale: none, low, moderate, high and maximal
Patient’s assessment of physical function	Validated Swedish version of the modified Health Assessment Questionnaire (HAQ) ⁹¹
Acute phase reactant	Westergren erythrocyte sedimentation rate <i>and</i> C-reactive protein
Disease activity index	Disease Activity Score based on 28 joints (DAS28) ⁶⁴

* rheumatologist’s evaluation

The following information is collected once at baseline: name; age; sex; date of symptom onset; diagnosis according to the 10th edition of the International Classification of Diseases; serum rheumatoid factor (RF) status; the name of the

clinic attended; the attending physician; and date of inclusion. Disease classification criteria are collected at baseline for incident RA.

Core set data as described in Table 2 and anti-rheumatic drug therapy decided upon by the rheumatologist are collected at each consultation. Traditional DMARDs, biological DMARDs and corticosteroids are recorded with name, dosage and dosing interval. NSAID are recorded as either yes or no. DAS28 is calculated automatically in the database. Radiographs of the hands and feet are recorded at baseline and thereafter at the discretion of the rheumatologist. Of note is that for incident RA in the SRQ, it is possible to evaluate if the ACR starter criteria have been fulfilled.

1.6.2 Data Collection

Before mid 2003, data were collected in a standardised fashion on paper forms by medical or nursing staff and transcribed into the participating out-patient clinics' local databases. Copies of the local databases were sent to the Swedish RA Register at regular intervals where they were integrated with the main database. Since 2003, the Register is accessed online so that no software is required to use it. The SRQ is not a part of the electronic medical record, however, in some hospitals the patient's SRQ summary page can be opened via an external function in the patient's medical record. ACR classification criteria, core set measures, DAS28 and information about current therapies can also be sent between the Register and specially structured medical records using an import/export function. Linkage to another database for the reporting of adverse events related to the use of biological DMARDs is another feature of the SRQ⁹². Registration is now completely web-based although data collection still occurs in some cases on paper.

1.6.3 Coverage

The SRQ aims to capture all patients in need of specialist care for their RA. Nearly all patients in Sweden who consult their general practitioner because of synovitis are referred to a rheumatologist. If these patients are diagnosed with a rheumatic disease requiring specialist care, they will continue to have contact with a rheumatologist. How frequently the patient is followed up will depend on the severity of the disease. Therefore, the data in the Register are likely to represent those with the most severe disease and most in need of monitoring.

Currently, all public and private rheumatology out-patient clinics participate in SRQ. Participation can vary, however, depending upon organisational factors such as mergers between hospitals and availability of rheumatologists.

Using population statistics and data from Dalarna County, the proportion of the estimated RA population that is captured by the Register can be approximated. The Swedish adult population at the end of 2007 was 7,383,271.⁹³ Patients of 16 years or younger are treated in paediatric care. All patients with RA in Dalarna are followed in the same clinic and included in SRQ. Currently (30 Sept 2008), Dalarna has 1240 RA patients (873 women, 367 men) and at 30 December 2007, a population of 275,618, giving a prevalence rate of approximately 0.45%. This is similar to prevalence rates (0.44%) in Oslo⁴⁰. In 1999, Simonsson et al estimated the prevalence of RA in Sweden to 0.51%³⁹. The proportion of women to men with RA in Dalarna is approximately 2.38:1. If the prevalence rate and sex distribution in Dalarna is

representative for the entire country, and all such patients are captured in SRQ, then there should be approximately 33,217 RA patients requiring specialist care. With 19,848 RA patients in the register to date, an estimated 59.8% are now covered by SRQ. The number of patient with RA in the SRQ up until 30 September 2008 and the ratio between women and men is shown in Table 5.

Table 5.

	Women	(%)	Men	(%)	Total	Ratio ♀: ♂
RA +	9830	(68.59)	3721	(67.45)	13551	2.64:1
RA-	3101	(21.64)	1331	(24.12)	4432	2.33:1
RA UNS*	1400	(9.77)	465	(8.43)	1865	3.01:1
Total	14331	(100.00)	5517	(100.00)	19848	2.60:1

+ Rheumatoid factor (RF) positive disease; -RF negative disease, * RF not specified

2 AIMS

The general aim of this thesis was to increase our knowledge about aspects regarding the clinical management of RA which are determined by the rheumatologist. Data from the Swedish Rheumatology Quality Register were used to characterise factors influencing prescription in incident RA and to explore the relationship between clinical rheumatologists' assessments of disease activity with the main outcome and process measure in the Register, DAS28.

The specified aims of the project were:

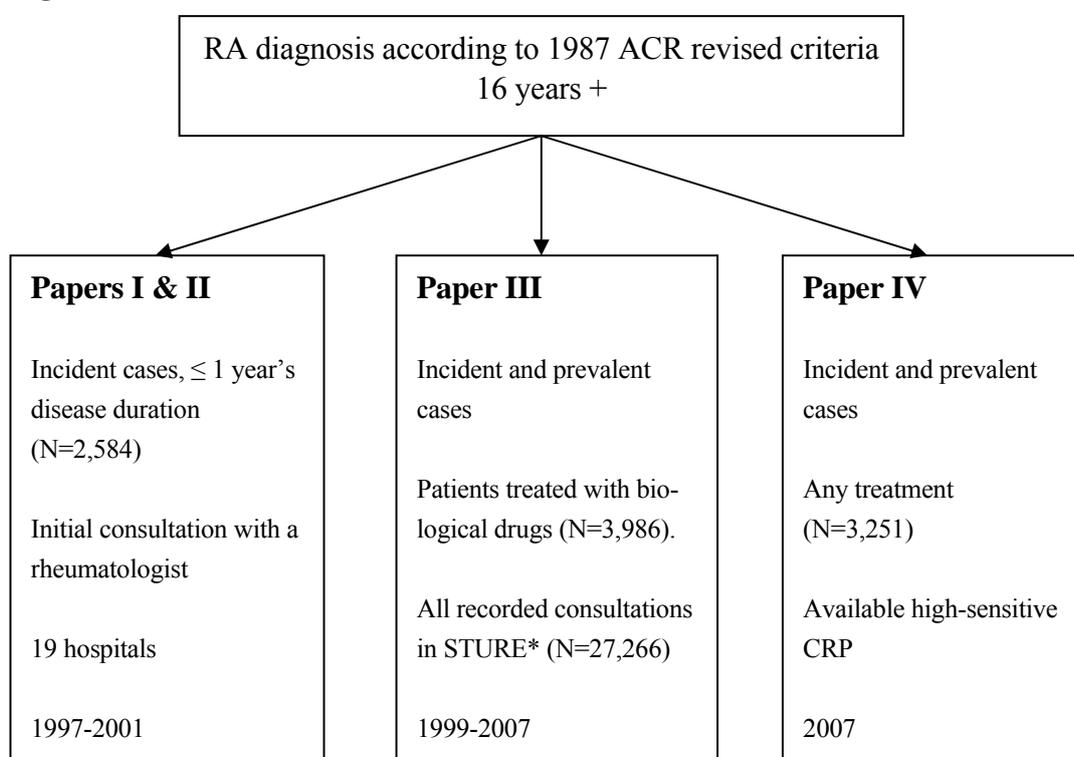
- To analyse factors associated with the prescription of anti-rheumatic pharmacotherapy at the initial consultation in early RA, 1997-2001.
- To identify time trends in the prescription of DMARDs for patients with early RA.
- To analyze the correlates, in terms of DAS28 and core variables, of the state of remission defined by Swedish rheumatologists as “disease activity: none”.
- To estimate cut-off levels for the disease activity score using C-reactive protein (DAS28-CRP) based on clinical rheumatologist's global assessment of disease activity.

3 MATERIALS AND METHODS

This thesis is based on observational data collected prospectively during consultations between patients and their rheumatologists in out-patient settings. The samples used in all four studies were taken from data in the SRQ Register, collected between 1997 and 2007. All studies were approved by the Karolinska Institutet/Karolinska University Hospital’s local ethics committee. Patients give informed consent for using the data (without disclosing patient identity) for studies when they agree to be included in the register. In the following section the main features of the methods used in the studies are described

Figure 1 provides a schematic summary of the general criteria used in all four studies plus the specific selection criteria for each study.

Figure 1.



*The Stockholm’s regional part of SRQ Register monitoring biologics

3.1 PAPER I

Temporal trends in the prescription of conventional anti-rheumatic pharmacotherapy for patients diagnosed with RA within one year of symptom debut were analysed in Paper I. Only those hospitals that had exported data to the Register for each and every year, from 1997-2001, were selected. This provided data on patient demographics, disease characteristics, calendar year of initial consultation, core set measures and prescribed treatments for 2,584 consultations from 19 hospitals. The initial consultation in this study includes tests ordered and treatments prescribed in connection with a RA diagnosis being made. Hospitals were grouped into university (n=8), county (n=6) or district hospitals (n=5) according to the affiliations they had in

the beginning of the study. Centres affiliated with a university were classed as university hospitals. Hospitals which were not affiliated with a university but were the central hospital for a whole county or region were classed as county hospitals.

Patients' age groups, RF status, disability (HAQ), and disease duration were compared by sex and year using cross-tabulation, while mean values for the DAS28 were compared by sex and year using analysis of variance.

A descriptive univariate analysis comparing those who did and did not receive DMARD therapy at the first consultation was conducted using logistic regression, with the receipt of DMARD as the dependent variable. DAS28 and duration of symptoms prior to diagnosis were modelled as continuous variables, while all the others were modelled as series of binary dummy variables. Simultaneous adjustment was made for all of these variables and for DAS28. DAS28 was modelled as a continuous measure, such that the odds ratio (OR) refers to the change in the probability of DMARD prescription for each one-unit increase in DAS28. Patients with at least one missing variable were excluded from this part of the analysis.

Univariate analysis was used to evaluate the potential confounding effect of the missing data. The unadjusted and adjusted ORs were calculated with the 95% confidence interval (CI).

The material was stratified by hospital type and analysed as above. Logistic regression was used to investigate the interaction of hospital type and DAS28 for the prescription of DMARDs with adjustment being made for all confounding factors and for the main effects. Prescription patterns for glucocorticosteroids (GC) were also examined.

3.2 PAPER II

Data on DMARD prescriptions (n=2559) from the first study were modelled as a binary variable (prescription and no prescription). Data were divided into groups according to the month and calendar year of the initial consultation, giving 60 groups of unequal size. The proportion of patients each month to receive a DMARD prescription was charted over 60 months, i.e., for the period 1997-2001. Statistical process control (SPC) was used to analyse and chart the data. In the second part of the analysis, the results of SPC were then confirmed using regression modelling. A dummy variable (time period) was created, splitting the data into two time periods (Jan 1997 – June 1998, and July 1998 – Dec 2001). The first model included only *the month and year of initial consultation* as the explanatory variable and the percentage of patients receiving a DMARD prescription as the dependent variable. A second model included *time period* as the only explanatory variable and a third model included both *the month and year of initial consultation* and *time period* as explanatory variables.

Statistical Process Control and p-charts

Central to the theory upon which the application of SPC is based is the assumption that variation is an inevitable part of all complex processes, and that variation can be attributed to either common-causes (normal) or special-causes. The prescription of DMARD at the initial consultation is one such complex process. Normal variation is

the result of small, random changes that are the cumulative effect of many small causes inherent to a process.⁹⁴ For example, factors such as age and sex, disease severity and patient preference will “cause” the rheumatologist to make a decision one way or the other about the prescription of DMARD for any particular patient. Special-cause variation arises from causes that are not an inherent part of an ongoing process, a practical example being the discovery of a new, more effective class of drug for RA.

The main tool used in SPC to determine the degree to which a process is subjected to normal or special-cause variation is the control chart. One kind of control chart, the *p*-chart, is used here to examine variation in the prescription of DMARD. Data regarding the prescription of DMARD (yes and no) are grouped according to month and year of the initial consultation and the percentages of patients prescribed a DMARD (yes) are calculated for each month. The percentages are then plotted on the *p*-chart against the *x*-axis (%) and *y*-axis (time). The mean of the percentages of the first 20 months are calculated together with upper and lower control limits. The control limits are usually defined by the 6-sigma (σ) rule (the central line $\pm 3\sigma$).^{94 95}

The fundamental criterion for evidence of a lack of statistical control is that 1 or more points fall outside the $\pm 3\sigma$ limits. If a process is in control nearly all observations will fall between these limits. Other changes during the period are identified using the additional tests for special causes (ref) including:⁹⁵

- 8 or more consecutive points on the same side of the central line
- 7 or more consecutive points ascending or descending
- 2 out of 3 consecutive points outside the 2σ limit on the same side of the central line
- 4 out of 5 consecutive points outside the 1σ limit on the same side of the central line

3.3 PAPER III

Data from all consultations with RA patients in the Stockholm region, who had at some stage received treatment with biological drugs during the years, 1999-2007, were selected for the study. The rheumatologist’s global assessment (PhGA) of disease activity is measured on a five point scale with the lowest being “ingen” in Swedish, which has been interpreted as “none”, or “no disease activity.” The PhGA in clinical trials is often measured using a visual analog scale. Therefore, rheumatologists in the out-patient clinic of the Karolinska University Hospital, Solna were asked in early 2008 to rate disease activity on a 100 mm visual analogue scale as well on the five point scale.

Data on the core set variables for each of the disease activity states determined by the rheumatologist were compared by analysis of variance (ANOVA) followed by Bonferroni-Dunn post-hoc analysis. The latter analysis, which can only be applied if the original ANOVA comparing all groups yields a statistically significant difference, requires a threshold for statistical significance for each of the possible comparisons that is lowered commensurately with the number of comparisons made. As the number of comparisons for each of the core set variables was ten (4+3+2+1), the *p*-value required to be considered statistically significant was 0.005 for these post-hoc comparisons.

Receiver operating characteristic (ROC) curves were created in both Papers III and IV to determine whether the current definitions of disease activity states are over-inclusive or under-inclusive. Benchmarking the DAS28-values of patients against the physician defined “disease activity: none”, a ROC was used to find the best trade-offs between true positive and false positive remissions.

3.4 PAPER IV

Data from SRQ for all RA patients in Sweden and who had had a consultation during 2007 were selected for the study. In the case of patients attending several consultations during the year, only the first was used in the analysis. DAS28 and DAS28-CRP are benchmarked against the rheumatologist’s global assessment of disease activity (PhGA), which is recorded on a 5-point scale using the terms: none, low, moderate, high and maximal. Patient characteristics, apart from sex and RF serology, were described using means (standard deviations) as well as median values (25th and 75th percentiles). Correlations between the DAS28-CRP and the DAS28 were analysed using Pearson’s correlation statistics.

Regression modelling was used to analyse whether ESR and hs-CRP are influenced by patients’ age, sex, disease duration, or RF, factors which are not directly related to disease activity. ESR and hs-CRP values were log-transformed for calculations. Only variables reaching the 0.5-level (sic) of significance in the linear regression model were included in the step-wise regression.

PhGA with “maximal” disease activity (n=20) were pooled together with the PhGA of “high” disease activity. Spearman’s rank correlation was used to evaluate the relationship between PhGA and the variables in the DAS28. The similarity in the distribution of PhGA and the distribution of disease activity levels according to EULAR for both DAS28 and DAS28-CRP were analysed using Bowker’s test of symmetry.⁹⁶ In contingency tables, Bowker's provides a chi-square test to determine if the marginal distributions are the same across the four levels of disease activity. Kappa statistics were used to evaluate the level of agreement between the PhGA and the EULAR definitions of disease activity. Finally, ROC curves were used to determine new disease activity thresholds for DAS28-CRP based on the PhGA.

4 RESULTS

4.1 TEMPORAL TRENDS IN PRESCRIPTION (PAPER I-II)

The main factors driving DMARD prescription were calendar year of inclusion, with some variation by hospital type, and disease activity as measured by DAS28. Comparing all other age groups with the age group 46-55, only patients over 65 years of age were less likely to receive a DMARD prescription (Table 6). Neither sex, disease duration nor RF serology influenced DMARD prescription.

Table 6. Factors influencing DMARD prescription at the initial consultation together with the unadjusted and adjusted odd ratios. Patients without a DMARD at the initial consultation but prescribed methotrexate at follow-up are included in the analysis. Results are adjusted for age, sex, disease duration, RF, hospital type, year of inclusion and DAS28.

	N (%) with DMARD	N (%) without DMARD	unadjusted OR(95% CI)	Sig (p)	adjusted (95% CI)	OR	Sig (p)
Type of hospital							
University	1038 (53.0)	168 (45.5)	1.00		1.00		
County	512 (26.1)	82 (22.2)	1.22 (0.94, 1.60)	0.141	1.05 (0.78, 1.41)		0.751
District	408 (20.8)	119 (32.2)	0.64 (0.50, 0.82)	0.000	0.53 (0.40, 0.69)		0.000
DAS28 at inclusion							
<i>Linear trend</i>	1958 (100.0)	369 (100.0)	1.28 (1.18, 1.40)	0.000	1.33 (1.21, 1.46)		0.000
Age group							
16-25	64 (3.3)	15 (4.1)	0.76 (0.42, 1.35)	0.345	0.70 (0.37, 1.32)		0.273
26-35	141 (7.2)	29 (7.9)	0.82 (0.53, 1.27)	0.378	0.76 (0.47, 1.25)		0.281
36-45	208 (10.6)	29 (7.9)	1.12 (0.73, 1.71)	0.606	1.13 (0.70, 1.82)		0.616
46-55	425 (21.7)	67 (18.2)	1.00		1.00		
56-65	466 (23.8)	76 (20.6)	1.08 (0.78, 1.51)	0.636	0.88 (0.61, 1.26)		0.472
66-75	429 (21.9)	98 (26.6)	0.78 (0.57, 1.06)	0.112	0.59 (0.42, 0.84)		0.004
76-85	220 (11.2)	51 (13.8)	0.71 (0.49, 1.02)	0.065	0.61 (0.43, 0.93)		0.021
86-95	5 (0.3)	4 (1.1)	0.11 (0.03, 0.46)	0.003	0.10 (0.02, 0.45)		0.003
Year of inclusion							
1997	359 (18.3)	119 (32.2)	1.00		1.00		
1998	422 (21.6)	92 (24.9)	1.49 (1.12, 1.99)	0.006	1.60 (1.17, 2.20)		0.003
1999	393 (20.1)	49 (13.3)	2.46 (1.77, 3.43)	0.000	2.76 (1.91, 3.99)		0.000
2000	394 (20.1)	54 (14.6)	2.41 (1.74, 3.35)	0.000	2.58 (1.80, 3.70)		0.000
2001	390 (19.9)	55 (14.9)	2.60 (1.86, 3.63)	0.000	2.36 (1.65, 3.38)		0.000
Total	1958 (100.0)	369 (100.0)					

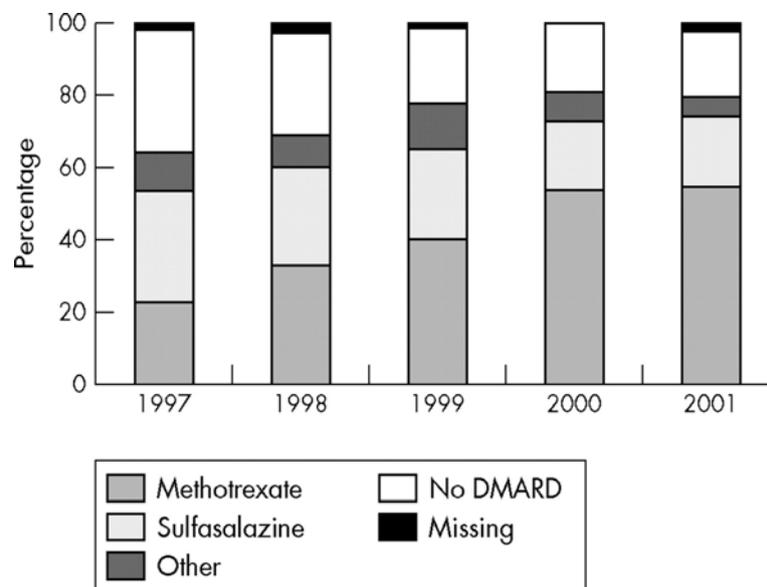
4.1.1 Disease Activity

Disease activity was associated with DMARD prescription such that for every one unit increase in the DAS28, there was a 33% greater likelihood of the patient being prescribed a DMARD.

4.1.2 Year of Inclusion

Although patient characteristics such as disease activity and demographics at the initial consultation remained stable for each of the five years, there was an overall increase in DMARD prescription from 1997 to 2001 with an adjusted odds ratio (adj. OR) of 0.43 (95% confidence interval (CI) 0.34-0.54), $p < 0.001$ (Figure 2). Methotrexate accounted for most of the increase at the expense of sulphasalazine and anti-malarial drugs. About 40% of patients received cortisone at their first consultation and most often in combination with DMARD. Average doses were low, 7,5-10mg, with no change in over the years.

Figure 2. Change in the proportion of the types of drugs prescribed over the years



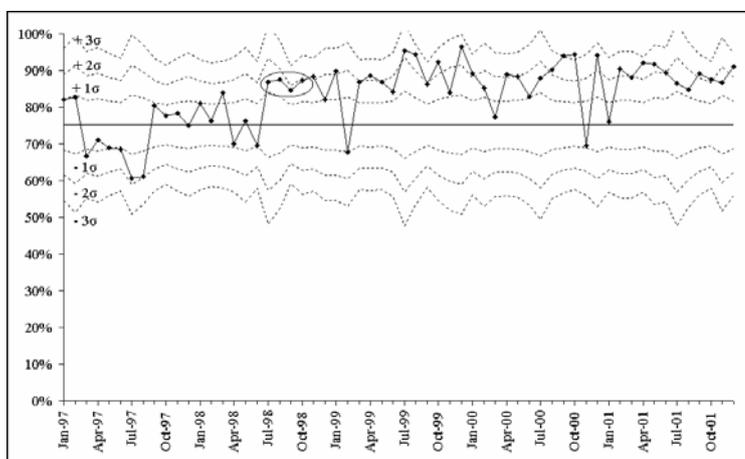
4.1.3 Hospital Type

When patients were stratified by hospital type, those attending district hospitals were less likely to be prescribed DMARDs than those in university hospitals (adj. OR = 0.53 (0.40 to 0.69), $p < 0.001$). However, when DMARDs were prescribed in district hospitals, the decision to do so seemed more likely to be driven by disease activity (OR = 1.65 (1.34 to 2.02), $p < 0.001$) than in university hospitals (OR = 1.23 (1.07 to 1.41), $p = 0.003$) or county hospitals (OR = 1.34 (1.01 to 1.63), $p = 0.003$). Interaction testing indicated that this difference was significant ($p = 0.007$), however, by the end of the study period the difference had all but disappeared.

4.2 TIME AS A DETERMINANT OF DMARD PRESCRIPTION (PAPER II)

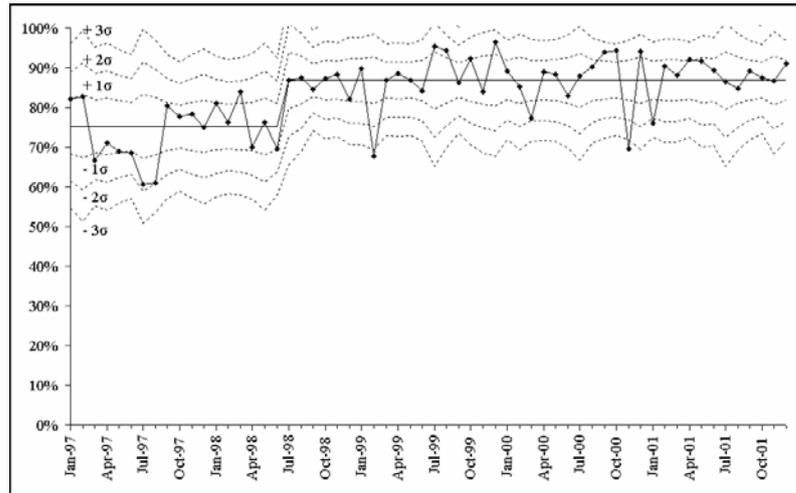
The influence of year in Paper I was examined more closely using time series analyses. Using Statistical Process Control (SPC) methodology, the process of DMARD prescription could be described as stable (i.e., showing only random variation) over the first 20 months, i.e., January 1997 - August 1998, as no point exceeded the $\pm 3\sigma$ limits and other tests of change were negative. The period from July until October 1998, (encircled in Figure 3) depicts how the increase in the proportion of prescribed DMARDs transitioned from random variation (July until September) to a sustained change in the process when even November was considered, according to the rules of SPC (see section 5.3.2).

Figure 3. P-chart with the average of the first 20 months extrapolated over the entire period together with upper and lower control limits. The encircled cluster defines a change in the process.



Regression analysis confirmed an increasing trend in DMARD prescription over the period as a whole, which was statistically significant ($p \leq 0.0001$). When data were instead modelled as two time periods, i.e., January 1997 – June 1998 and July 1998 – Dec 2001, a statistically significantly greater proportion of patients received a DMARD prescription in the later period compared with the earlier, $p < 0.0001$. When both variables, *the month and year of initial consultation* and *time period*, were included in the model, only the variable time period was statistically significant, $p = 0.0095$. The trends within the two time periods were not statistically significant, $p = 0.5934$, $p = 0.7497$ respectively (Figure 4).

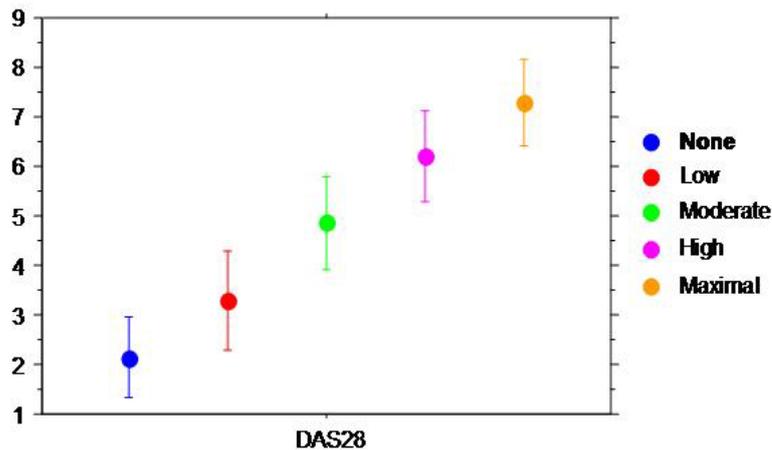
Figure 4. P-chart with recalculated averages and control limits.



4.3 REMISSION CRITERIA (STUDY III)

Disease activity “none” was indicated by the physician in 5,014 of a total of 27,266 consultations with 1,081 of 3,986 patients. Means and standard deviations for swollen and tender joint counts were 0.31 ± 0.85 and 0.53 ± 1.91 , respectively, and for DAS28, 2.14 ± 0.81 . The relationship between DAS28 and disease activity states as defined by the rheumatologist is shown in Figure 5.

Figure 5. DAS28 values with means and standard deviations plotted against the physician’s global assessment of disease activity.



Patients, whose disease activity was described as “none” on at least one occasion, were significantly different in terms of sex distribution to those patients with disease activity and showed a small but statistically significant difference in age. A somewhat higher proportion of patients with no disease activity according to the physician were RF-negative. The erythrocyte sedimentation rate and C-reactive protein, clustered relatively tightly around the means while greater variance was seen for patient-derived variables. The ROC curve identified a DAS28 cut-off at 2.8 as optimal for this disease state.

4.4 DAS28-CRP (STUDY IV)

Data from 9,648 patients, of which 3,251 had hs-CRP values, were used in the analysis. There were no clinically significant differences between the hs-CRP and non-hs-CRP groups.

Both ESR and CRP were influenced by age, sex and the presence of rheumatoid factor (Table 7). ESR was further influenced by disease duration and the interaction of duration with sex.

Table 7. P-values for non-inflammatory variables which influence the ESR and CRP. Only variables reaching the 0.5-level (sic) of significance in the linear regression model were included in the step-wise regression model.

	Sex	Age (yrs)	Duration (months)	RF	Duration*Sex
Log ESR	0.0025	<0.0001	0.0066	<0.0001	0.0280
Log CRP	0.0056	<0.0001	0.0832	0.0034	-

The correlation between DAS28 and DAS28-CRP was excellent, $r=0.96$. Agreement between PhGA and levels of disease activity according to EULAR was somewhat better when applied to DAS28-CRP, $K=0.39$ (95% CI 0.36-0.41) compared with DAS28, $K = 0.35$ (95% CI 0.33-0.38).

ROC curves, plotted using DAS28-CRP values and the PhGA, defined new cut-offs separating the four levels with the highest sensitivity and specificity. These were 2.41 (specificity 82.2%, sensitivity 83.1%), 3.69 (specificity 87.3%, sensitivity 87.5%), and 4.26 (specificity 94.4%, sensitivity 82.9%), respectively.

Comparing the new cut-offs for DAS28-CRP with the PhGA (Table 8), the agreement according to Bowker's test of symmetry improved further as did the kappa value, $K = 0.42$ (95% CI 0.40-0.44).

Table 8. Agreement (%) between PhGA and the new thresholds for DAS28-CRP for low, moderate and high disease activity based on 2,756 observations.

PhGA*	Remission	Low	Moderate	High	Total (%)
None	17.35	3.29	0.18	0.04	20.86
Low	14.04	23.19	5.44	2.54	45.21
Moderate	0.22	3.96	5.62	12.41	22.21
High	0.07	0.15	0.47	11.03	11.72
Total	31.68	30.59	11.72	26.02	100.00

*PhGA: physician's global assessment of disease activity

Applying adjusted cut-off limits for DAS28-CRP at 2.4, 3.7 and 4.25 respectively improved agreement, $K = 0.42$ (95% CI 0.40-0.44).

5 DISCUSSION

In the studies reported in this thesis, data derived from a national quality register for rheumatic diseases were used to investigate certain aspects of the clinical management of RA as determined by the rheumatologist. Rheumatologists prescribe the drugs to treat RA, therefore, factors associated with the decision to prescribe or not prescribe are of interest. This is especially so in the early stages of RA, when DMARDs can have the most effect⁴⁹. This may be the first study to use observational data to describe factors driving prescription over time for incident RA in usual care. Since it is presumed that the decision to prescribe anti-rheumatic pharmacotherapy is related to disease activity the associations between the rheumatologist's assessment of disease activity and currently used measures of disease activity were also studied.

Factors driving prescription trends at the initial consultation

In the present study, calendar year of RA diagnosis was one of the factors associated with the likelihood of DMARD prescription at first consultation with a rheumatologist. The increase from 1997-2001 described in Paper I is without doubt part of a longer secular trend. There was an overall increase by about 38% in the prescription of DMARD in Sweden between 1987 and 1997.⁹⁷ Similar increases in overall DMARD prescription, and particularly for methotrexate, have been reported elsewhere for the period prior to and during this study.^{10-12 14}

Nevertheless, when the influence of year was examined further using SPC, the method could rather accurately determine that the increase during 1997-2001 was driven by a single upward shift in 1998. The sudden increase suggests that some very specific factor or combination of factors had influenced rheumatologists' prescribing habits during that time. Interestingly, the first Swedish treatment recommendations were produced during 1998 by collaboration between the Swedish Society for Rheumatology (SSR) and the national Medical Products Agency (MPA). These were published in November 1998.⁹⁸ The promulgation of guidelines is clearly a possible reason for the change in prescribing habits of the rheumatologists partaking in this study. Importantly, the method used for this study was inherently a prospective one, and therefore, it may have detected changes in existing patterns earlier than comparable studies using traditional designs.

Only two studies were found that specifically described trends in DMARD prescription for early RA.^{13 14} In the one study, increasing DMARD prescription was reported from 1997-2000, based on the responses to questionnaires by 44 physicians working in rheumatology.¹⁴ In one very large study from the United Kingdom, there was no increase in DMARD prescription from 1987-2002 with about 52-62% of patients with a new diagnosis (<24 months duration) receiving a DMARD as their first prescription. The database included all contacts with general practitioners in the UK. The proportion of patients prescribed methotrexate increased from about 10% in 1997 to 25% in 2001.¹³ In the present study, methotrexate increased from 22-54% during the same period. The differences can perhaps be explained by differences in the proportion of patients treated by primary care physicians as opposed to rheumatologists in the UK and Sweden.¹¹

Rheumatoid factor is a predictor of disease severity,^{99 100} however, it did not seem to influence the decision to prescribe DMARD in this study. The influence of hospital type may reflect the spread of treatment modalities, or institutional differences in practice. Older patients were less likely to receive DMARD than younger which has also been observed in other studies.^{10 15}

The DAS28 was significantly associated with the prescription in all hospital types, and as such the study supports the use of DAS28 in clinical (non-trial) care where large differences in effect size can be expected, such as when beginning treatment for patients with active disease. This is the area for which the DAS28 and other such indices were developed.

Redefining disease activity states for routine care

In studies III and IV, the associations between the rheumatologist's global assessment of disease activity and the DAS28-defined disease states were examined. DAS28 in our unselected (Paper IV) population has low to moderate correlation with the rheumatologist's global assessment of disease activity. The DAS28 has some shortcomings as a measure for disease activity in clinical practice partly due to the omission of the lower extremities and partly due to the way in which the different parts of the DAS28 are weighted in the DAS28 algorithm.¹⁰¹⁻¹⁰³ DAS28-CRP correlated well with the DAS28. However, when both indices were benchmarked against the PhGA, DAS28-CRP correlated better with the PhGA. Both DAS28 and DAS28-CRP, however, tended to overestimate disease activity.

The cut-off between remission and low disease activity in RA as defined by DAS28-based cut-off levels, is a distinction with some clinical importance because of the increasing perception that remission is both desirable as a treatment goal and achievable for many patients thanks to modern anti-rheumatic therapies.¹⁰⁴ There are several definitions of remission for RA¹⁰⁵⁻¹⁰⁷ and remission rates can vary in usual care depending on the definition of remission used.¹⁰⁸ Whether rheumatologists' understanding of remission and "disease activity: none" are one and the same in RA has not been studied previously. For the purpose of these studies, however, the PhGA is used as the benchmark against which other definitions of remission are measured. Remission was assessed in both study III and study IV and the results may at first appear inconsistent since on the one hand the DAS28 overestimates disease activity (Paper III) and on the other that the DAS28 definition of remission underestimates disease activity (Paper IV). Therefore, it is important to regard in detail the methods by which these cut-offs were determined and how they perform in analyzing groups of patients as well as their practical implications.

In study III, the physicians' global assessment, as determined on a five-point scale, was taken to be the gold standard for determination of remission ("disease activity: none"), and using this measure, the sensitivity and specificity were determined for various DAS28 cut-offs. In this manner, it was determined that the EULAR-definition of remission at a level of DAS28=2.6 performed with the following characteristics: sensitivity 75.3%, specificity 85.9%. The ROC curve illustrates how these two parameters are influenced by the cut-off level. It can easily be seen that a greater sensitivity can be achieved at the cost of a lessened specificity and vice versa.

Next, it can be asked what the optimal characteristics are for an outcome such as this, and to this question there is no unequivocal answer. It could be argued that the

average of sensitivity and specificity should be as high as possible, and this is the case when they are as similar as possible; for the study here that level is around 2.85, which was an interesting conclusion as the OMERACT group had previously recommended the use of exactly this cut-off as the level of "minimal disease activity", a terminology obviously chosen to avoid confrontation with those who had proposed definitions of remission.

It is also possible to conceptualize this result by saying that, if in a population of patients $N\%$ are identified as being in remission by the DAS28 cut-off, then the true number of patients in remission is also $N\%$, because equally many are misclassified in the one direction as in the other. This use of this cut-off for analyses of register and trial populations is therefore supported by these results. However, it is important to understand the metrological properties if a DAS28 cut-off of 2.8 is, indeed, chosen. Here, the concepts of "positive predictive value (PPV)" and "negative predictive value (NPV)" are important. The former answers the question: if the chosen definition identifies a patient as being "in remission", then what is the likelihood that this is indeed the case in truth? - and vice versa for the NPV. In contrast to the sensitivity and specificity, these important concepts depend on the a priori likelihood that this is the case, or to put it differently, on the prevalence of the phenotype in the population under study. In the example of study III, the true prevalence of remission "disease activity: none" was around 20%, so for a randomly chosen patient the likelihood of being in remission was one in five. Because of this, the PPV for the DAS28 cut-off at 2.8 for this particular population is around 55% and this demonstrates that applying this cut-off to the individual patient will not be particularly useful (in contrast, the NPV will have a rather high value ($>90\%$) because the a priori likelihood of being not-in-remission was around 80%).

These reflections demonstrate that the optimal cut-off level chosen for the analysis of register- or trial populations may be very different for the optimal determination of a characteristic at the individual patient level, and the more so if the distribution of the characteristic under study in the population is more lopsided. In study IV, the DAS28 (and DAS28CRP) cut-off for remission was analyzed by use of the Bowker's statistic. This statistic lead to a lower level than that proposed by EULAR (2.6) and also lower than the optimal level as defined in study III. The explanation is simple: the Bowker's statistic determines the cut-off that provides the most correct identification at the individual patient level, and because remission is infrequent in the population, a lower cut-off is needed to achieve a "balanced" misclassification (equal likelihood of assigning "remission" to a patient who isn't in remission vs. likelihood of assigning "non-remission" to a patient who is, or in other words, equal PPV and NPV).

One may ask the question which cut-off level is the "right" one, but the above reflections make it clear that this question cannot be answered other than by first defining in what setting the cut-off is proposed to be used. For analyses of groups of patients the cut-off proposed in study III may be the best one, whereas at the individual patient level (and assuming the prevalence of true remission is around 20%), the lower cut-off may be more appropriate.

Methodological considerations

The randomised control trial (RCT) is considered the gold standard when evaluating treatment effects in the short term, since they most effectively control confounding

factors. However, RCT are less suited to evaluating the long-term, multi-dimensional outcomes in chronic disease for a number of reasons.^{109 110} Inclusion criteria for most clinical trials are so strict as to exclude many RA patients seen in routine clinical care, and thus raising concerns about the external validity of the results.¹⁰⁹⁻¹¹²

Studies based entirely on register data are not without limitations however. It is difficult to evaluate the validity of a nation-wide register with many participants and a limited budget, an experience this register shares with others such as the Dutch Standard Diagnosis Register of Rheumatic Diseases.¹¹³ The data used for Papers I and II were based on 19 hospital that sent data to the register during all five years. For the STURE Register (Paper III) it has been estimated that about 90% of all RA patients treated with biological DMARDs have been captured in the Stockholm region since STURE's inception in 1999. In 2007, the SRQ included all private-practising rheumatologists and all hospital rheumatology clinics in Sweden, so we assume that the data used for Paper IV are sufficient to give a good indication of the average rheumatologist's assessments of disease activity. About 5% of core set data for RA in the SRQ were missing in 1997, and we assume that the attrition is random. We believe that the data in SRQ reflects the minds of Swedish rheumatologists quite well. As they were not aware that the data would be used as it has in these studies, the data is unlikely to be subject to bias by observation. The exception to this, of course, may be when the rheumatologists were asked to assess disease activity using both the 5-point scale and the VAS.

A number of clinical databases have been established in Europe during the last two decade. In particular, the National Database of the German Collaborative Arthritis Centres which was established 1993,¹¹⁴ has been successful in identifying deficits and trends in health care, and describing current treatment practices, practice variations and individual burden of diseases. It has also been used for quality assessment.¹¹⁵ Databases such as this one are an ideal source for the selection of random samples of patients for clinical studies.¹¹⁴ It has been proposed that the availability of an infrastructure of standard data in all RA databases would enhance clinical research in early RA.¹¹⁶ It is reasonable that such a structure could also enhance quality of routine clinical care and this is what SRQ provides for all Swedish rheumatologists.

6 CONCLUSIONS

The availability of large amounts of clinical data through a national quality register for RA has enabled the exploration of clinical population management as determined by the rheumatologist beyond the usual measurements of response to drug therapy over time. In particular, a broader understanding of the utility of DAS28 in routine clinical practice has been gained.

In the sub-population of patients with incident RA, the higher the patient's disease activity as measured by the DAS28, the more likely the rheumatologist was to prescribe a DMARD independent of disease and patient characteristics (except age) or temporal factors. This suggests that DAS28 in this particular clinical context has good concurrent validity. The increasing temporal trend in DMARD prescription indicates that rheumatologists in this study adopted an increasingly aggressive approach to the treatment of early RA from 1997-2001. The influence of hospital type on the prescription of DMARDs and the lesser likelihood that patients over 65 years would receive a DMARD may indicate that patients do not always receive care equitably. Further examination of the temporal trend for DMARD prescription using SPC enabled the trend to be depicted in more detail than otherwise when using traditional analytical methodology. Although we could only speculate that the increase in DMARD prescription may have been in response to the promulgation of treatment recommendations and related activities during 1998, the study clearly demonstrates the potential for SPC's usefulness where large amounts of data are prospectively collected, as is the case in SRQ.

Comparing the DAS28 and the physician's assessment of disease activity in patients treated with biological DMARDs, we could determine that "disease activity: none" most closely approximates the OMERACT definition of "minimal disease activity" at the group level. In an unselected clinical RA population, DAS28-CRP was found to be less biased by non-inflammatory confounders than the DAS28 using the ESR. While the DAS28 and DAS28-CRP both have a reasonable correspondence with the rheumatologists' global assessment, they both tend to give a somewhat higher estimate of disease activity. We were able to provide adjusted cut-offs for the DAS28-CRP-based disease activity states based on the rheumatologist's assessment of disease activity.

It is likely that DAS28 will remain useful for monitoring quality on a group level and to evaluate response to treatment in certain patients but it cannot replace the rheumatologist's global assessment to justify treatment decisions or limitations at the individual patient level. This approach of benchmarking standardised outcomes of RA against a large patient population, I believe will lead to better applicability of outcome measures in areas such as health care management, quality assurance, and most importantly, in the development of treatment strategies for clinical practice.

7 SAMMANFATTNING PÅ SVENSKA

Reumatoid artrit (RA) är en kronisk, autoimmun sjukdom med oförutsägbar utveckling och tilltagande funktionsnedsättning som vanligen kräver livslång uppföljning i sjukvården. Ett kvalitetsregister för RA etablerades 1995 med syfte att stödja både patienten och läkaren i deras gemensamma ansträngningar att optimera patientens framtida hälsa. Registrets data speglar en del av den vård som ges vid svenska reumatologiska mottagningar.

Syftet med denna avhandling är att öka kunskapen i delar av det kliniska handhavandet av RA som bestäms av läkaren. Data från Svenskt Reumatologiskt Kvalitetsregister används för att analysera faktorer som påverkar förskrivning vid tidig RA och för att studera förhållandet mellan reumatologens kliniska bedömning av sjukdomsaktivitet och standardiserade utfallsmått, speciellt DAS28.

I den första studien av tidig RA, var det år som patienten först träffade en reumatolog och fick diagnosen RA, och sjukdomsaktivitet mätt med DAS28 associerade med en ökad sannolikhet att få anti-reumatiskt läkemedel (DMARD) förskrivet. Indelningen av data efter sjukhustyp visade att sannolikheten att få DMARD förskrivet var större för patienter vid läns- eller universitetssjukhus än för patienter vid länsdelssjukhus. Dessa skillnader var nästan borta mot slutet av studieperioden, 1997-2001. Närmare analys med statistisk process kontroll (SPC) av den tidstrend som sågs i första studien kunde påvisa att trenden berodde på ett enskild ökning i förskrivning av DMARD juli 1998. I efterhand skulle detta kunna ses som en effekt av arbete med och publicering av svenska riktlinjer för behandling av RA under detta år.

I de två senare studierna, där uppföljningsbesök inkluderades, sågs en viss inkongruens mellan läkarens bedömning av sjukdomsaktivitet och EULAR definitioner av aktivitetsnivåer baserade på DAS28. Läkarens bedömning av ”ingen sjukdomsaktivitet” för patienter som behandlats med biologiska DMARD var närmare ”minimal sjukdomsaktivitet” än remissionskriterier föreslagna av Pinals eller EULAR. I ett tvärsnitt av RA-patienters uppföljningsbesök visade såväl DAS28 (som inkluderar sänka) som den DAS28-algoritm som byter ut sänka mot C-reactive protein (DAS28-CRP) en tendens att överskatta sjukdomsaktivitet jämfört med läkarens globala bedömning av sjukdomsaktiviteten. Nya brytpunkter för de olika sjukdomsaktivitetsnivåerna enligt DAS28-CRP föreslås.

Sammanfattningsvis, har det nationella kvalitetsregistret för RA gjort det möjligt att få en inblick i vilka faktorer som kan förklara vilka patienter som får DMARD under en period av förändring i svensk reumatologisk behandlingspraxis. Studierna har också genererat kunskap om användbarheten av de olika versionerna av DAS28 i den kliniska vardagen. Det är troligt att DAS28-CRP kan användas för att mäta sjukdomsaktivitet på gruppnivå men varken den eller DAS28 kan ersätta, men väl komplettera reumatologens globala bedömning av sjukdomsaktivitet vid behandling av individuella patienter.

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