HEIDI MÄKINEN

Disease Activity and Remission in Rheumatoid Arthritis

Comparison of Available Disease Activity Measures and Development of a Novel Disease Activity Index

The Mean Overall Index for Rheumatoid Arthritis (MOI-RA)

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio for public examination in Auditorium 2, Agora, Jyväskylä, on Saturday 18th October 2008, at 12 noon

Department of Internal Medicine
University of Kuopio
Disease Activity and Remission in Rheumatoid Arthritis. Comparison of Available Disease Activity Measures and Development of a Novel Disease Activity Index- the Mean Overall Index for Rheumatoid Arthritis (MOI-RA). Kuopio University Publications D. Medical Sciences 441.2008.129 p.
ISSN 1235-0303

ABSTRACT
Treatment of rheumatoid arthritis (RA) should be targeted at remission. The best strategy to achieve this goal is tight disease control and intensive monitoring of disease activity.

The purpose of the present study was to compare different definitions of remission in RA, to study sustainability of remission, and to evaluate DAS28 as an index in the assessment of remission and disease activity in RA. Furthermore, we set out to develop a new, simple disease activity index for RA: the Mean Overall Index of disease activity for RA (MOI-RA).

Two patient populations were analyzed: 1) the clinical cohort included all adult RA patients who were diagnosed at Jyväskylä Central Hospital in 1997 and 1998 (237 patients), and 2) the FIN-RACo trial patients (195 patients).

At five years, 17% of the clinical cohort patients met the ACR remission criteria, 37% met the clinical remission criteria (no tender or swollen joints and normal erythrocyte sedimentation rate [ESR]), and 55% met the criteria for radiographic remission (no worsening of erosions and no new erosions from baseline to five years). Only 12% of the patients met all three sets of remission criteria. In patients with DAS28 remission (DAS28<2.6), 23% had tender joints, 9% had swollen joints, and 6% had both tender and swollen joints.

In the FIN-RACo trial, 68% of the patients who received combination therapy with traditional DMARDs and 41% of the monotherapy patients were in DAS28 remission at 2 years, and remission was sustained in 51% and 16% of the patients, respectively.

ESR had the greatest effect on DAS28 in the FIN-RACo population, followed by tender joint count (TJC), global health, and swollen joint count (SJC).

MOI-RA is the mean of standardized values of TJC and SJC, self reported physical function on the Health Assessment Questionnaire (HAQ), patient’s and physician’s assessments of global health and patient’s assessment of pain, and ESR. All seven components are standardized, and the mean of standardized values is calculated. The range of MOI-RA is 0-100, higher values indicating poorer outcomes.

The reproducibility of MOI-RA with different joint counts was 0.97. Correlation between MOI-RA28 and DAS28 was 0.90. A simulation in which 15% of the component values of MOI-RA were randomly omitted indicated an intraclass correlation coefficient of 0.98 between incomplete and complete data.

The rate of remission in RA depends on the criteria used. Sustained remission, which is more often achieved by patients receiving combination therapy, protects RA patients against radiographic joint damage. A substantial proportion of patients below the DAS28 cutoff point for remission had tender and/or swollen joints.

The new disease activity index for RA (MOI-RA) proved to be a simple and feasible index for assessment of disease activity and treatment response.

National Library of Medicine Classification: WE 346

Medical Subject Headings: Arthritis, Rheumatoid; Remission Induction; Arthritis, Rheumatoid/therapy; Arthritis, Rheumatoid/drug therapy; Disease Progression; Disability Evaluation; Severity of Illness Index; Arthritis, Rheumatoid/physiopathology; Drug Therapy, Combination; Antirheumatic Agents/therapeutic use; Blood Sedimentation; Arthritis, Rheumatoid/radiography; Health Status
ACKNOWLEDGEMENTS

This project started in 2002, when Tuulikki Sokka asked me to examine RA patients who had been diagnosed at Jyväskylä Central Hospital in 1997. This sounded like a good idea at the time because I was tired of the long drive to my job at Jokilaakso Hospital and I needed some rest and a change of routine. However, my agreement to simply examine these patients led to hours of sitting at my laptop in a windowless room, and just when I thought the work was done a new project appeared. I am nevertheless grateful to Tuulikki for presenting me with such a great opportunity to get to know this new area for me of rheumatologic research. I also want to thank Tuulikki for our coffee breaks; they were most inspiring - and besides she always paid for my coffee.

I planned to become a pulmonologist before I met Professor Pekka Hannonen, who subsequently taught me almost everything I know about internal medicine and rheumatology. He was always willing to help me with this project, and if I had something to ask he responded immediately.

I have spent many memorable days in Äänekoski, where our statistician Hannu Kautiainen works. His enthusiasm for our sometimes less than brilliant ideas was matched only by his ability to transform them into bright new versions. He is such a genius that I sometimes needed female statistician Salme Järvenpää to translate his ideas into language I could understand. Without Hannu I would never had the chance to visit a very nice café in Äänekoski.

I am grateful for the opportunity to use the FIN-RACo data in my doctoral thesis. I want to thank everyone involved in collecting this data. Special thanks go to Professor Timo Möttönen and Professor Marjatta Leirisalo-Repo for making this possible. I also want to thank one particular member of the FIN-RACo group, Docent Markku Korpela. As my boss at Tampere University Hospital he has been most encouraging and given me free time to do my scientific work.

I warmly thank the reviewers of this work Professor Tom Pettersson and Dr Ilkka Kunnamo for their constructive comments.

Thanks to my friends for taking me out and about in the real world while I was buried in the project. I am especially grateful to Päivi Jokiranta for her hospitality - there was always a room in her home for me. Arja Helin-Salmivaara offered me valuable advice on many practical issues, for which I am thankful. When I had setbacks I was always able to call my sisters Anna-Maria and Helena. I appreciate their unfailing honesty, even though it was tough to take on occasions. I also want to thank my parents for supporting me, and my children Eli and Pyry for just for being who they are.

Tampere 28. September 2008

Heidi Mäkinen
CONTENTS

1. LIST OF ORIGINAL PUBLICATIONS
2. ABBREVIATIONS
3. INTRODUCTION
4. REVIEW OF THE LITERATURE
   4.1 Rheumatoid arthritis (RA)
   4.2 Assessment of disease activity in RA
      4.2.1 Single measures of disease activity in RA
         4.2.1.1 Joint counts
         4.2.1.2 Assessment of pain in RA
         4.2.1.3 Global assessments of severity in RA
         4.2.1.4 Assessment of function in RA: Health Assessment Questionnaire (HAQ)
         4.2.1.5 Acute-phase reactants
         4.2.1.6 Assessment of fatigue in RA
         4.2.1.7 Assessment of morning stiffness in RA
   4.2.2 Radiological Assessment in RA
   4.2.3 Pooled indices in disease activity assessment of RA
   4.2.4 Indices based on the American College of Rheumatology (ACR) core data set disease activity measures
      4.2.4.1 ACR response criteria
      4.2.4.2 ACR-N and the Hybrid Measure of ARC response
   4.2.5 Disease Activity Score (DAS)
4.2.3.1. European League Against Rheumatism (EULAR) response criteria

4.2.4. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI)

4.2.5. Patient Reported Outcome (PRO) Indices

4.3. Remission in RA

4.3.1. ACR remission criteria

4.3.2. Remission criteria based on DAS

4.3.3. Remission criteria based on simplified disease activity indices

4.3.4. Radiographic remission

4.4. Minimal Disease Activity (MDA)

4.5. Remission rates in selected clinical cohorts and randomized clinical trials

5. AIMS OF THE STUDY

6. PATIENTS AND METHODS

6.1. Selection of patients and study design

6.1.1. The clinical cohort patients

6.1.2. The Finnish Rheumatoid Arthritis Combination Therapy (FINRACo) patients

6.1.3. Definitions of remission

6.1.4. Definition of sustained remission
6.1.5. Definitions of disease activity indices and overlapping
(distribution of values of individual variables between defined
disease activity states)

6.1.5.1. DAS28

6.1.5.2. Effects of the individual components of DAS28 on the total
DAS28 score (‘theoretical model’)

6.1.5.3. Definition of overlapping

6.1.6. Mean Overall Disease Activity Index (MOI-RA)

7. STATISTICAL ANALYSIS

7.1. Statistical analysis (Study I)

7.2. Statistical analysis (Study II)

7.3. Statistical analysis (Study III)

7.4. Descriptive statistics (Study V)

7.5. Criterion validity (Study V)

7.6. Responsiveness (Study V)

7.7. Sensitivity to change (Study V)

8. RESULTS

8.1. The clinical cohort and the FIN-RACo trial patients

8.2. Remission in RA

8.3. DAS28 and MOI-RA in early RA

9. DISCUSSION

10. SUMMARY AND PROSPECTS

11. REFERENCES

12. ORIGINAL PUBLICATIONS
1. LIST OF THE ORIGINAL PUBLICATIONS


## 2. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ACR-N</td>
<td>Continuous index based the percentage change in the ACR core set of disease activity measures</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>Anti-cyclic citrullinated peptide antibodies</td>
</tr>
<tr>
<td>ARA</td>
<td>American Rheumatism Association</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve</td>
</tr>
<tr>
<td>CDAI</td>
<td>Clinical Disease Activity Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>DAS</td>
<td>Disease Activity Score</td>
</tr>
<tr>
<td>DAS28</td>
<td>Disease Activity Score with 28 joints</td>
</tr>
<tr>
<td>DMARD</td>
<td>Disease modifying antirheumatic drug</td>
</tr>
<tr>
<td>EGA</td>
<td>Evaluator’s global assessment of disease activity</td>
</tr>
<tr>
<td>ES</td>
<td>Effect size</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte Sedimentation Rate</td>
</tr>
<tr>
<td>EULAR</td>
<td>European League against Rheumatism</td>
</tr>
<tr>
<td>FIN-RACo</td>
<td>Finnish Rheumatoid Arthritis Combination Therapy Trial</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GEE</td>
<td>Generalized estimating equations</td>
</tr>
<tr>
<td>GH</td>
<td>Global health</td>
</tr>
<tr>
<td>GL</td>
<td>Physician’s global assessments</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Granulocyte-macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>HAQ</td>
<td>Stanford Health Assessment Questionnaire</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>HAQ Disability Index</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>IP</td>
<td>Interphalangeal (joint)</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass correlation</td>
</tr>
<tr>
<td>JSN</td>
<td>Joint space narrowing</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>MCP</td>
<td>Metacarpophalangeal (joint)</td>
</tr>
<tr>
<td>MDA</td>
<td>Minimal Disease Activity for Rheumatoid Arthritis</td>
</tr>
<tr>
<td>MOI-RA</td>
<td>Mean Overall Disease Activity Index for Rheumatoid Arthritis</td>
</tr>
<tr>
<td>MTP</td>
<td>Metatarsophalangeal (joint)</td>
</tr>
<tr>
<td>nACR</td>
<td>Number of core set measures improved by ≥ 20%</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PGA</td>
<td>Patient global assessment of disease activity</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient Reported Outcome</td>
</tr>
<tr>
<td>PIP</td>
<td>Proximal interphalangeal joint</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>RADAI</td>
<td>Rheumatoid Arthritis Disease Activity Index</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>RADAR</td>
<td>Rapid Assessment of Disease Activity in Rheumatology</td>
</tr>
<tr>
<td>RAPID</td>
<td>Routine Assessment of Patient Index Data</td>
</tr>
<tr>
<td>RF</td>
<td>Rheumatoid factor</td>
</tr>
<tr>
<td>SE</td>
<td>Shared epitope</td>
</tr>
<tr>
<td>SDAI</td>
<td>Simplified Disease Activity Index</td>
</tr>
<tr>
<td>SJC</td>
<td>Swollen joint count</td>
</tr>
<tr>
<td>SRM</td>
<td>Standardized response mean</td>
</tr>
<tr>
<td>TJC</td>
<td>Tender joint count</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analog scale</td>
</tr>
</tbody>
</table>
3. INTRODUCTION

The current treatment approach for patients with rheumatoid arthritis (RA) involves early initiation of aggressive therapy with disease modifying drugs (DMARDs) and biologic agents (Möttönen et al., 2002; Goekoop-Ruiterman et al., 2005; Sokka et al., 2005). The goal of treatment is remission (Emery & Salmon, 1995; Möttönen et al., 1999). Measurement of disease activity is useful for guiding therapy (Grigor et al., 2004; Fransen et al., 2005; Goekoop-Ruiterman et al., 2005) and a single standardized disease activity index would be most desirable for scientific purposes. Nevertheless, several different definitions of remission and various disease activity indices are currently in use.

The ACR (American College of Rheumatology - formerly ARA, American Rheumatism Association) remission criteria are strict and include nonspecific symptoms such as fatigue (Pinals et al., 1981). More recently, remissions based on the Disease Activity Score (DAS) and DAS28 have been described (Prevoo et al., 1996; van Riel & van Gestel, 2000). However, patients who meet DAS28 remission with values of < 2.6 may still have tender and/or swollen joints (Aletaha et al., 2005b). The ACR remission criteria are more rigorous than those of DAS28<2.6. Newer tools for evaluation of RA activity include the Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI). Remission cut off points for these new composite indices have also been defined (Aletaha & Smolen, 2005). The use of the stringent ACR remission criteria has been replaced with DAS28 remission
criteria that provide higher remission rates. ACR remission criteria have not been used for RA in randomized controlled trials (RCTs) to test the efficacy of biological agents (Mäkinen et al., 2006).

Regular assessments of disease activity can successfully be used in the clinic for guiding treatment (Grigor et al., 2004; Fransen et al., 2005; Goekoop-Ruiterman et al., 2005; Verstappen et al., 2007). Indices are also needed in RCTs to prove the efficacy of a new therapy. Indices used in RCTs to document the efficacy of a treatment of RA include the American College of Rheumatology (ACR) improvement criteria (Felson et al., 1995) (Table 1), later known as the ACR20 response and then succeeded by higher thresholds for improvement, the ACR50 and ACR70 (Felson et al., 1998). The DAS (van der Heijde et al., 1990; van der Heijde et al., 1993) and its modified version including 28 joints (DAS28)(Prevoo et al., 1995), provide European League Against Rheumatism (EULAR) response criteria. The ACR and EULAR response criteria are the current standards for monitoring treatment response in RA clinical trials (van Gestel et al., 1996). Minimal disease activity (MDA) of RA can be assessed using definitions that are based on either DAS28 or the ACR core set criteria (Wells et al., 2005).

Recently, additional composite indices have been presented: SDAI (Smolen et al., 2003) and CDAI (Aletaha et al., 2005a). Both are based on a simple sum of the values of outcome parameters: tender (TJC) and swollen (SJC) joint count based on 28 joints, patient’s global assessment of disease activity [visual analog scale (VAS) 0-10 cm], physician’s global assessment of
disease activity (VAS 0-10 cm), and C-reactive protein (CRP is not included in CDAI). ACR-N (Bathon et al., 2000), the Hybrid Measure of ACR (Committee, 2007) and other continuous indices which are based on ACR core data set measures, assess percentage change in disease activity instead of current disease activity. Indices based only on patient reported outcomes such as the patient activity score (Wolfe et al., 2003) also discriminate effectively between active and control treatments in clinical trials (Pincus et al., 2003; Pincus et al., 2005a; Pincus et al., 2006).

The present study was focused on measurement of disease activity and remission in early RA. The purpose of the study was to compare different definitions of remission in RA, to study sustainability of remission, and to evaluate DAS28 as an index for assessing disease activity in RA. In addition, we set out to develop a novel simple and feasible disease activity index for RA including various dimensions of disease activity.

4. REVIEW OF THE LITERATURE

4.1. Rheumatoid arthritis (RA)

RA is a heterogeneous autoimmune disease with variable outcome. The primary target of inflammation in RA is the synovium. However, RA is a systemic disease, sometimes with features such as fatigue (Pollard et al., 2006), low-grade fever (Pinals, 1994), anemia (Wolfe & Michaud, 2006), or/and elevations of acute phase reactants (Yildirim et al., 2004).
The currently accepted classification criteria for RA are based on the 1987 American College of Rheumatology criteria. These criteria comprise seven components, four of which must be fulfilled (Arnett et al., 1988). Early initiation of treatment is needed to reduce structural damage in RA (Möttönen et al., 2002). The classification criteria for RA were developed in patients with established disease, not early RA. Therefore, the use of these criteria for diagnostic purposes is not reasonable in clinical practice, although they are widely used in RA studies.
Table 1. 1987 Criteria for the Classification of Rheumatoid Arthritis (Arnett et al., 1988)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Morning stiffness</td>
<td>Morning stiffness in and around joints, lasting at least 1 hour before maximal improvement</td>
</tr>
<tr>
<td>2. Arthritis of 3 or more joint areas</td>
<td>At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints</td>
</tr>
<tr>
<td>3. Arthritis of hand joints</td>
<td>At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint</td>
</tr>
<tr>
<td>4. Symmetric arthritis</td>
<td>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)</td>
</tr>
<tr>
<td>5. Rheumatoid nodules</td>
<td>Subcutaneous nodules over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician</td>
</tr>
<tr>
<td>6. Serum rheumatoid factor</td>
<td>Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result have been positive in &lt; 5% of normal control subjects</td>
</tr>
<tr>
<td>7. Radiographic changes</td>
<td>Radiographic changes typical of rheumatoid arthritis on posteroanterior 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)</td>
</tr>
</tbody>
</table>

For classification purposes, a patient shall be said to have RA if he/she has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least six weeks.
The prevalence of RA varies between countries and areas of the world. The median prevalence estimate for the total population in south European countries is 0.3%, for north European countries 0.5% and for developing countries 0.4% (Alamanos et al., 2006). A retrospective study from USA showed a prevalence of 1% (Gabriel et al., 1999). In Finland 0.8% of the adult population has RA (Hakala et al., 1993; Aho et al., 1998). The annual incidence of RA lies between 26 and 46/100 000 (Symmons et al., 1994; Uhlig et al., 1998; Riise et al., 2000; Soderlin et al., 2002) in most adult populations. The annual incidence of RA in Finland was studied from a nationwide sickness insurance register in a district with a population base of about 1.8 million adults; the incidence of RA was 31.7/100 000 in 1995 (Kaipiainen-Seppänen et al., 2001). The same register was used in 2000, and the incidence of RA was 29.1/100 000 (Kaipiainen-Seppänen & Kautiainen, 2006). A declining trend has been noted in the incidence of rheumatoid factor (RF) positive RA between 1980 and 2000 (Kaipiainen-Seppänen & Kautiainen, 2006). The annual incidence of RA in Kuopio, Finland was 36/100 000 in 2000 (Savolainen et al., 2003).

The etiology of RA is largely unknown. According to epidemiologic studies both genetic and environmental factors contribute to the onset of RA. RA has a heredity of approximately 60% (MacGregor et al., 2000). The genetic and environmental risk factors for RA may be different in different disease subtypes [RF positive/negative, anti-cyclic citrullinated peptide antibody (anti-CCP) positive/negative] (Klareskog et al., 2006a). The most impressive
evidence of an environmental factor exists for smoking (Heliövaara et al., 1993). Klareskog et. al. (Klareskog et al., 2006b) have presented a hypothesis for the etiology of anti-CCP positive RA, in which an environmental agent (smoking) induces citrullination of lung proteins. Adjuvants in the smoke also stimulate the innate immune system, and help to induce immunity to citrullinated proteins preferentially in individuals carrying the HLA-DR shared epitope (SE) genes.

The development of arthritis in RA patients is preceded by the occurrence of autoantibodies years before disease onset (Aho et al., 1985; Klareskog et al., 2006a). Practically every immune cell type and inflammatory mediator has been implicated in the disease process over the course of time (Firestein, 2005). Hypotheses on B-cells are currently of interest because of B-cell targeted therapies (Edwards et al., 2004). T-cell directed treatment approaches have also proved to be effective (Kremer et al., 2003). Cytokines such as tumor necrosis factor alpha (TNF-alpha) and interleukin-1 (IL-1), IL-6, IL-18 and granulocyte-macrophage colony-stimulating factor (GM-CSF) play a crucial role in the pathogenesis of RA (Feldmann et al., 1996). Chronic synovitis is characterized by a complex interplay between multiple cell types and inflammatory mediators.

The most dominant feature of RA is arthritis. The most commonly affected joints are the small joints of hands and feet, with a symmetric pattern of inflammation. The clinical features reflecting systemic involvement in RA include fever, malaise, fatigue and weight loss. RA patients may also have extra-
Articular manifestations affecting the vascular system, lungs, kidneys, nervous system, eyes and skin.

The clinical course of RA varies from self-limiting or episodic to prolonged and progressive chronic arthritis. The latter may result in extensive joint destruction (Ollier et al., 2001). Today the clinical status of RA patients who have been actively treated is improved compared to previous decades, according to disease activity (Bergstrom et al., 1999; Pincus et al., 2005b), function and structural outcomes (Sokka et al., 2000b; Sokka et al., 2004a; Heiberg et al., 2005; Pincus et al., 2005b; Sokka et al., 2007a), work disability (Puolakka et al., 2005) and mortality (Krause et al., 2000; Choi et al., 2002).

4.2. Assessment of disease activity in RA

A single ‘gold standard’ measure does not exist for the assessment of RA disease activity, such as blood pressure or serum cholesterol, to be used in clinical trials, clinical research and clinical care (Pincus & Sokka, 2005). Therefore, a pooled index of several individual measures is required (Smythe et al., 1977).

The ACR preliminary core set of disease activity was published in 1993. These measures consist of tender joint count, swollen joint count, patient’s assessment of pain, patient’s and physician’s assessments of disease activity, self-reported physical function, and laboratory evaluation of an acute-phase reactant. For studies lasting one year or longer, radiographs are recommended (Felson et al., 1993). Measures were selected based on their
sensitivity to change, their lack of redundancy, their content validity (whether they sampled multiple domains of RA activity), and whether they predicted important outcomes in RA, including disability, radiographic damage and death. The ACR criteria for remission (Pinals et al., 1981), the ACR improvement criteria (Felson et al., 1995), and different continuous disease activity indices include these measures in various combinations.

4.2.1. Single measures of disease activity in RA

4.2.1.1. Joint counts

The most important phenomenon in RA is inflammation of joints; consequently measurement of tender and swollen joint counts is an essential part of disease activity measurement in RA. Formal joint counts used in most studies have ranged from 28 to 68 joints.

Joint counts are the principal components of the ACR remission criteria (Pinals et al., 1981) and the ACR core set for clinical trials (Felson et al., 1995). Tender and swollen joint counts are also included in the DAS (van der Heijde et al., 1990; van der Heijde et al., 1993) and in a modified version of the DAS including 28 joints (DAS28) (Prevoo et al., 1995), as well as in newer, more simple indices derived from them: SDAI (Smolen et al., 2003) and CDAI (Aletaha et al., 2005a). Joint counts should be included in the clinical examination of every RA patient at each visit (Scott et al., 2003). However, most visits to a rheumatologist do not include a formal joint count (Pincus & Segurado, 2006).
Abnormalities assessed in joints include swelling, tenderness, pain on motion, limited motion, and deformity. Effusion is a characteristic feature in swollen joints, not bony enlargement or deformity. Joint tenderness is defined as pain induced by pressure or motion on joint examination. Pressure tenderness is often difficult or impossible to assess in shoulder and hip joints. Thus the tenderness of these joints is assessed by pain in motion (Sokka & Pincus, 2005).

The most frequently used joint counts are presented in Table 2. The joint counts including 66/68 joints have been replaced with more limited joint counts in DAS28, SDAI and CDAI. In the original DAS the tender joint count is substituted by the Ritchie Articular Index (Ritchie et al., 1968), which constitutes 52 joints (Table 2). Joints are assessed using the following grading: 0 = non-tender, 1 = tender, 2 = tender with wincing, and 3 = tender with wincing and withdrawal. The range of the Ritchie Index is 0 to 78. The swollen joint count of the original DAS ranges from 0 to 44 (van der Heijde et al., 1990; van der Heijde et al., 1993) (Table 2).

Joint counts may also be a part of self administered questionnaires assessing disease activity in RA. The Rapid Assessment of Disease Activity in Rheumatology (RADAR) index includes the patient self reported joint count as a component (Mason et al., 1992). The Rheumatoid Arthritis Disease Activity Index (RADAI) is a further development of RADAR (Stucki et al., 1995). In the RADAI-index, the patients rate their joint pain as 0= none, 1= mild, 2=...
moderate, 3=severe in the right and left shoulders, elbows, wrists, fingers, hips, knees, ankles and toes.
Table 2. Joints included in different joint counts.

<table>
<thead>
<tr>
<th>Joints</th>
<th>28 joints (Fuchs et al., 1989a)</th>
<th>42 joints (Sokka &amp; Pincus, 2003a)</th>
<th>44 joints (van der Heijde et al., 2006)</th>
<th>66/68 joints</th>
<th>Ritchie Index (Ritchie et al., 1968)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporomandibular</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Sternoclavicular</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acromioclavicular</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Shoulder</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Elbow</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Wrist</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Metacarpophalangeal (1-5)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Proximal interphalangeal (1-5)</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Distal interphalangeal (2-5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Hip (assessed for tenderness only)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Knee</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ankle</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Talocalcaneal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Tarsus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Metatarsophalangeal (1-5)</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Proximal interphalangeal (1-5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
4.2.1.2. Assessment of pain in RA

Pain is a common symptom in the general population and its prevalence increases with advancing age. Pain is the major reason for RA patients to seek medical care and is the priority area for improvement of health for RA patients (Heiberg & Kvien, 2002). However, pain is not generally recorded by health professionals. The experience of pain is subjective and difficult to measure (Sokka, 2003). Extensive self-report research questionnaires have been developed to measure the quantitative and qualitative properties of pain (Huskisson, 1974). These questionnaires may be difficult and time-consuming to use in clinical settings.

A visual analog pain scale was initially used in psychology in the early 1900s (Sokka, 2005). This approach was adopted by rheumatologists in the 1970s, with the emphasis that ‘severity of pain is only known to the sufferer’ (Huskisson, 1974). The standard visual analog scale (VAS) is a 10 cm scale with a border at each end. The left border represents ‘no pain’ and the severity of pain increases to the right; accordingly the right border is characterized as ‘pain as severe as it could be’.

Widespread musculoskeletal pain was reported by a quarter of 1002 community dwelling elderly women in the US (Leveille et al., 2001). Pain was found to be the leading reason for a general practitioner visit in Finland. In the 15-74 year old Finnish population, 35.1% suffer from chronic pain, and the prevalence of pain increases with age (Mäntyselkä et al., 2003).
Pain is a component of the ACR response criteria (Felson et al., 1995), and absence of joint pain is included in the ACR remission criteria for RA (Pinals et al., 1981). On a 100 mm VAS scale < 10 mm has been interpreted as no pain (Sokka & Pincus, 2003b). The Minimal Disease Activity for Rheumatoid Arthritis (MDA) core set definition for pain cut-off is ≤ 20 mm on a VAS (Wells et al., 2005). In an elderly Finnish population the mean pain VAS was 20 mm (Krishnan et al., 2005).

4.2.1.3. Global assessments of severity in RA

All disease activity indices include a patient self-report global measure; this is defined as ‘global health’ (GH) in the DAS and the DAS28 indices, and as ‘patient global assessment of disease activity’ (PGA) in the SDAI and the CDAI indices. Global health includes a broader spectrum of aspects of health, and not all are directly related to RA. Smedstad et al. (Smedstad et al., 1997) found strong correlations between GH and pain, depression, disability and tender joints, while ESR, CRP, and X-ray abnormalities correlated weakly with GH. The physician’s impression of disease activity is supposed to influence clinical decisions with regard to intensifying or reducing treatment of RA. Patients often score their disease activity at a higher level than physicians do (Yazici et al., 2001; Nicolau et al., 2004). Physicians seem to weight findings which are regarded as more objective, like abnormal laboratory tests or swollen joint counts. Both GH and physician’s global
assessments (GL) are part of the ACR core set of improvement for RA and SDAI, while GL is not included in DAS and DAS28.

4.2.1.4. Assessment of function in RA: The Health Assessment Questionnaire (HAQ)

Patient-reported outcomes (PROs) provide knowledge about patient’s health, functional status, symptoms, treatment preferences, satisfaction and quality of life from their own personal perspective. The Health Assessment Questionnaire (HAQ) introduced in 1980 is among the first PRO instruments that was initially designed to present a model of patient-oriented outcome assessment (Fries et al., 1980; Bruce & Fries, 2005).

HAQ consists of the HAQ Disability Index (HAQ-DI), pain VAS, and patient global VAS. HAQ-DI includes questions about fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both the upper and lower extremities. There are 20 questions in eight categories of functioning: dressing, arising, eating, walking, hygiene, reaching, gripping, and performing tasks. Patient’s responses describing abilities over the past week are scored as follows: 0= without any difficulty, 1= with some difficulty, 2= with much difficulty, and 3= unable to do it. The highest component in each category determines the score of that category, unless aids or devices are required. Dependence on equipment or physical assistance increases a lower score to the level of 2. A complementary scoring method ignores the score for aids and devices and represents residual disability after compensatory
efforts. The HAQ-DI score ranges from 0 to 3: scores of 0 to 1 are generally considered to represent mild to moderate disability, from 1 to 2 moderate to severe disability, and from 2 to 3 severe to very severe disability (Bruce & Fries, 2003). The HAQ has been translated into numerous languages, has been used extensively in RA studies, and is a component of ACR response criteria (Felson et al., 1995). HAQ has been assessed in a random sample of 1530 elderly Finnish population, producing a mean value of 0.25; at least some disability was seen in 32% of responders (Krishnan et al., 2004).

The modified HAQ, derived from the original HAQ, was published in 1983 (Pincus et al., 1983). The number of questions was limited to eight instead of 20, and one question in each category of HAQ was included. The sum of scores for the questions is divided by eight to achieve a score of 0-3.
HEALTH ASSESSMENT QUESTIONNAIRE (HAQ)

ID _____________________________ Date of Birth _____________________________ Today’s Date _____________________________

This questionnaire includes information not available from blood tests, X-rays, or any source other than you. Please try to answer each question, even if you do not think it is related to you at this time. There are no right or wrong answers. Please answer exactly as you think or feel. Thank you.

1. We are interested in learning how your illness affects your ability to function in daily life. Please check (✓) the one best answer which best describes your usual abilities OVER THE PAST WEEK:

<table>
<thead>
<tr>
<th>DRESSING &amp; GROOMING</th>
<th>Without ANY Difficulty (0)</th>
<th>With SOME Difficulty (1)</th>
<th>With MUCH Difficulty (2)</th>
<th>UNABLE To Do (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(X) Dress yourself, including tying shoelaces and doing buttons?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Shampoo your hair?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISING</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stand up from a straight chair?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(X) Get in and out of bed?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EATING</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cut your meat?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(X) Lift a full cup or glass to your mouth?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Open a new milk carton?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WALKING</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(X) Walk outdoors on flat ground?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Climb up five steps?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Please check any AIDS OR DEVICES that you usually use for any of these activities:

- Cane
- Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
- Walker
- Built up or special utensils
- Crutches
- Special or built up chair
- Wheelchair
- Other (Specify: ________________)

3. Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- Dressing and Grooming
- Eating
- Arising
- Walking

4. How much pain have you had OVER THE PAST WEEK? Place a mark on the line below to indicate how severe your pain has been:

NO PAIN ____________ PAIN AS BAD IT COULD BE ____________
5. Please check the response which best describes your usual abilities OVER THE PAST WEEK:

<table>
<thead>
<tr>
<th>HYGIENE</th>
<th>Without ANY Difficulty(0)</th>
<th>With SOME Difficulty(1)</th>
<th>With MUCH Difficulty(2)</th>
<th>UNABLE To Do(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(X) Wash and dry your body?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Take a tub bath?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Get on and off the toilet?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REACH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(X) Bend down to pick up clothing from the floor?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRIP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Open car doors?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Open jars which have previously been opened?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(X) Turn faucets on and off?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTIVITIES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Run errands and shop?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(X) Get in and out of a car?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Do chores such as vacuuming or yard work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Please check any AIDS OR DEVICES that you usually use for any of these activities:

- Raised toilet seat
- Bathtub bar
- Bathtub seat
- Long-handled appliances for reach
- Jar opener (for jars previously opened)
- Long-handled appliances in bathroom
- Other (Specify: __________________)

7. Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- Hygiene
- Gripping and opening things
- Reach
- Errands and chores

8. Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing:

<table>
<thead>
<tr>
<th>VERY WELL</th>
<th>VERY POORLY</th>
</tr>
</thead>
</table>

(X) Questions of the modified HAQ
4.2.1.5. Acute-phase reactants

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are used to determine the acute phase reactions in disease activity measures for RA. They also increase in other inflammatory conditions, infections and malignancies. Although acute-phase reactants are non-specific they correlate with disease activity and radiographic damage in RA (Graudal et al., 2000; Yildirim et al., 2004). However, 25-50% of patients with RA have normal ESR values, and more than a quarter of patients with severe or very severe RA has been reported to have an ESR value of 20 mm/h or less (Wolfe & Michaud, 1994; Sokka & Pincus, 2003b).

CRP is more sensitive to short term changes in disease activity than ESR. Furthermore, ESR can be influenced by factors such as age, gender, fibrinogen levels, hypergammaglobulinemia, RF and anemia (Miller et al., 1983; Talstad et al., 1983; Kushner, 1991). CRP correlated better with other measures of disease activity than ESR (Mallya et al., 1982). However, CRP concentrations also tend to increase with age. Gender influences CRP, too, with higher values in women than men. (Wener et al., 2000).

ESR and CRP have proven to be equally useful as an acute phase component of the ACR20 improvement criterion (Paulus et al., 1999). Originally DAS and DAS28 included ESR. The formula to calculate DAS28-CRP is suggested to provide a good estimation of DAS28-ESR values on a group level. However, DAS28-CRP significantly underestimates disease activity and overestimates the improvement of disease activity compared to DAS28-ESR.
(Matsui et al., 2007a), and the threshold values of DAS28-CRP should be reconsidered (Inoue et al., 2007). CDAI is the only disease activity index without an acute-phase reactant (Aletaha et al., 2005a)

4.2.1.6. Assessment of fatigue in RA

Experience of fatigue has been reported by a large proportion of people with RA (Kirwan & Hewlett, 2007). The causality of RA fatigue is multidimensional, involving inflammation, pain, anemia, poor sleep and psychosocial factors (Wolfe et al., 1996). It has been shown that fatigue is strongly associated with pain (Huysen et al., 1998; Pollard et al., 2006). Clinically relevant levels of fatigue are present in 41-80% of patients with RA (Wolfe et al., 1996; Pollard et al., 2006). However, fatigue is shown to be even more common in patients with fibromyalgia (Wolfe et al., 1996). Requirement of no fatigue is included in the ACR remission criteria (Pinals et al., 1981).

4.2.1.7. Assessment of morning stiffness in RA

Prolonged morning stiffness is regarded as a characteristic symptom of inflammatory arthritis and in particular of RA. However, Yazici et al. (Yazici et al., 2001) observed that morning stiffness did not differ among patients with RA and those with osteoarthritis. Duration of morning stiffness exceeding 15 min is not allowed in the ACR remission criteria (Pinals et al., 1981).
4.2.2. Radiological Assessment in RA

Radiographic imaging may be regarded as the 'gold standard' when assessing disease progression in RA (van der Heijde, 2000). Plain radiography of hands and feet are still performed, although newer methods such as magnetic resonance imaging and power-doppler ultrasound are available. Radiographs of hands and feet can easily be performed; they are relatively cheap, and standardized scoring methods have been established.

Two major scoring systems with a number of modifications are available: the Larsen method (Larsen et al., 1977; Larsen, 1995; Scott et al., 1995) and the Sharp (Sharp et al., 1971; van der Heijde, 1999) method. In the original version of the Larsen method, joints of hands and feet are graded as follows: 0= normal, 1= slight abnormalities [periarticular soft tissue swelling, periarticular osteoporosis and joint space narrowing (JSN)], 2= definite early abnormalities, 3= medium destructive abnormalities, 4= severe definite abnormalities, 5= mutilating abnormalities. Each wrist is considered as one unit and the score is multiplied by five; the other joints included are ten DIP, eight PIP, ten MCP, ten MTP and two IP joints of big toes. Modifications of the Larsen score include omitting soft tissue swelling and osteoporosis that are often impossible to detect. A new grading was designed as: 0= intact bony out line and normal joint space, 1= erosion less than 1 mm in diameter or joint space narrowing, 2= one or several small erosions (diameter > 1mm), 3= marked erosions, 4= severe erosions: there is usually no joint space left, 5= mutilating changes, the original bony outlines have been destroyed (Larsen, 1995).
Based on the number of joints included the maximal score ranges from 100 to 250 (Kaarela & Kautiainen, 1997; Korpela et al., 2004). A standard set of radiographs for grading exists.

As the original Sharp method grades only the radiographs of hands, the modification of van der Heijde is applied in many studies (van der Heijde, 1999). This modification scores the presence of erosions in 16 joints of hands and wrists (graded from 0 to 5), and in six joints of the feet (graded from 0 to 10), and the presence of JSN in 15 joints of the hands and wrists (graded from 0 to 4) and in six joints of the feet (graded from 0 to 4). The maximal grade for erosions is 280 units and for JSN 168; the maximum total score is 448.

4.2.3. Pooled indices in disease activity assessment of RA

As no single measure can serve as a ‘gold standard’ to assess disease activity in RA, a pooled index of several individual measures is required (Smythe et al., 1977).

Indices used in RCTs to document the efficacy of a treatment include the ACR improvement criteria (Felson et al., 1995) (presented in Table 4), and the DAS (van der Heijde et al., 1990; van der Heijde et al., 1993) and DAS28 (table 5) (Prevoo et al., 1995), which provide the European League Against Rheumatism (EULAR) response criteria for RA (presented in Table 6). Recently, additional composite indices have been presented: SDAI (Smolen et al., 2003) and CDAI (Aletaha et al., 2005a)
Table 3. Measures of ACR core set of disease activity and composite indices.

<table>
<thead>
<tr>
<th>Measures</th>
<th>ACR core set of disease activity</th>
<th>DAS</th>
<th>DAS28</th>
<th>SDAI</th>
<th>CDAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tender joints</td>
<td>68</td>
<td>RAI (52 joints)</td>
<td>28 joint count</td>
<td>28 joint count</td>
<td>28 joint count</td>
</tr>
<tr>
<td>Number of swollen joints</td>
<td>66</td>
<td>44 joint count</td>
<td>28 joint count</td>
<td>28 joint count</td>
<td>28 joint count</td>
</tr>
<tr>
<td>Patient’s assessment of pain</td>
<td>VAS 0-100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient’s global assessment of disease activity</td>
<td>VAS 0-100</td>
<td>-</td>
<td>-</td>
<td>VAS 0-10</td>
<td>VAS 0-10</td>
</tr>
<tr>
<td>Patient’s global health</td>
<td>-</td>
<td>VAS 0-100</td>
<td>VAS 0-100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Evaluator’s (physician’s) global assessment of disease activity</td>
<td>VAS 0-100</td>
<td>-</td>
<td>-</td>
<td>VAS 0-10</td>
<td>VAS 0-10</td>
</tr>
<tr>
<td>Patient’s assessment of physical function</td>
<td>HAQ 0-3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acute phase reactants</td>
<td>ESR/CRP</td>
<td>ESR (formula for DAS-CRP also available)</td>
<td>ESR (formula for DAS28-CRP also available)</td>
<td>CRP in mg/dL (0.1-10.0)</td>
<td>-</td>
</tr>
</tbody>
</table>
4.2.4.Indices based on the American College of Rheumatology (ACR) core data set disease activity measures

4.2.4.1. ACR response criteria for RA

The ACR preliminary definition of improvement in RA (Table 4), published in 1995, has been widely adopted as a primary outcome measure in RA clinical trials (Felson et al., 1995). Validation studies have confirmed the ability of ACR20 to discriminate active treatment from placebo (Pillemer et al., 1997). The improvement in disease activity achieved in ACR20 is not very large, so higher thresholds for improvement such as ACR50 and ACR70 have also been used in clinical trials. ACR response criteria are further widely used in RCTs to show the efficacy of a new drug compared to placebo (Genovese et al., 2005; Breedveld et al., 2006; Emery et al., 2006; van der Heijde et al., 2006). One proposed way to use ACR response criteria is nACR, where n is the number of core set measures improved by ≥ 20% (Committee, 2007).

The set of ACR improvement criteria has some shortcomings. Being based on a change of disease activity it cannot be used in cross sectional settings. Furthermore, the ACR response criteria do not recognize possible worsening of the patient’s status.
Table 4. ACR core data set for RA trials and ACR improvement criteria requirements

<table>
<thead>
<tr>
<th>ACR core set of disease activity for RA trials</th>
<th>ACR improvement criteria requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender joints</td>
<td>≥ 20% improvement</td>
</tr>
<tr>
<td>Swollen joints</td>
<td>≥ 20% improvement</td>
</tr>
<tr>
<td>Patient’s assessment of pain (VAS)</td>
<td>≥ 20% improvement in 3 of the 5 measures</td>
</tr>
<tr>
<td>Patient’s global assessment of disease activity (VAS)</td>
<td></td>
</tr>
<tr>
<td>Physician’s global assessment of disease activity (VAS)</td>
<td></td>
</tr>
<tr>
<td>Patient’s assessment of physical function</td>
<td></td>
</tr>
<tr>
<td>Acute-phase reactant value</td>
<td></td>
</tr>
</tbody>
</table>

4.2.4.2. ACR-N and the Hybrid Measure of ACR response

ACR-N (Bathon et al., 2000) and the Hybrid Measure of ACR (Committee, 2007) are continuous indices based on ACR core data set measures and they both assess percentage change in disease activity instead of current disease activity in RA patients.

The ACR-N provides a single number that characterizes the percentage of improvement from baseline that a patient has experienced, in analogy to ACR20, ACR50 and ACR70 responses. ACR-N is determined by calculating the smallest degree of improvement from baseline in the following three criteria: number of tender joints, number of swollen joints, and median value of the five remaining measures of the core set of disease activity measures. A patient with an ACR-N of X means that they have achieved an improvement of at least X% in tender and swollen joints and an improvement of at least X% in three of the other five parameters (Siegel & Zhen, 2005). ACR-N
can also be used to define worsening of disease by negative values. Another way to apply ACR-N in a clinical trial is to compare area under curve (AUC) by patient over time. This approach may substantially increase the power to detect small differences between treatment arms (Siegel & Zhen, 2005).

The ACR committee reevaluated the improvement criteria and proposed a revision of the ACR20 in 2007: the Hybrid Measure of ACR (Committee, 2007). This measure combines the ACR20, ACR50 and ACR70 and is a continuous score of the mean improvement in core set measures. This continuous measure assesses the change of disease activity, but current disease activity cannot be measured. However, this new measure has greater statistical power to distinguish the efficacy of treatments than the ACR20 improvement.

### 4.2.5. Disease Activity Score (DAS)

Disease Activity Score (DAS) was proposed in the early nineties to assess disease activity in RA (van der Heijde et al., 1990; van der Heijde et al., 1993). DAS was developed from physician’s decisions to cease, maintain or start DMARDs in RA patients. DAS is a continuous index using four selected components. Square root and logarithm are used to provide normal distribution (Fransen & van Riel, 2005) (Table 5).

The original DAS contains the Ritchie Articular Index (Ritchie et al., 1968) (RAI, range 0-78), a 44 swollen joint count (range 0-44), ESR, and patient’s general health (GH) on VAS (0-100). DAS has a continuous scale from
0 to 10. Level of disease activity can be interpreted as low (DAS≤ 2.4), moderate (2.4< DAS ≤ 3.7) or high (DAS> 3.7). DAS< 1.6 corresponds to remission according to the ACR remission criteria. Different versions of DAS include one without GH, and a version in which ESR is replaced with CRP (Table 5).

DAS28 is an index derived from the original DAS with fewer joints included (Figure 1). DAS28 consists of a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), ESR, and GH on a VAS scale (range 0-100) (Table 5) (Prevoo et al., 1995). DAS28 is a continuous index ranging from 0 to 9.4. Although DAS and DAS28 cannot be directly compared, a formula to transform DAS to DAS28 is available (van Gestel et al., 1998). Low disease activity is defined as DAS28≤ 3.2, moderate as 3.2< DAS28 ≤ 5.1, and high as DAS28> 5.1 (van Gestel et al., 1998). A commonly used cutoff point for remission is DAS28< 2.6 (Fransen et al., 2004).
 Modifications of DAS28 include one in which ESR is substituted by CRP and another with only three components (GH omitted). A recent large observational study indicated that values of DAS28-CRP are significantly lower than those of the original DAS28 (Matsui et al., 2007a). DAS28-CRP threshold values corresponding to remission, low disease activity, and high disease activity have been shown to be lower than the corresponding threshold values for original DAS28: 2.3 vs. 2.6, 2.7 vs. 3.2 and 4.1 vs. 5.1, respectively (Inoue et al., 2007). DAS formulas require complex calculations involving square roots and log transformations. However, calculators are easily obtained from the web site (DAS).
Table 5. Different DAS formulas

<table>
<thead>
<tr>
<th>Different DAS formulas</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS = 0.54 * sqrt (RAI) + 0.065 * (SJC44) + 0.33 * Ln (ESR) + 0.0072 * GH</td>
</tr>
<tr>
<td>DAS(3) = 0.54 * sqrt (RAI) + 0.065 * (SJC44) + 0.33 * Ln (ESR) + 0.22</td>
</tr>
<tr>
<td>DAS-CRP = 0.54 * sqrt (RAI) + 0.065 * (SJC44) + 0.17 * Ln (CRP + 1) + 0.0072 * GH + 0.45</td>
</tr>
<tr>
<td>DAS-CRP(3) = 0.54 * sqrt (RAI) + 0.065 * (SJC44) + 0.17 * Ln (CRP + 1) + 0.65</td>
</tr>
<tr>
<td>DAS remission &lt; 1.6, low ≤ 2.4, moderate &gt; 2.4 and ≤ 3.7, and high disease activity &gt; 3.7</td>
</tr>
<tr>
<td>DAS28 = 0.56 * sqrt (TJC28) + 0.28 * sqrt (SJC28) + 0.70 * Ln (ESR) + 0.014 * GH</td>
</tr>
<tr>
<td>DAS28(3) = [0.56 * sqrt (TJC28) + 0.28 * sqrt (SJC28) + 0.70 * Ln (ESR)] * 1.08 + 0.16</td>
</tr>
<tr>
<td>DAS28-CRP = 0.56 * sqrt (TJC28) + 0.28 * sqrt (SJC28) + 0.36 * Ln (CRP + 1) + 0.014 * GH + 0.96</td>
</tr>
<tr>
<td>DAS28-CRP(3) = [0.56 * sqrt (TJC28) + 0.28 * sqrt (SJC28) + 0.36 * Ln (CRP + 1)] * 1.10 + 1.15</td>
</tr>
<tr>
<td>DAS28 remission &lt; 2.6, low ≤ 3.2, moderate &gt; 3.2 and ≤ 5.1, and high disease activity &gt; 5.1</td>
</tr>
<tr>
<td>DAS28 = 1.072 * DAS + 0.932</td>
</tr>
</tbody>
</table>

4.2.5.1. European League against Rheumatism (EULAR) response criteria

In general, the efficacy of a therapy is defined by comparing means of changes in disease activity variables between the treatment and placebo groups. However, the difference between mean changes in groups of patients does not indicate the number of patients who have responded to treatment. Therefore, in addition to disease activity, the response of individual patients to
anti-inflammatory therapy is essential in clinical trials. Based on good group results, we do not know whether a large number of patients have improved moderately or a small number of patients have improved substantially.

The EULAR response criteria were based on DAS (van Gestel et al., 1996) and later validated on DAS28 (van Gestel et al., 1998). The EULAR response criteria classify patients as good, moderate or non-responders, using the amount of change in the DAS/DAS28 of an individual patient, and the DAS/DAS28 value achieved. A change of 1.2 is considered significant (Table 6).

A high level of agreement between ACR and EULAR improvement has been shown (van Gestel et al., 1999). Both can be applied in clinical trials. Van Gestel et al (van Gestel et al., 1999) recommend assessing the components of both criteria and choosing in advance which criteria to use as primary and secondary endpoints.

Table 6. EULAR improvement criteria

<table>
<thead>
<tr>
<th>Value achieved</th>
<th>Change in DAS or DAS28 from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>DAS</td>
</tr>
<tr>
<td>≤ 3.2</td>
<td>≤ 2.4</td>
</tr>
<tr>
<td>&gt; 3.2 and ≤ 5.1</td>
<td>&gt;2.4 and ≤ 3.7</td>
</tr>
<tr>
<td>&gt; 5.1</td>
<td>&gt; 3.7</td>
</tr>
</tbody>
</table>
4.2.6. The Simplified Disease activity index (SDAI) and the Clinical Disease Activity Index (CDAI)

In addition to DAS, the currently available composite disease indices providing a single number on a continuous scale are the Simplified Disease Activity Index (SDAI) (Smolen et al., 2003) and the Clinical Disease Activity Index (CDAI) (Aletaha et al., 2005a). SDAI constitutes a simple numerical addition of individual measures on their original scale. The range of SDAI is 0.1-86.0. This idea overcomes the problems of transformations and weighting. SDAI includes both the evaluator’s and patient’s assessments of disease activity. The inclusion of CRP instead of ESR was made for several reasons: CRP is the most reliable variable of the acute phase response and CRP levels have prognostic value in RA (Otterness, 1994), and CRP is less confounded by other factors than ESR, and has been shown to correlate better with other disease activity measures (Mallya et al., 1982) (Table 3. and Table 7.).

CDAI was derived from SDAI and is the only composite index without an acute phase reactant. It is also a simple sum of disease activity measures ranging from 0 to 76. In the validation study of CDAI, Aletaha et al. (Aletaha et al., 2005a) conclude that acute phase reactants add little information beyond the combination of clinical variables included in SDAI. The authors suggest that CDAI will prove of greatest value in clinical practice rather than
research, where acute phase reactants are nearly always available (Table 3 and Table 7).

SDAI and CDAI are feasible indices for which a calculator is not necessary. They are also easy to understand for the patient, which may improve outcomes, as has been the case in other chronic diseases (Egan et al., 2003; Rachmani et al., 2005).
Table 7. Formulas for the Simplified Disease Activity Index and the Clinical Disease Activity Index

<table>
<thead>
<tr>
<th>SDAI and CDAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDAI= SJC28+ TJC28+ PGA+ EGA+ CRP (in mg/dl)</td>
</tr>
<tr>
<td>CDAI= SJC28+ TJC28+ PGA+EGA</td>
</tr>
</tbody>
</table>

PGA= patient’s global assessment of disease activity VAS 0-10
EGA= evaluator’s global assessment of disease activity VAS 0-10
CRP range 0.1-10.0, CRP more than 10 are replaced by value 10

4.2.7. Patient self-report outcomes (PRO) indices

It has been shown that RA patients are reliable and accurate reporters of their own symptoms and signs (Stewart et al., 1990; Mason et al., 1992). Rheumatologists have rated examination of joints the most important measure of disease activity in both randomized trials and clinical care (Wolfe et al., 2003). Nonetheless, most visits to rheumatologists do not include a formal quantitative joint count (Pincus & Segurado, 2006). A practical quantitative index, like the patient self report joint count, to monitor clinical status without formal joint counts by the rheumatologist could be of considerable value in a busy clinical setting (Pincus et al., 2007a). The value of such an index in discriminating active and control treatments has also been confirmed (Pincus et al., 2006). On this basis, the use of patient reported outcome indices has been suggested to be useful both in clinical work and clinical trials.
The Rapid Assessment of Disease Activity in Rheumatology (RADAR) questionnaire is a one page (2 sides) questionnaire about disease activity, clinical status and joint pain/tenderness, which includes six items and can be completed by the patient alone (Mason et al., 1992). The Rheumatoid Activity Index (RADAI) is also a self-administered questionnaire based on RADAR, and it combines five items in a single index. The items ask the patient about their 1) global disease activity in the last six months, 2) disease activity in terms of current tender and swollen joints, 3) arthritis pain, 4) duration of morning stiffness, and 5) tender joints to be rated in a joint list. The first three items are rated from 0 to 10, and duration of morning stiffness from 0 to 6, and tender joints from 0 to 48, but are transformed into a single 0 to 10 scale. The values of items are summed and divided by the number of items. The original goal of the RADAI was to provide an easily used assessment of disease activity in RA (Stucki et al., 1995).

The Patient Activity Scale (PAS) is composed of pain VAS, patient global VAS, and the HAQ. The index is formed by multiplying HAQ by 3.33 and dividing the sum of these items by three (Wolfe et al., 2005a). Pincus et al. (Pincus et al., 2003) reported already in 2003 a similar index, and showed its ability to distinguish active treatment from placebo. It was later named RAPID 3. RAPID 4 adds a RADAI self-report joint count to RAPID 3. The RADAI score scale of 0-48 is converted to 0-10. The raw RAPID is divided by four to give a score of 0-10 (Pincus et al., 2007a). Pincus et al. (Pincus et al., 2007b)
proposed a continuous quality improvement strategy based on routine assessment of patient index data (RAPID) scores in standard clinical care.

4.3. Remission in RA

No single definition for remission exists and several criteria for remission have been developed. Previously, definitions of remission included phrases such as “full recovery” (Corrigan et al., 1974), “no joint swelling” (Sharp et al., 1982), “absence of swollen joints or tender joints” (McCarty et al., 1995), “inactive disease” (Duthie et al., 1957), “complete control of synovitis and normal erythrocyte sedimentation rate” (Sambrock et al., 1982), and “being symptom free” (Nissilä et al., 1983; Wolfe et al., 1993). In some studies remission has been an outcome without any definition (Csuka et al., 1986; Williams et al., 1992; Hannonen et al., 1993).

Remission is usually defined using ACR remission criteria or is based on a continuous disease activity index with a cutoff point for remission usually derived from the ACR remission criteria. This means that most patients with disease activity below that cutoff point are in remission, but some may still have active disease (Aletaha et al., 2005b; Mierau et al., 2007). Composite indices with a cutoff point for remission include DAS, DAS28, SDAI and CDAI. In addition to cross sectional remission, sustained remission has been studied (van der Heijde et al., 2005; Listing et al., 2006; Mierau et al., 2007).
4.3.1. ACR remission criteria

Preliminary remission criteria for RA were proposed by a committee of ARA (now ACR) in 1981 (Pinals et al., 1981) (Table 8). To develop these criteria, 35 rheumatologists were asked to collect information from 35 RA patients concerning symptoms, laboratory data, and information on results of joint examination. These rheumatologists then classified patients into four categories: complete remission without drugs, complete remission with drugs, partial remission, and active disease. These variables were analyzed to select those that best discriminated patients in remission from those with active disease. Of these criteria sets tested among RA patients in remission or with partial remission or active disease, six criteria were chosen. If four of the criteria were met, sensitivity was 90% and specificity 69% for complete remission. If five of the criteria were met, the corresponding figures were 72% and 92%. A duration requirement of two months was chosen, as 90% of patients in remission fulfilled this criterion. The use of the ACR remission criteria has been heterogeneous; requirement of no fatigue is often omitted and the number of criteria required for remission varies among different studies.
Table 8. The ACR criteria for clinical remission in rheumatoid arthritis (Pinals et al., 1981).

<table>
<thead>
<tr>
<th>Five or more of the following requirements must be fulfilled for at least two consecutive months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Duration of morning stiffness not exceeding 15 minutes</td>
</tr>
<tr>
<td>2. No fatigue</td>
</tr>
<tr>
<td>3. No joint pain (by history)</td>
</tr>
<tr>
<td>4. No joint tenderness or pain in motion</td>
</tr>
<tr>
<td>5. No soft tissue swelling in joints or tendon sheaths</td>
</tr>
<tr>
<td>6. Erythrocyte sedimentation rate (Westergren method) less than 30 mm/hour for a female or 20 mm/hour for a male</td>
</tr>
</tbody>
</table>

4.3.2 Remission criteria based on DAS

DAS (van der Heijde et al., 1990; van der Heijde et al., 1993) and its modified version DAS28 (Prevoo et al., 1995) including 28 joints were developed to assess disease activity in RA. Cutoff points for both indices corresponding to the ACR remission criteria have been defined. Prevoo et al. (Prevoo et al., 1996) compared ACR and DAS remission criteria with the observation that DAS<1.6 corresponds to ACR remission criteria. A remission cut point of DAS28<2.6 was found to correspond to DAS <1.6 based on a formula developed to convert DAS to DAS28 (van Riel & van Gestel, 2000), and therefore DAS28<2.6 has been used to define remission in RA. In the study of Fransen et al. (Fransen et al., 2004) DAS28< 2.6 corresponded with fulfillment of the modified ACR remission criteria. DAS28-CRP remission was used as the outcome measure in one RCT (Genovese et al., 2008).
4.3.3. Remission criteria based on simplified disease activity indices

Aletaha et al. (Aletaha & Smolen, 2005) analyzed ratings of RA patients by expert rheumatologists for disease activity to define a cutoff point for SDAI and CDAI remissions. The cutoff points for remission for SDAI and CDAI were defined as 3.3 and 2.8, respectively.

4.3.4. Radiographic remission

Radiographic imaging may be regarded as the 'gold standard' for assessing disease progression in RA (van der Heijde, 2000). The Food and Drug Administration (FDA) has formulated the most rigorous definition of remission: ACR remission criteria must be met in addition to radiological arrest of joint damage progression (Sharp/van der Heijde or Larsen method). These criteria include a time period requirement of six months (Sesin & Bingham, 2005; van der Helm-van Mil AHM, 2006).

Jäntti et al. (Jäntti et al., 2001) assessed radiographs of hands and feet over 20 years according to the Larsen score (scale 1–100). If the score did not increase more than one point compared to radiographs taken 5–19 years earlier, the patient was considered to be in radiographic remission; the radiographic remission rate was 26% at 20 years.

4.4. Minimal disease activity for RA (MDA)

The need for a definition of MDA for patients with RA originated from the observation that achieving and maintaining low disease activity is
probably more important in the long term than the high percentage improvement from very high disease activity level which was documented in many RCTs. Furthermore, strict remission is not a common feature in clinical practice. The threshold for MDA is between moderate disease activity and remission and according to the definition anyone in remission will also be in MDA (Wells et al., 2005).

All patients with no swollen joints, no tender joints and ESR ≤ 10 mm/h are in MDA. Besides, MDA has two different definitions: the core set definition (Figure 2) and DAS28 definition (Figure 3). The DAS28 defines that patients are in MDA when DAS28 ≤ 2.85. According to the core set definition five of seven of the following criteria have to be fulfilled: 1) pain (0-10) ≤ 2; 2) swollen joint count (0-28) ≤ 1; 3) tender joint count (0-28) ≤ 1; 4) Health Assessment Questionnaire (HAQ 0-3) ≤ 0.5; 5) physician global assessment of disease activity (0-10) ≤ 1.5; 6) patient global assessment of disease activity (0-10) ≤ 2; 7) ESR ≤ 20 (Wells et al., 2005).
Figure 2. The core set definition for minimal disease activity for RA. Pain ≤ 2; swollen joint count (SJC) ≤ 1; tender joint count (TJC) ≤ 1; Health Assessment Questionnaire (HAQ) ≤ 0.5; physician global assessment ≤ 1.5; patient global assessment ≤ 2; ESR ≤ 20 mm/h.
Figure 3. The DAS based definition for minimal disease activity for RA. SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; DAS: disease activity score
4.5. Remission rates in selected clinical cohorts and randomized clinical trials

ACR remission criteria have been used in randomized clinical trials concerning traditional DMARDs, with remission rates of 7% to 37% (Wolfe & Hawley, 1985; Möttönen et al., 1999; Ferraccioli et al., 2002; Gerards et al., 2003; Korpela et al., 2004), and in clinical cohorts with remission rates of 0% to 32% (Suarez-Almazor et al., 1994; Möttönen et al., 1996; Eberhardt & Fex, 1998; Young et al., 2000; Lindqvist et al., 2002; Khanna et al., 2007). The ACR remission criteria have not been used in RCTs of biological agents.

The FIN-RACo trial used a rigorous modification of the ACR remission criteria, requiring all five criteria (fatigue excluded) to be met. Nonetheless, after two years, 37% of the patients who received therapy with a combination of methotrexate, sulfasalazine, hydroxychloroquine and prednisolone were in remission (Möttönen et al., 1999).

DAS28 remission levels from 15% to 53% (St Clair et al., 2004; Breedveld et al., 2006; van der Heijde et al., 2006; van Riel et al., 2006; Mancarella et al., 2007) were found in several clinical trials using biological agents, and were highest in patients treated with a combination of methotrexate and a biological agent (infliximab, etanercept or adalimumab). In the PREMIER study (Breedveld et al., 2006), the remission rate at two years was 25% when adalimumab was used alone and 49% when it was used in combination with methotrexate. In the TEMPO trial (van der Heijde et al., 2006) remission rates were 29.6% (etanercept as a single agent) and 53.7% (etanercept in combination with methotrexate). The remission rate was 31% at one year in the
study of St Clair et al. (St Clair et al., 2004) in RA patients who were treated with a combination of methotrexate and infliximab (dose 6 mg/kg). In the abatacept study, patients with inadequate response to anti-TNF therapy were treated with abatacept for two years. Remission was assessed according to (DAS28-CRP< 2.6) with remission rates at six months and two years of 11% and 20%, respectively (Genovese et al., 2008).

Mierau et al. (Mierau et al., 2007) studied sustained remission in RA patients. Sustainability of remission was defined as remission at two consecutive visits. Four different definitions were used: modified ACR remission (four of the five items had to be met, fatigue excluded), DAS28 remission, and SDAI and CDAI remission. The proportion of patients in remission at any one of the two visits was highest for DAS28 (43%), followed by modified ACR remission (39%) and SDAI and CDAI remission (34% each). Sustained remission was observed in much lower proportions of patients (between 17 and 20 depending on the instrument.). Van der Heijde et al. (van der Heijde et al., 2005) studied sustainability of DAS and DAS28 remissions and ACR70 response in the TEMPO trial, which compared the efficacy of combined MTX and etanercept therapy to the efficacy of these drugs as monotherapies in patients with advanced RA. Remission was assessed at four-week intervals or less frequently over one year. Patients treated with combination therapy scored better than those treated with either of the monotherapies with respect to the number of remission periods and sustainability of remissions.
5. AIMS OF THE STUDY

The purposes of the present study were to examine the methods used to assess disease activity and remission in RA, and to develop a new continuous index for the measurement of disease activity in RA.

More precisely, the study set out to answer the following questions:

1) What is the frequency of remission at five years after diagnosis when three sets of criteria are used in patients with RA in an inception cohort?

2) Is remission more often sustained in RA patients treated with a combination of traditional DMARDs and prednisolone compared to patients treated with a single DMARD with or without prednisolone? Does sustained remission protect against radiographic progression?

3) Is DAS28 an appropriate tool to assess remission in patients with RA?

4) What is the influence of components of DAS28 (tender joint count, swollen joint count, patient’s general health and erythrocyte sedimentation rate) on the total DAS28 score? Does overlapping occur in the four individual components in RA patients with low, moderate or high disease activity?

The final study aim was:

5) To develop a new disease activity index for RA based on the American College of Rheumatology Core set of disease activity measures.
6. PATIENTS AND METHODS

6.1. Selection of patients and study design

Two different patient populations were chosen for this study: patients from a clinical cohort and patients from an RCT comparing two different treatment strategies.

6.1.1. The clinical cohort patients

Jyväskylä Central Hospital is the only rheumatology center in the Central Finland District; it served a population of 270,000/ year in 2007 (250 000/ year in 1997). All new RA patients in this area are referred to the hospital for diagnosis and initiation of treatments. All new inflammatory arthritis patients older than 16 years who did not meet criteria or show clinical signs of other specific arthritides (crystal deposit disease and spondylarthropathies) were included in the RA 1997 inception cohort. A total of 127 patients were included in the study. These patients received rheumatology care at Jyväskylä Central Hospital for two years after the diagnosis by a multidisciplinary team, and were subsequently invited to participate in a five-year study. Later, 110 patients whose diagnosis was made in 1998 were also included in the study cohort. At this stage a subgroup of patients (161 of 237 patients with clinical diagnosis of early RA) who cumulatively fulfilled the ARA criteria for RA was analyzed. Disease-modifying anti rheumatic drugs (DMARDs) were started at the time of the diagnosis. The target of therapy was clinical remission.
Measures at baseline and at two and five years included: 68 tender and 66 swollen joint counts (Felson et al., 1993); laboratory tests including ESR, CRP, and RF; self-report pain and global health on 100 mm VAS, functional capacity according to the HAQ, morning stiffness in minutes on self-report; and radiographs of the hands and feet. Wrists, I-V metacarpophalangeal (MCP) joints, I-V metatarsophalangeal (MTP) joints and interphalangeal (IP) joints of the big toes were assessed according to the Larsen score (Larsen et al., 1977; Kaarela & Kautiainen, 1997). Medications were recorded at each visit. The date of initiation and discontinuation of each DMARD was recorded.

6.1.2. The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) patients

In the FIN-RACo study (Möttönen et al., 1999) 195 patients with recent onset RA were randomized to receive either DMARD combination therapy (COMBI) or DMARD monotherapy (SINGLE). Patients with previous DMARD therapy or those who had taken glucocorticoid therapy within two weeks prior to enrollment were excluded. The inclusion criteria were: age between 18 and 65 years, duration of symptoms less than two years, active disease with ≥ three swollen joints, and at least three of the following: ESR ≥28 mm/h or CRP >19mg/L, morning stiffness ≥ 29 min, > five swollen joints, and >10 tender joints. All patients had to fulfill the ARA criteria for rheumatoid arthritis (Arnett et al., 1988; Möttönen et al., 1999).
The goal of treatment was remission in both groups. In the COMBI group, the initial DMARDs were sulfasalazine (SSZ) 500 mg twice daily, methotrexate (MTX) 7.5 mg/week, and hydroxychloroquine (HCQ) 300 mg daily. Prednisolone 5 mg daily was instituted simultaneously with the DMARDs. Drug doses were adjusted if a patient did not improve by 50% or more in two of the three criteria: number of swollen joints, number of tender joints, and ESR or CRP. The highest doses allowed were SSZ 2 g/day, MTX 15 mg/week, HCQ 300 mg/day, and prednisolone 10 mg/day. SSZ or HCQ could be replaced by auranofin (3-6 mg/day) and MTX by azathioprine (2 mg/kg/day) if the former drugs were discontinued either for inefficacy or adverse effects.

In the SINGLE arm the treatment was performed according to the “sawtooth” strategy (Fries, 1990; Sokka & Hannonen, 1999) with remission as the target. The first DMARD was SSZ 2 g/day and the dose could be increased up to 3 g/day. Simultaneous oral prednisolone treatment was not mandatory, but it was allowed up to 10 mg/day at the discretion of the treating rheumatologist. SSZ could be replaced by MTX (or other single DMARD) in the case of an adverse event or lack of efficacy.

Intraarticular glucocorticoid injections were allowed according to the judgment of the attending physician in all patients (Möttönen et al., 1999).

Patients were evaluated at baseline, and at six, 12 and 24 months. Clinical assessments included tender joint count (68 joints) and swollen joint count (66 joints), duration of morning stiffness in minutes, physician’s and
patient's overall assessments and pain on VAS (0-100 mm), physical function on patient self report (HAQ), ESR and CRP.

Radiographs of hands and feet were taken at baseline, and at six and 24 months. Radiographs of 163 patients were available at baseline. Radiographs were assessed blinded to the clinical data, and were scored according to the Larsen method (0-200) (Larsen et al., 1977), including I-V MCP and I-V PIP joints of both hands, II-V MTP joints, IP joints of big toes, and wrists (multiplied by five), with a total score of 200.

6.1.3. Definitions of remission

We used four separate sets of criteria to define remission, as shown in Table 9. The ACR remission criteria require: 1) no joint or tendon sheet swelling, 2) no joint tenderness, 3) normal ESR, 4) morning stiffness ≤ 15 minutes, and 5) no joint pain by history (we used VAS ≤10 mm on a scale of 1-100 mm) (Sokka & Pincus, 2003b). The requirement of fatigue was excluded, but the five criteria above had to be fulfilled. Clinical remission was defined as: 1) no tender and 2) no swollen joints, and 3) normal ESR. Radiographic remission was defined as: 1) no worsening of erosions, and 2) no new erosions from baseline to five years. DAS28 remission was defined as DAS28< 2.6.
6.1.4. Definition of sustained remission

Sustained remission indicates remission at six, 12, and 24 months. Sustainability of remission was expressed as the percentage of patients in sustained remission at each visit.
Table 9. Remission criteria used in this study

<table>
<thead>
<tr>
<th>Remission criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified ACR remission criteria</strong> (criteria 1 to 5 must be fulfilled)</td>
</tr>
<tr>
<td>1. No joint swelling or soft tissue swelling of tendon sheets</td>
</tr>
<tr>
<td>2. No joint tenderness or pain on motion</td>
</tr>
<tr>
<td>3. Normal ESR of $&lt; 30$ in women and $&lt; 20$ in men</td>
</tr>
<tr>
<td>4. Morning stiffness of 15 minutes or less</td>
</tr>
<tr>
<td>5. Absence of joint pain by history interpreted as pain VAS score $\leq 10$ on a scale of 1-100</td>
</tr>
<tr>
<td>(6. Absence of fatigue)</td>
</tr>
<tr>
<td><strong>DAS28 remission</strong></td>
</tr>
<tr>
<td>DAS28 $&lt; 2.6$</td>
</tr>
<tr>
<td><strong>Clinical remission</strong></td>
</tr>
<tr>
<td>1. No joint swelling</td>
</tr>
<tr>
<td>2. No joint tenderness or pain on motion</td>
</tr>
<tr>
<td>3. Normal ESR</td>
</tr>
<tr>
<td><strong>Radiographic remission</strong></td>
</tr>
<tr>
<td>1. No worsening of erosions</td>
</tr>
<tr>
<td>2. No new erosions from baseline to five years</td>
</tr>
</tbody>
</table>
6.1.5. Definitions of disease activity indices and overlapping (distribution of values of individual variables between defined disease activity states)

6.1.5.1. DAS28

DAS28 was calculated with the formula $0.56 \times \sqrt{\text{tender joints 28}} + 0.28 \times \sqrt{\text{swollen joints 28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}$ (van Gestel et al., 1996).

Disease activity was graded as follows: low disease activity DAS28 $\leq 3.2$, moderate disease activity DAS28 $> 3.2$ and $\leq 5.1$, and high disease activity DAS28 $> 5.1$ (van Gestel et al., 1999).

6.1.5.2 Effects of the individual components of DAS28 on the total DAS28 score ('theoretical model')

Using a ‘theoretical model’ the effects of the individual components of DAS28 (TJC, SJC, ESR, and GH) were calculated according to the DAS28 formula. In the model it was presumed that the other three components remained at 0 (ESR 1) while the value of the component studied varied from 0 (ESR 1) to its clinically relevant maximum. The effect of TJC was calculated as follows: $0.56 \times \sqrt{\text{range from 0 to 28}} + 0.28 \times \sqrt{0} + 0.70 \times \ln 1 + 0.014 \times 0$; the effect was calculated similarly for the other three components.

6.1.5.3. Definition of overlapping

Overlapping was calculated as follows. The higher limit for overlapping was defined as the highest SJC (on a 66 joint count) in the low
disease activity group, and the lower limit as the lowest SJC in the high disease activity group; the percentage of patients who fell between these limits represents overlapping in SJC. Overlapping was calculated similarly for TJC (on a 68 joint count), ESR and GH.

6.1.6. The Mean Overall Index for RA (MOI-RA)

The MOI-RA is the mean of standardized values of tender and swollen joint counts (28, 42 or 66/68 joint counts), patient’s (GH) and physician’s (GL) assessments of global health, and patient’s assessment of pain on VAS (0-100 mm), the HAQ (0-3), and ESR (1-100). In ESR, all values above 100 are replaced by 100. Standardization means that the effect of an individual component on the total score is equal: the HAQ value (range 0-3) is divided by its maximum, which is 3, and multiplied by 100. Similar calculations are performed with the other components: they are standardized to range from 0 to 100. The mean of the standardized values is calculated. The range of MOI-RA is 0-100; higher values indicate poorer outcomes. If values of 1-3 components of MOI-RA are missing, standardized values are calculated from the available component values and the mean of the standardized values is recorded.
7. STATISTICAL ANALYSIS

The results were presented as mean and median, standard deviation (SD) or interquartile range (IQR), percentages and 95% confidence intervals (CI).

7.1. Statistical analysis (Study I)

The agreement of the remission criteria was tested using the Jaccard test, which calculates the proportion of positive observations in both variables (the ACR and clinical remission criteria) over positive observations in either variable (the ACR or clinical remission criteria). Cochran's Q was used to test the equality of the remission proportions in the three dichotomous remission criteria variables.

7.2. Statistical analysis (Study II)

The sustainability of treatment response was analyzed by applying generalized estimating equation (GEE) models with an exchangeable correlation structure. Odds ratios with confidence intervals were based on the GEE models with baseline disease activity on DAS28 as a covariate.

The median change in the Larsen score from baseline to two years is presented with Hodges-Lehmann estimates (Hollander & Wolfe, 1999). Permutation type analysis of covariance with baseline radiographic scores as covariates was applied to compare radiographic progression between the groups concerning remission.
7.3. Statistical analysis (Study III)

Receiver operating characteristic (ROC) curves were constructed to determine the cutoff point of DAS28 with the highest possible sensitivity and specificity corresponding to the ACR remission criteria and clinical remission criteria. The 95% confidence intervals for the areas under ROC were obtained by bias corrected and accelerated bootstrapping.

Sensitivity, specificity, positive predictive value, likelihood ratio, and their 95% CI values were calculated for each of the remission criteria.

7.4. Descriptive statistics (Study V)

Distributions of MOI-RA and DAS28 were represented as skewness and kurtosis. The coefficient of variation was calculated for both indices using the formula: (SD/mean value of index at baseline) x 100. Confidence intervals (95% CI) were obtained from bias corrected bootstrapping (5000 replications).

Assumptions of normality in the baseline index values were evaluated by the Kolmokorov-Smirnov test with Monte Carlo p-values. The internal consistency between components of MOI-RA was estimated by calculating Cronbach’s alpha, and the reproducibility of MOI-RA by calculating the intra class correlation coefficient (ICC).
7.5. Criterion validity (Study V)

MOI-RA was compared both with ACR response criteria and DAS28. The mean change in MOI-RA from baseline to six months was calculated in patients 1) who did not meet ACR20 response criteria, and 2) in patients who met ACR20 but not ACR50 response, 3) ACR50 but not remission, and 3) in patients who met ACR remission criteria. Possible relationships between MOI-RA and different ACR response classes were studied using analyses of covariance (ANCOVA). Agreement between MOI-RA and DAS28 was tested using Pearson’s correlation coefficient.

7.6. Responsiveness (Study V)

Responsiveness was calculated as the standardized response mean (SRM) and effect size (ES). SRM was defined as the mean change of the score from baseline divided by the standard deviation (SD) of this change (Liang et al., 1985). ES was defined as the mean change from baseline divided by the SD of the baseline score (Kazis et al., 1989). Confidence intervals of ES and SRM values were obtained by bias corrected bootstrapping (5000 replications).

7.7. Sensitivity to change (Study V)

The sensitivity to change of the MOI-RA index was analyzed in the FIN-RACo patient population from baseline to six months, and compared to DAS28. To be able to include all information on the patient population at all time
points (baseline, six and 12 months) repeated measures analyses were performed using generalized linear mixed models.

8. RESULTS

8.1. The clinical cohort and the FIN-RACo trial patients

The clinical cohort included 127 early RA patients diagnosed at Jyväskylä Central Hospital in 1997; 111 of these patients attended the five-year control visit (Study I). A further 110 patients diagnosed in 1998 were also included in the clinical cohort. A total of 196 patients diagnosed in 1997-1998 (237 patients at baseline) attended the five-year visit and 161 of those diagnosed in 1997-1998 cumulatively fulfilled the ACR criteria for RA and were included in the analysis (Study III). Patients were actively treated with DMARDs and the goal of treatment was remission. DMARD therapy was started from the diagnosis.

Patients from a RCT were also analyzed: the original FIN-RACo study included 195 patients: 97 were in the COMBI arm and 98 in the SINGLE arm. The mean age of all patients was 47 years, 62% were female, 70% were rheumatoid factor positive, and 48% of the patients had erosions in hand and/or feet radiographs at baseline. The present analyses include 169 patients with complete data (79 COMBI, 90 SINGLE) who were assessed for remission and good treatment response at six, 12 and 24 months (Table 10)(Study II, IV and V).
Table 10. Comparison of demographic variables and disease characteristics of all patients at baseline in the FIN-RACo trial and patients included in this analysis

<table>
<thead>
<tr>
<th></th>
<th>All 195 patients</th>
<th>169 patients analyzed for sustained remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>COMBI patients</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>47 (10)</td>
<td>47 (10)</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>121 (62%)</td>
<td>106 (63%)</td>
</tr>
<tr>
<td>Patients with positive rheumatoid factor (%)</td>
<td>136 (70%)</td>
<td>120 (71%)</td>
</tr>
<tr>
<td>Patients with erosions (%)</td>
<td>94 (48%)</td>
<td>83 (49%)</td>
</tr>
<tr>
<td>Duration of symptoms before diagnosis, months, median (IQR)</td>
<td>6 (4, 10)</td>
<td>6 (4, 10)</td>
</tr>
<tr>
<td>Tender joints, median (IQR)</td>
<td>17 (13, 25)</td>
<td>17 (13, 24)</td>
</tr>
<tr>
<td>Swollen joints, median (IQR)</td>
<td>13 (9, 16)</td>
<td>13 (9, 16)</td>
</tr>
<tr>
<td>Patient global assessment, median (IQR)</td>
<td>48 (31, 64)</td>
<td>47 (29, 61)</td>
</tr>
<tr>
<td>Physician global assessment DAS28, mean (SD)</td>
<td>44 (31, 59)</td>
<td>42 (31, 59)</td>
</tr>
<tr>
<td></td>
<td>5.6 (1.0)</td>
<td>5.6 (1.0)</td>
</tr>
</tbody>
</table>
8.2. Remission in RA

In the clinical cohort 19 [17% (95% CI 11% to 25%)] of the 111 examined patients diagnosed in 1997 as having RA met the ACR remission criteria, 41 patients [37% (95% CI 28% to 47%)] met the clinical remission criteria (no tender, no swollen joints and normal ESR), and 61 patients [55% (95% CI 49% to 68%)] met the radiographic remission criteria (no worsening of erosions and no new erosions from baseline to five years). Only 13 [12% (95% CI 6% to 19%)] patients met all three sets of remission criteria and 74 [67% (95% CI 57% to 75%)] met at least one of the criteria (Figure 4)(Study I).

The similarity between the criteria was 0.46 (95% CI 0.31 to 0.29) for the ACR versus clinical remission, 0.19 (95% CI 0.10 to 0.29) for the ACR versus radiographic remission, and 0.38 (95% CI 0.27 to 0.49) for clinical versus radiographic remission criteria. The rate of remission was statistically different between the three sets of remission criteria according to Cochran’s Q (p < 0.001)(Study I).
When the RA patients diagnosed in 1997 and 1998 were included, at five years 19 (12% [95% CI 7% to 18%]) of the 161 examined RA patients met the ACR remission criteria, including 106 (66%) with no swollen joints, 69 (43%) with no tender joints, 119 (74%) with normal ESR, 65 (40%) with morning stiffness ≤15 minutes, and 32 (20%) patients with no pain (Table 11). A total of 55 patients [34% CI 27% to 42%] met the simple set of clinical remission criteria at five years (Study III).

The positive predictive value for the ACR remission criteria was lowest for normal ESR (16%), and highest for no history of joint pain (56%). Similarly, the likelihood ratio was lowest for normal ESR (1.40) and highest for no joint pain (10.0). According to the less rigorous ACR remission criteria (four of the five ACR remission criteria had to be fulfilled and fatigue was excluded),
40 [25% (95% CI 19% to 33%)] of the patients were in remission at five years (Table 11) (Study III).
Table 11. Patients fulfilling each ARA remission criterion and the positive predictive value and likelihood ratio of each criterion

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Criteria present</th>
<th>ACR remission</th>
<th>Clinical remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Sensitivity</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td>No swollen joints</td>
<td>106 (66)</td>
<td>100</td>
<td>39 (31 to 47)</td>
</tr>
<tr>
<td>No tender joints</td>
<td>69 (43)</td>
<td>100</td>
<td>65 (56 to 73)</td>
</tr>
<tr>
<td>No pain</td>
<td>32 (20)</td>
<td>100</td>
<td>90 (84 to 94)</td>
</tr>
<tr>
<td>Normal ESR</td>
<td>119 (74)</td>
<td>100</td>
<td>29 (21 to 37)</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>65 (40)</td>
<td>100</td>
<td>65 (57 to 73)</td>
</tr>
</tbody>
</table>

* Likelihood ratio positive (ratio of the sensitivity of a test to the false positive error rate of the test) ¹ Positive predictive value (proportion of the subjects with positive test results who were in remission) ² Pain VAS ≤ 10 mm ³ Duration of morning stiffness 15 minutes
In the clinical cohort, only 23 patients [21 % (95% CI 14% to 29%)] were in clinical remission both at two and five years (Study I). In the FIN-RACo trial, 20 (25%) of the COMBI patients were in ACR remission at six months, of whom 13 and 11 patients were also in remission at 12 and 24 months, respectively. The corresponding figures were 11 (12%), three and three for the SINGLE patients. Thus, remission was sustained in 11 [14% (95% CI 7% to 23%)] COMBI and three [3% (95% CI 1% to 9%)] SINGLE patients (p=0.013) (Figure 4). The odds ratio for COMBI vs. SINGLE patients to be in sustained ACR remission was 4.61 (95% CI 1.17 to 16.99), adjusted for baseline DAS28 values (Study II).

The sustainability of DAS28 remission was analyzed in the FIN-RACo trial patients: a total of 40 [51% (95% CI 39% to 62%)] COMBI and 14 [16% (95% CI 10% to 24%)] SINGLE patients (p<0.001) met sustained DAS28 remission (Figure 5)(Study II).
Figure 5. Percentage of patients in sustained ACR remission and DAS28 remission in COMBI and SINGLE therapy groups in the FIN-RACo trial

Sustainability of remission and good treatment response and their influence on radiographic progression is presented in Table 12.
Table 12. Radiographic progression and sustainability of remission and good treatment response in the 163 patients of the FIN-RACo trial with radiographs over two years.

<table>
<thead>
<tr>
<th>Improvement criteria</th>
<th>Number of patient</th>
<th>Baseline Larsen median (IQR)</th>
<th>Change in Larsen score from 0 to 24 months median (95%CI)</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR remission</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>No remission at six months</td>
<td>132</td>
<td>2 (0, 6)</td>
<td>4 (2 to 8)</td>
<td></td>
</tr>
<tr>
<td>Remission at six months, no sustained remission</td>
<td>17</td>
<td>2 (0, 8)</td>
<td>4 (0 to 10)</td>
<td></td>
</tr>
<tr>
<td>Sustained remission†</td>
<td>14</td>
<td>0 (0, 3)</td>
<td>0 (0 to 2)</td>
<td></td>
</tr>
<tr>
<td><strong>DAS28 remission</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No remission at six months</td>
<td>82</td>
<td>0 (0, 4)</td>
<td>6 (2 to 10)</td>
<td></td>
</tr>
<tr>
<td>Remission at six months, no sustained remission</td>
<td>30</td>
<td>2 (0, 10)</td>
<td>4 (2 to 16)</td>
<td></td>
</tr>
<tr>
<td>Sustained remission†</td>
<td>51</td>
<td>2 (0, 6)</td>
<td>1 (0 to 2)</td>
<td></td>
</tr>
<tr>
<td><strong>DAS28 good treatment response</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No good treatment response at six months</td>
<td>62</td>
<td>0 (0, 4)</td>
<td>6 (2 to 10)</td>
<td></td>
</tr>
<tr>
<td>Good treatment response at six months; no sustained good response</td>
<td>28</td>
<td>4 (0, 9)</td>
<td>10 (4 to 16)</td>
<td></td>
</tr>
<tr>
<td>Sustained good treatment response*</td>
<td>73</td>
<td>0 (0, 5)</td>
<td>1 (0 to 6)</td>
<td></td>
</tr>
</tbody>
</table>

† Remission at six, 12 and 24 months. ‡ Hodges-Lehman estimates of median difference. * Permutation-type analysis of covariance. Baseline values are used as covariates. * Good treatment response at six, 12 and 24 months.
The ROC curves of DAS28 were used to define the presence or absence of remission in the clinical cohort using the modified ACR criteria and the clinical remission criteria (Figure 6). The area under ROC was 0.87 (95% CI 0.82 to 0.93) for the ACR remission criteria, 0.90 (95% CI 0.84 to 0.94) for the clinical remission criteria and 0.89 (95% CI 0.83 to 0.94) for the less rigorous ACR remission criteria (Study III).

The cutoff value for DAS28 was 2.32 (sensitivity 100%, specificity 73%) for the modified ACR remission criteria, 2.60 (sensitivity 93%, specificity 76%) for the less rigorous set of the ACR remission criteria, and 2.68 (sensitivity 91%, specificity 79%) for the clinical remission criteria (Study III).
Table 13. The estimated cutoff points of DAS28 corresponding to the ACR and the clinical remission criteria

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Remission criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACR* (95% CI)</td>
</tr>
<tr>
<td>Cut-off point</td>
<td>2.32</td>
</tr>
<tr>
<td>Area under ROC†</td>
<td>0.87 (0.82 to 0.93)</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>100 (82 to 100)</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>73 (64 to 80)</td>
</tr>
<tr>
<td>PPV‡, %</td>
<td>33 (21 to 46)</td>
</tr>
<tr>
<td>LR*, %</td>
<td>3.64 (2.66 to 4.71)</td>
</tr>
</tbody>
</table>

*ACR remission criteria, all five criteria must be fulfilled (fatigue excluded)
‡ACR remission criteria, four of the five criteria must be fulfilled (fatigue excluded)
† Area under the ROC curves with 95% confidence interval obtained by bias corrected and accelerated bootstrapping (5000 replications).
‡ Positive predictive value (proportion of the subjects with positive test results who were in remission).
* Likelihood Ratio Positive (ratio of the sensitivity of a test to its false-positive error rate).
Of the 57 patients who had DAS28<2.32, five (9%) had tender joints, four (7%) had swollen joints, and two (4%) had both tender and swollen joints on the 28 joint count. On the 66 joint count the corresponding figures were 11 (19%), six (11%) and four (7%) (Table 15). If we had used the previously
proposed cutoff point of 2.6 as the limit of DAS28 remission in our cohort, a higher proportion of our patients [66 (41%) patients] would have been included in the remission group. Of these 66 patients, 15 (23%) had tender and six (9%) swollen joints, and four (6%) had both tender and swollen joints (66 joint count) (Table 15)(Study III).
Table 15. Cutoff values of DAS28 and number of patients not fulfilling each individual ACR remission criterion.

<table>
<thead>
<tr>
<th></th>
<th>1) DAS28 &lt;2.32</th>
<th>2) DAS28 &lt;2.6</th>
<th>3) DAS28 &lt;2.68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n</td>
<td>57</td>
<td>66</td>
<td>72</td>
</tr>
<tr>
<td>Patients with tender joints n (%) 28 joint count</td>
<td>5 (9%)</td>
<td>6 (9%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Patients with swollen joints n (%) 28 joint count</td>
<td>4 (7%)</td>
<td>5 (8%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Patients with tender and swollen joints n (%) 28 joint count</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Patients with elevated ESR n (%)</td>
<td>2 (4%)</td>
<td>3 (5%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Patients with morning stiffness n (%)</td>
<td>23 (40%)</td>
<td>25 (38%)</td>
<td>27 (38%)</td>
</tr>
<tr>
<td>Patients with joint pain n (%)</td>
<td>33 (58%)</td>
<td>38 (58%)</td>
<td>44 (61%)</td>
</tr>
</tbody>
</table>

1) The cutoff point corresponding to the ACR remission criteria in this study (all the five ACR remission must be fulfilled and fatigue excluded)
2) The generally accepted cutoff point of DAS28 in remission and the cutoff point of ACR remission in this study when modified ACR criteria are used (four of the five ACR remission criteria must be fulfilled and fatigue excluded)
3) The cutoff point corresponding to the clinical remission criteria defined as no tender or swollen joints and normal ESR
8.3. DAS28 and MOI-RA in early RA

In the FIN-RACo trial, the mean value of the DAS28 was 2.78 at six months. The relative contribution of the mean values of the component variables to the total DAS28 score according to the DAS28 formula was as follows: 1) the mean of \((0.56 \times \sqrt{TJC})\) was 0.71 while the median TJC was 2 (range 0-24), 2) the mean of \((0.28 \times \sqrt{SJC})\) was 0.23 while the median SJC was 0 (range 0-20), 3) the mean of \([0.70 \times \ln(ESR)]\) was 1.56 while the median ESR was 10 (range 1-65), and 4) the mean of \((0.014 \times GH)\) was 0.28 while the median GH was 15 (range 0-77). Thus the sum of 1 to 4 (0.71+0.23+1.56+0.28) was 2.78 (total DAS28 score). Therefore, in this patient population ESR had the greatest effect on the DAS28 score with 56% of the total DAS28 score, followed by TJC (26%), GH (10%), and SJC (8%)(Study IV).

In the ‘theoretical model’, TJC (28 joint count) shows the greatest effect on the total DAS28 score: when TJC rises from zero to 28, DAS28 increases from zero to 2.94, provided that the other components remain at zero (ESR 1). Accordingly, ESR has the second largest effect on DAS28: when ESR rises from zero to 20, DAS28 goes from zero to 2.1. Further, when ESR rises to 100 DAS28 increases to 3.22. ESR exceeds the effects of all the other components when its value is above 70. SJC has the third most powerful effect on DAS28 followed by GH, the similarly calculated values of DAS28 being 1.5 and 1.42, respectively (Figure 7)(Study IV).
Figure 7. Effect of each component of DAS28 in the 'theoretical model': tender joint count, swollen joint count, erythrocyte sedimentation rate (ESR), and patient’s general health on DAS28 presuming that the remaining three components are at zero (ESR 1).
Of the 169 FIN-RACo patients, 107 (63%) had DAS28 ≤ 3.2 (low disease activity), 51 (30%) had DAS28 > 3.2 and ≤ 5.1 (moderate disease activity), and 11 (7%) had DAS28 > 5.1 (high disease activity) at six months. In the high disease activity group the lowest SJC on a 66 joint count was 1 while the highest SJC in the low disease activity group was 11. In the low disease activity group 42 patients and in the moderate and high disease activity groups 43 and seven patients, respectively, had a SJC from 1 to 11. In the whole patient population, 92 of the 169 patients had a SJC between those limits, so the overlapping rate was 92/169 (54%). The similarly calculated overlapping rates regarding GH, TJC (68 joint count) and ESR were 49%, 45% and 31%, respectively (Figure 8 and Figure 9)(Study IV).
Figure 8. Overlapping in the number of swollen and tender joints on a 66/68 joint count in RA patients with low (DAS28≤ 3.2), moderate (DAS28> 3.2 and DAS28≤ 5.1) and high disease activity (DAS28> 5.1) according to DAS28. Each circle represents one patient of the FIN-RACo trial.

Figure 9. Overlapping in the erythrocyte sedimentation rate and patient’s general health in RA patients with low (DAS28≤ 3.2), moderate (DAS28> 3.2 and ≤ 5.1) and high disease activity (DAS28> 5.1) according to DAS28. Each circle represents one patient of the FIN-RACo trial.
MOI-RA was examined in the FIN-RACo study. The mean MOI-RA28 decreased from 38.5 to 13.3 from baseline to six months, compared to a decrease of DAS28 from 5.55 to 2.77. Descriptive statistics and the internal consistency of MOI-RA are presented in Table 17. Coefficients of variation were higher in MOI-RA than DAS28. Assumptions of normal distribution were satisfied: DAS28 (p= 0.81), MOI-RA28 (p=0.71), MOI-RA42 (p= 0.64) and MOI-RA66/68 (p=0.66). The reproducibility between MOI-RA indices with different joint counts was 0.97 (95%CI 0.88 to 0.99)(Study V).
Table 17. Distributions and internal consistency of MOI-RA and DAS28 at baseline

<table>
<thead>
<tr>
<th></th>
<th>DAS28</th>
<th>MOI-RA28</th>
<th>MOI-RA42</th>
<th>MOI-RA66/68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>5.55 (0.98)</td>
<td>38.5 (13.6)</td>
<td>39.2 (13.3)</td>
<td>35.6 (12.8)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.53 (4.90, 6.17)</td>
<td>38.8 (28.7, 46.8)</td>
<td>38.6 (28.3, 47.1)</td>
<td>35.5 (26.5, 42.7)</td>
</tr>
<tr>
<td>Range</td>
<td>3.03-8.03</td>
<td>13.2-73.3</td>
<td>16.1-72.2</td>
<td>13.8-71.6</td>
</tr>
<tr>
<td>Coefficient of variation*, % (95%CI)</td>
<td>18 (16 to 20)</td>
<td>35 (32 to 39)</td>
<td>34 (31 to 37)</td>
<td>36 (32 to 39)</td>
</tr>
<tr>
<td>Skewness (95% CI)</td>
<td>0.12 (-0.17 to 0.37)</td>
<td>0.40 (0.18 to 0.64)</td>
<td>0.41 (0.21 to 0.67)</td>
<td>0.45 (0.23 to 0.69)</td>
</tr>
<tr>
<td>Kurtosis (95% CI)</td>
<td>2.9 (2.5-3.4)</td>
<td>2.8 (2.4 to 3.4)</td>
<td>2.7 (2.3 to 3.2)</td>
<td>2.8 (2.4 to 3.4)</td>
</tr>
<tr>
<td>Internal consistency† (95% CI)</td>
<td>0.49 (0.37 to 0.59)</td>
<td>0.78 (0.72 to 0.82)</td>
<td>0.80 (0.75 to 0.84)</td>
<td>0.80 (0.75 to 0.84)</td>
</tr>
</tbody>
</table>

* (SD of the index at baseline/ mean value of the index at baseline) × 100. † Confidence interval obtained from bias corrected bootstrapping (5000 replications). ‡ Internal consistency between components of MOI-RA was estimated by calculating Cronbach’s alpha.
Figure 10 illustrates the mean baseline adjusted change in MOI-RA from baseline to six months in patients who did not meet the ACR20, who met ACR20 but not ACR50, who met ACR50 but not remission, and who met ACR remission criteria. When compared to the ACR response categories (20/50), changes in MOI-RA versions (using 28/42/66 joints) were similar (Figure 10). The correlation between MOI-RA and DAS28 was between 0.84 and 0.90 (Table 18)(Study V).
Table 18. Correlation* between MOI-RA (with joint counts 28, 42 and 66/68) and DAS28

<table>
<thead>
<tr>
<th></th>
<th>DAS28 (95%CI)</th>
<th>MOI-RA 28 (95%CI)</th>
<th>MOI-RA 44 (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOI-RA 28</td>
<td>0.90 (0.86 to 0.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOI-RA 42</td>
<td>0.86 (0.82 to 0.89)</td>
<td>0.99 (0.97 to 1.00)</td>
<td></td>
</tr>
<tr>
<td>MOI-RA 66/68</td>
<td>0.84 (0.79 to 0.87)</td>
<td>0.98 (0.97 to 0.99)</td>
<td>0.99 (0.97 to 1.00)</td>
</tr>
</tbody>
</table>

* Correlation was calculated with Pearson’s coefficient

The mean MOI-RA (SD) values at baseline with 28, 42 and 66/68 joint counts were 38.5 (13.6), 39.2 (13.3), and 35.6 (12.8), respectively, indicating a decrease in the MOI-RA values from baseline to six months of approximately 65%. The mean DAS28 (SD) at baseline was 5.55 (0.98), and a 50% decrease during the same time period was seen (Table 19). The sensitivity to change of MOI-RA and DAS28 is shown in Figure 11; both indices discriminate the two treatment arms significantly. The SRM and ES of both DAS28 and MOI-RA for all joint counts were excellent (Table 19)(Study V).
Table 19. Responsiveness of MOI-RA and DAS28

<table>
<thead>
<tr>
<th>Index</th>
<th>Change from baseline to six months mean (95%CI)</th>
<th>Change from baseline to six months %</th>
<th>SRM*</th>
<th>ES*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>-2.78 (-2.88 to 2.57)</td>
<td>50%</td>
<td>2.0 (1.8 to 2.3)</td>
<td>2.8 (2.5 to 3.2)</td>
</tr>
<tr>
<td>MOI-RA28</td>
<td>-25.2 (-27.3 to -23.1)</td>
<td>65%</td>
<td>1.8 (1.6 to 2.1)</td>
<td>1.9 (1.6 to 2.1)</td>
</tr>
<tr>
<td>MOI-RA42</td>
<td>-25.4 (-27.4 to -23.4)</td>
<td>65%</td>
<td>1.8 (1.7 to 2.1)</td>
<td>1.9 (1.7 to 2.1)</td>
</tr>
<tr>
<td>MOI-RA66/68</td>
<td>-23.1 (-25.0 to -21.2)</td>
<td>64%</td>
<td>1.8 (1.6 to 2.1)</td>
<td>1.8 (1.6 to 2.0)</td>
</tr>
</tbody>
</table>

SRM = standardized response mean, ES = effect size
* Confidence interval obtained by bias corrected bootstrapping (5000 replications)
Figure 11. Decrease of DAS28 and MOI-RA in the monotherapy (SINGLE) and combination therapy (COMBI) arm of the FIN-RACo trial from baseline to 12 months

A simulation in which 15% of the component values of MOI-RA were randomly omitted (0-3 of the seven measures of one patient could be missing) was performed: the ICC was 0.98 (95%CI 0.97 to 0.99) between incomplete and complete data (Study V).
9. DISCUSSION

The contemporary approach to treatment of patient with RA involves aggressive therapy with DMARDs and biologic agents (Möttönen et al., 2002; Grigor et al., 2004; Goekoop-Ruiterman et al., 2005; Sokka et al., 2005). The goals of treatment are to prevent structural damage, functional impairment, work disability, and premature mortality. According to the current guidelines, treatment of RA should be targeted at remission (Emery & Salmon, 1995; Möttönen et al., 1999). However, remission remains an ambitious aim, which may be achieved infrequently in standard clinical care (Wolfe & Hawley, 1985; Listing et al., 2006; Mancarella et al., 2007). In previous studies ACR remission rates in clinical RA cohorts range from 0% to 32% (Suarez-Almazor et al., 1994; Möttönen et al., 1996; Eberhardt & Fex, 1998; Young et al., 2000; Lindqvist et al., 2002; Khanna et al., 2007) and in randomized clinical trials of traditional DMARDs from 7% to 37% (Wolfe & Hawley, 1985; Möttönen et al., 1999; Ferraccioli et al., 2002; Gerards et al., 2003; Korpela et al., 2004).

In the present study, rates of remission were studied in a clinical cohort using three different definitions of remission: the strict ACR remission criteria (fatigue excluded, the other five criteria had to be fulfilled), practical clinical remission (no tender joints, no swollen joints, ESR≤ 10mm/h), and radiographic remission (no worsening of erosions, no new erosions from baseline to five years). Our five-year remission rate of 17% according to the ACR criteria lies within the wide range reported in the literature. As expected, the rate of clinical remission, which includes three ACR remission criteria but
not pain and morning stiffness (or fatigue), was considerably higher compared
to the ACR remission rate. The high percentage (55%) of patients with no
radiographic progression over five years was somewhat surprising, but similar
to results from another cohort in our clinic (Sokka et al., 2004a).

Wolfe et al. (Wolfe & Hawley, 1985) reported that the sensitivity and
specificity of the ACR remission criteria were good. Alarcon et al. (Alarcon et al.,
1987) found the criteria to be highly specific but with low sensitivity in some
patient groups. Nevertheless, fatigue is often excluded when the ACR remission
criteria are used (Suarez-Almazor et al., 1994; Möttönen et al., 1999; Möttönen
et al., 2002). In some studies the criteria are considered to be met if all the other
five items are fulfilled (Suarez-Almazor et al., 1994; Möttönen et al., 1999;
Möttönen et al., 2002), while in other studies only four of the remaining five
items are required for remission (Eberhardt & Fex, 1998; Lindqvist et al., 2002).
Low remission rates are not a surprise since the strict ACR remission criteria
are not fulfilled by the majority of people aged over 50 in the general population
(Sokka et al., 2007c).

All patients fulfilling our definition of clinical remission (no tender
joints, no swollen joints, ESR≤ 10 mm/h) also met the MDA definition (Wells et
al., 2005). The proportions of patients fulfilling this definition in early RF positive
RA patients treated with traditional DMARDs were as follows: 3%, 2% and 3%
at six, 12 and 24 months (Khanna et al., 2007). In another study, adalimumab
was started in active RA patients, and this definition was fulfilled by 13% of
patients at 12 weeks (Burmester et al., 2007). The proportion of these patients
who met the criteria are markedly lower than in our study although differences in the patient populations do not allow direct comparisons between the studies.

One could anticipate that radiographic remission would be the most rigorous of all remission criteria, since information from previous decades shows that radiographic damage starts early and that progression is most rapid during the first years of the disease (Fuchs et al., 1989b; Eberhardt et al., 1990; van der Heijde et al., 1995; Fex et al., 1996; Kaarela & Kautiainen, 1997; Eberhardt & Fex, 1998; Plant et al., 1998; Hulsmans et al., 2000; Jäntti et al., 2002; Lindqvist et al., 2003; Sokka et al., 2004b). In the study of Lindqvist et al. (Lindqvist et al., 2003), almost all (96%) RA patients had erosions at 10 years. In the present study, 42% of the patients remained non-erosive throughout the five-year follow-up period. In two previous early RA cohorts from our clinic, 67% to 86% of patients had erosions within five years (Sokka et al., 2004b).

Remission is our goal; however, we should not be satisfied with transient remission and sustained remission should remain the ultimate target. In the FIN-RACo, patients in sustained remission had less radiographic progression over two years compared to patients who were in remission at six months and lost it later. Less than 50% of our clinical cohort patients who were in clinical remission at two years were also in remission at five years. Molenaar et al. (Molenaar et al., 2004) followed RA patients in remission for two years. Remission persisted in 52% of the patients after two years. The sustainability of DAS and DAS28 remissions was also studied in the TEMPO trial comparing the efficacy of the combination of MTX and etanercept to the efficacy of these drugs
as monotherapies in patients with advanced RA. Remission was assessed frequently over one year. Patients who were treated with the combination therapy managed better than patients who were treated with either of the monotherapies with respect to the number and durability of remission periods (van der Heijde et al., 2005). Accordingly, our analysis of the FIN-RACo study shows that therapy with a combination of traditional DMARDs in patients with clinically active early RA leads to sustained remission more often than DMARD monotherapy. Furthermore, results from the RABBIT (German biologics register) show that biological drugs seem to be superior to conventional DMARDs concerning remissions. The overall success rates, however, remain low and relapses common. Sustained remission rates of 7.7% for DAS28 remission and 4.5% for ACR remission were found in patients receiving biologics during the follow up time of 12 months (Listing et al., 2006).

There is a shift towards less stringent remission criteria, especially in RA RCTs. DAS28 (DAS28< 2.6) remission with higher remission rates has replaced the more strict ACR remission criteria in RCTs investigating the efficacy of biologic agents (Mäkinen et al., 2006). In the present study DAS28<2.32 corresponded to the fulfillment of the modified ACR remission criteria and DAS28<2.68 corresponded to the clinical remission criteria (no tender or swollen joints and normal ESR). We also calculated the cutoff point of DAS28 using a less rigorous set of ACR remission criteria than in previous studies (Balsa et al., 2004; Fransen et al., 2004) and the cutoff point was 2.6 in agreement with the study of Fransen et al. (Fransen et al., 2004). Even a higher
cutoff point of DAS28 2.81 for this set of ACR remission criteria was reported by Balsa et al. (Balsa et al., 2004). DAS28-CRP remission was not examined in this study, and even though DAS28-CRP and DAS28-ESR are well correlated, the threshold values for remission should be reconsidered (Inoue et al., 2007; Matsui et al., 2007a). A DAS28-CRP remission cut-off point of 2.6 has been used in one abatacept study (Genovese et al., 2008).

The preliminary RA remission criteria by Pinals et al. (Pinals et al., 1981) require that five of the six criteria have to be fulfilled. The criteria explicitly accept that patients with either tender or swollen joints can be considered to be in remission, although not if both tender and swollen joints are present. In our study 6% of the patients who were in DAS28 remission (DAS28<2.6) had both tender and swollen joints. In another study, a cutoff point of 2.4 allowed the presence of up to 12 swollen joints (Aletaha et al., 2005b).

It appears that remission and sustained remission can be best achieved by tight disease control, which is facilitated by using disease activity indices. In the TICORA (Tight Control for Rheumatoid Arthritis) (Grigor et al., 2004) study the target of intensive therapy was to achieve DAS<2.4. The intensive strategy was markedly more beneficial than ‘routine care’ with regard to disease activity, radiographic progression, physical function, and quality of life. At 18 months, 65% of patients in the intensive care group were in DAS remission vs. 16% in the routine care group. The BeSt study (Goekoop-Ruiterman et al., 2005) compared four treatment strategies in early RA: sequential monotherapy, step up combination therapy, and initial combination
therapy with either high dose prednisone or infliximab. Treatment was required to be intensified if DAS exceeded 2.4. After one year, patients in the initial combination therapy had better functional improvement and less radiographic joint damage (Goekoop-Ruiterman et al., 2005) compared to the other groups. In the CAMERA study, (Computer Assisted Management in Early Rheumatoid Arthritis) (Verstappen et al., 2007) intensive and conventional monitoring strategies were compared in early RA patients. In the tight control group treatment decisions were based on a computer decision program. Remission was defined as no swollen joints and two out of three of the following variables: number of tender joints ≤ 3, ESR ≤ 20 mm/h, and VAS general wellbeing ≤ 20 mm. After two years, 50% of the patients in the intensive group versus 37% in the conventional group had been in remission for at least six months during the study. Dougados et al. (Dougados et al., 2007) suggest that low disease activity, intensive monitoring, and rapid adjustments in treatment offer the best benefit for RA patients.

Composite scores of disease activity such as DAS28 are of great value in RA clinical trials for evaluating the treatment response. However, measures with a good discriminatory power in groups of patients may not be optimal in individual patients. In our study a substantial proportion of the patients with low, moderate and high disease activity defined by DAS28 had overlapping values with the other disease activity groups with respect to all four disease activity components (TJC, SJC, GH, and ESR).
The Ritchie index has a major impact on the original DAS score, followed by SJC, ESR and GH (van der Heijde et al., 1993). Similarly, we found in the theoretical model that TJC had the highest impact on DAS28, followed by ESR, SJC, and GH. The finding that GH had only a minor impact on the DAS28 score is not compatible with the fact that GH closely correlates with pain, and pain has a substantial impact on the quality of life and function of patients with RA (Sokka et al., 2000a; Mäntyselkä et al., 2003). In the present patient population, ESR showed the most powerful impact on DAS28 at six months, although the median ESR was only 10.

The use of biologic agents in many countries has been restricted only to patients with high disease activity according to DAS28 (Hjardem et al., 2005; Ledingham & Deighton, 2005; Gear, 2007). However, the categorical application of DAS28 in clinical decision making may be unfeasible and inappropriate, as best illustrated by real life patients. One patient in our cohort had 21/11 tender (68 joint count/28 joint count) and 12/11 swollen (66 joint count/28 joint count) joints, ESR of 5 and GH of 60. Her DAS28 score of 4.76 indicated only moderate disease activity. Another patient had 4/1 tender (68 joint count/28 joint count) and 11/8 swollen joints (68 joint count/28 joint count), ESR of 5 and GH of 4 with a DAS28 score of 2.54, indicating DAS28 remission. It might be desirable that in addition to DAS28, patient function and potential radiographic joint damage (van der Heijde, 2000) are routinely be taken into account in adjusting therapies for RA. I agree with the statement of Wolfe et al.
(Wolfe et al., 2005b) that DAS28 may not be suitable as the sole criterion for initiation and evaluation of therapy with biologics in a clinical setting.

Although many indices for the assessment of disease activity in RA are available, measurement tools with the precision and accuracy of those available in other specialties, such as cardiology, do not exist in rheumatology (Harth & Pope, 2004). Our purpose when designing MOI-RA was to create an index with the highest possible accuracy, by capturing all the important domains of disease activity in RA. MOI-RA is a continuous index that enables the assessment of current disease activity and can therefore be used in cross-sectional studies. By definition, MOI-RA can recognize worsening in clinical status. Furthermore, in the calculation of MOI-RA no complex mathematical functions are needed, and it is easy to understand and calculate.

MOI-RA results were similar regardless of which joint count (28, 42 and 66/68) was used. In other indices, joint counts are fixed. In DAS28 (Prevoo et al., 1995) and SDAI (Smolen et al., 2003), 28 joint counts are used and in the DAS score, a 44-joint count is applied (van der Heijde et al., 1993; Smolen et al., 2003). In DAS, the tender joint count is replaced by the Ritchie articular index (Ritchie et al., 1968).

Clinical RA studies require efforts to collect complete data from patients. It is not rare for some data to be missing. If values of patients’ general health, for example, are missing, DAS28 cannot be calculated and these patients have to be omitted from the analyses. The high imputation stability of
MOI-RA provides an opportunity to include patients with incomplete data in analyses.

Two different patient populations were chosen for this study of disease activity and remission in RA: patients from an RCT comparing two different treatment strategies and patients from a clinical cohort. Disease activity indices and remission needed to be tested in both circumstances; in the first case, the RA patients included were selected according to inclusion criteria for high disease activity, while the latter cohort included all RA patients diagnosed in a rheumatology clinic.

The results of the present study indicate that the rate of remission in RA depends on the criteria used. We also showed that sustained remission, which is more often achieved by patients receiving combination therapy, protects RA patients against radiographic joint damage. Furthermore, although the widely used definition of remission, DAS28 remission, is less stringent than ACR remission, a substantial proportion of patients below the DAS28 cutoff point for remission had tender and/or swollen joints. Finally, I remain somewhat skeptical about the notion of a perfect disease activity index in RA. Indices may work properly at a group level, but may fail to do so in individual patients due to factors that are not associated with inflammation (Leeb et al., 2004), such as gender (Leeb et al., 2007). The MOI-RA index represents an attempt to develop an instrument for measuring overall disease activity in RA.
10. SUMMARY AND PROSPECTS

A modern approach to the treatment of RA includes tight control of the disease. This is made possible by frequent follow up visits, systematic assessment of disease activity and modification of therapy accordingly (Fransen et al., 2005). The target of therapy is a sustained state of remission or minimal disease activity, which can be achieved by combining traditional DMARDs or methotrexate and biologics (van der Heijde et al., 2005). However, no single measure of disease activity and remission in RA exists; various methods have been reported and are in use.

In the present study two different patient cohorts were evaluated: patients from a clinical cohort and patients from a RCT. Clinical data were analyzed in a cohort including all RA patients diagnosed in 1997-1998 at Jyväskylä Central Hospital, and the clinical trial data were acquired from early RA patients in the FIN-RACo trial (Möttönen et al., 1999) comparing two different treatment strategies.

We showed that frequency of remission depends on the definition used. Further, sustained remission can be achieved with a combination of traditional DMARDs. Moreover, sustained remission protects against radiographic progression. On the other hand, patients who are in remission according to the widely used DAS28< 2.6 remission may still have residual disease activity. Although DAS28 has proven to work well at group level, there are individual patients whose disease activity may be high despite a DAS28 value indicating low disease activity. Finally, we developed a new disease
activity index for use in RCTs and clinical settings, the Mean Overall Index of
disease activity (MOI-RA), which captures most dimensions reflecting disease
activity of RA.

Patients in the clinical cohort and in the FIN-RACo trial were treated
actively with traditional DMARDs. This probably contributed to the good
outcomes - progressive joint destruction was rare. However, the global picture
of outcomes of RA patients is modest (Sokka et al., 2007b). In the future,
effective therapy (with traditional DMARDs in the first place) should be made
available and given to all RA patients worldwide.

New information technology will facilitate the follow-up of RA
patients, including the collection of patient information. A new technology has
been implemented in data collection in our rheumatology clinic. RA patients
complete self-report questionnaires using a touch screen with immediate
storage in a database. This decreases possible data entry mistakes, and the
data are readily available for the treating health professionals. Diagrams of
patient’s disease activity and treatments can be produced. In the future, most of
the data collection may be completed by the patient and a trained nurse instead
of a physician.

In conclusion, rheumatologists worldwide should become aware
that benefits for the patient can be obtained by combining the optimal treatment
strategy with the most appropriate outcome measures. Low disease activity,
intensive monitoring, and rapid adjustments of treatment appear to promise the
greatest benefit for the RA patient (Dougados et al., 2007).
11. REFERENCES


DAS. Disease Activity Score in Rheumatoid Arthritis (http://www.das-score.nl/www.das-score.nl/index.html).


Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 36, 729-740.


sedimentation rate, and hemoglobin: longterm course and association to radiographic progression. J Rheumatol 27, 47-57.


MANCARELLA, L., BOBBIO-PALLAVICINI, F., CECCARELLI, F., FALAPPONE, P. C., FERRANTE, A., MALESCI, D., MASSARA, A., NACCI, F., SECCHI, M. E.,


PAULUS, H. E., RAMOS, B., WONG, W. K., AHMED, A., BULPITT, K., PARK, G., STERZ, M. & CLEMENTS, P. (1999). Equivalence of the acute phase reactants C-reactive protein, plasma viscosity, and Westergren erythrocyte sedimentation rate when used to calculate American College of Rheumatology 20% improvement criteria or the Disease Activity Score.


a modified Stanford Health Assessment Questionnaire. Arthritis Rheum 26, 1346-1353.


12. ORIGINAL PUBLICATIONS


