Early identification and treatment - the Norwegian perspective

Till Uhlig
Dept of Rheumatology
Diakonhjemmet Hospital
Oslo, Norway

Oslo Rheumatoid Arthritis Registry (ORAR)

Very early Arthritis Clinic NOR-VEAC

DMARD Registry NOR-DMARD

Oslo Rheumatoid Arthritis Registry (ORAR)

Extended report

Rheumatoid arthritis is milder in the new millennium: health status in patients with rheumatoid arthritis 1994–2004

T Uhlig,[1] T Heiberg,[2] P Mowinckel,[1] T K Kvien[1]

Ann Rheum Dis 2008;67:1710-15

Physical function changes in cross-sectional Oslo RA population 1994-2004

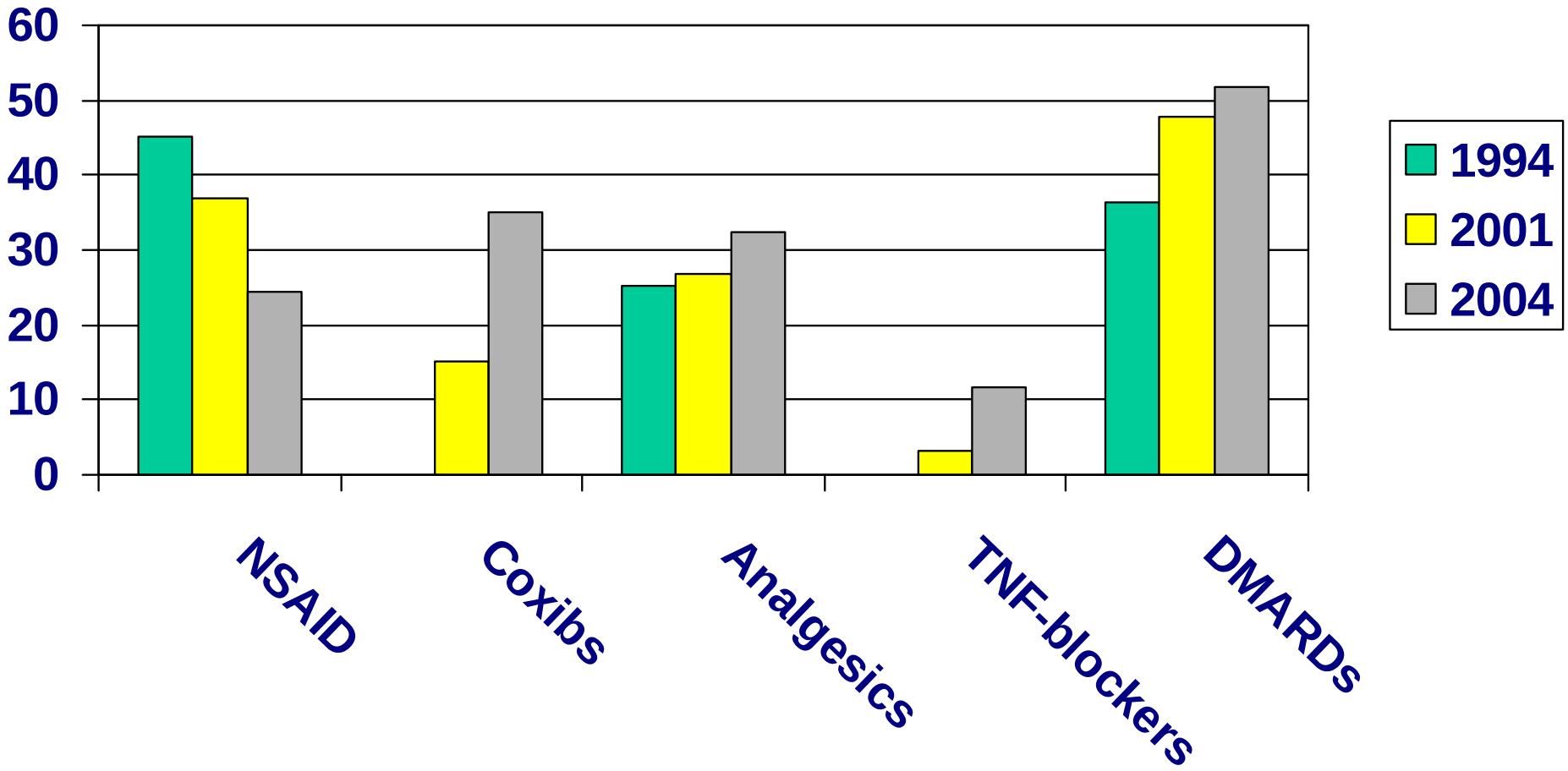
	1994	1996	2001	2004
MHAQ	1.68 (1.64;1.71)	1.65 (1.62;1.69)	1.58 (1.54;1.62)	1.55 (1.51;1.58)
SF-36 PCS	31.4 (30.7;32.2)	32.0 (31.3;32.7)	32.7 (31.9;33.5)	33.7 (32.9;34.4)
AIMS2 Physical	2.77 (2.64;2.90)	2.75 (2.63;2.87)	2.24 (2.12;2.36)	2.01 (1.90;2.12)

Means and CI

Uhlig T et al. Ann Rheum Dis 2008:67:1710-5

Rheumatoid arthritis is milder in the new millennium: health status in patients with rheumatoid arthritis 1994 2004

T Uhlig, T Heiberg, P Mowinckel and T K Kvien



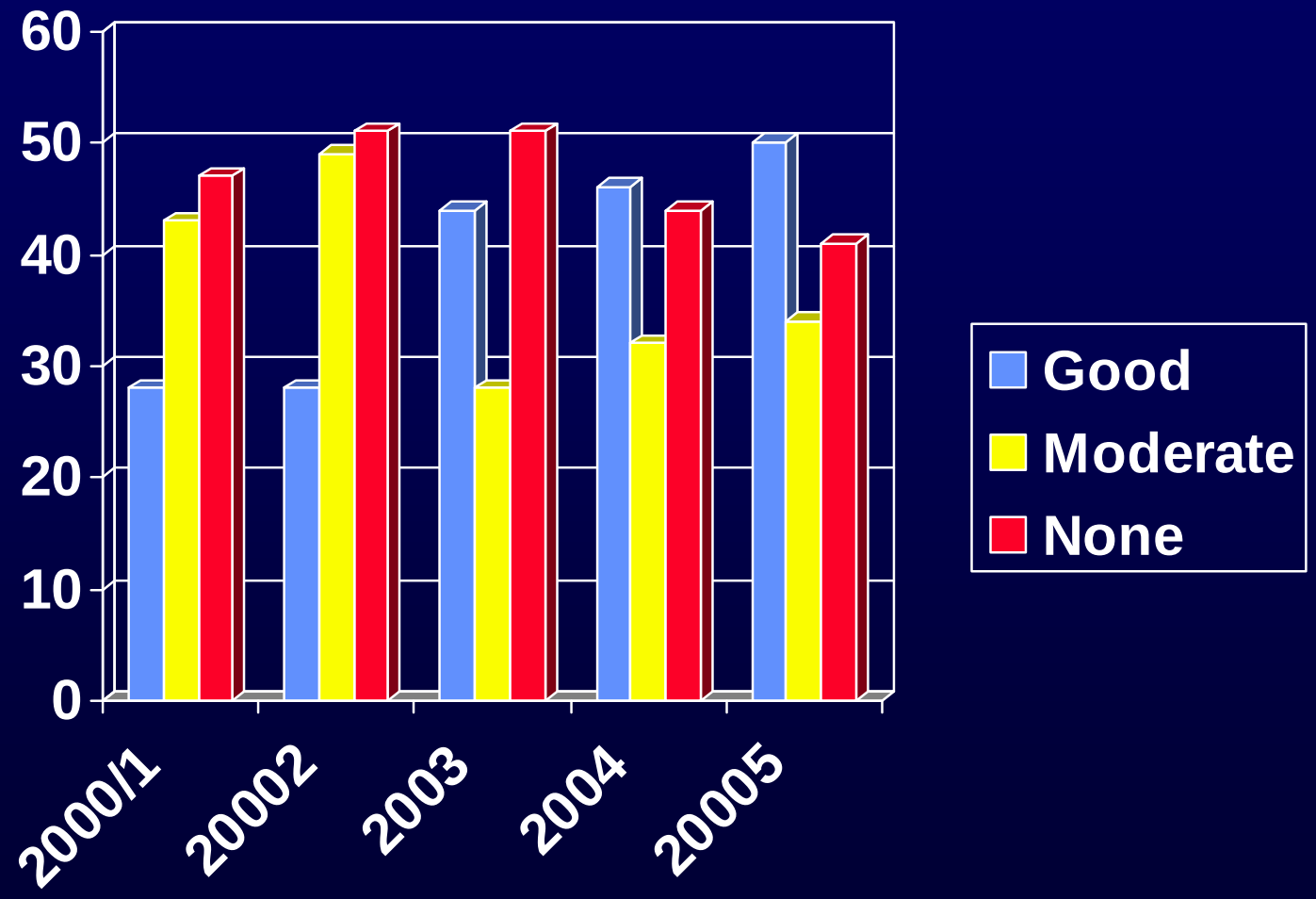
Uhlig T et al. Ann Rheum Dis 2008:6767:1710-5.

Changes in health status in Oslo RA population (1994-2009)

	1994	1996	2001	2004	2009
MHAQ (1-4)	1.68 (1.64; 1.71)	1.65 (1.62; 1.69)	1.58 (1.54; 1.62)	1.55 (1.51; 1.58)	1.44 (1.40; 1.47)
SF-36 PCS (0-100)	31.4 (30.7; 32.2)	32.0 (31.3; 32.7)	32.7 (31.9; 33.5)	33.7 (32.9; 34.4)	36.4 (35.6; 37.2)
SF-36 MCS (0-100)	46.3 (45.5; 47.2)	45.3 (44.5; 46.0)	47.0 (46.2; 47.9)	47.5 (46.7; 48.3)	46.9 (46.1; 47.7)
SF-6D utility (0-1)	0.616 (0.607; 0.625)	0.617 (0.608; 0.625)	0.639 (0.629; 0.649)	0.647 (0.638; 0.656)	0.670 (0.660; 0.680)
Pain (0-100)	46.0 (44.4; 47.5)	37.7 (36.2; 39.1)	35.8 (34.1; 37.4)	34.5 (33.0; 36.1)	34.2 (32.6; 35.8)
Fatigue (0-100)	50.0 (48.2; 51.8)	44.1 (42.3; 45.9)	46.9 (44.9; 48.9)	46.1 (44.2; 48.1)	44.7 (42.8; 46.6)
Pat.glob (0-100)	48.5 (47.0; 50.0)	44.8 (43.5; 46.2)	39.8 (38.1; 41.6)	38.2 (36.6; 39.8)	37.1 (35.4; 38.8)

Austad C et al. Ann Rheum Dis 2010;69(suppl):SAT0058

EULAR response in DANBIO improves

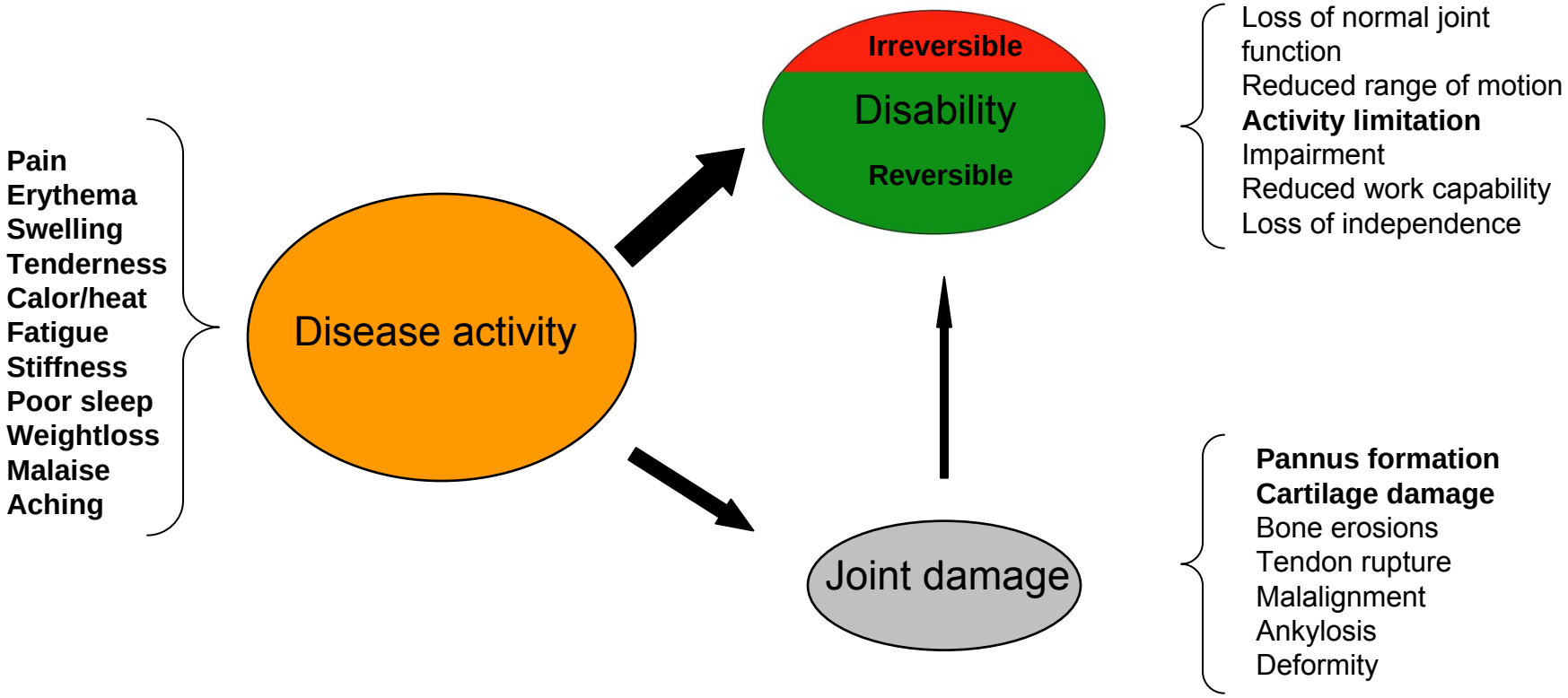


Hetland M et al. Ann Rheum Dis 2008;67:1023-8

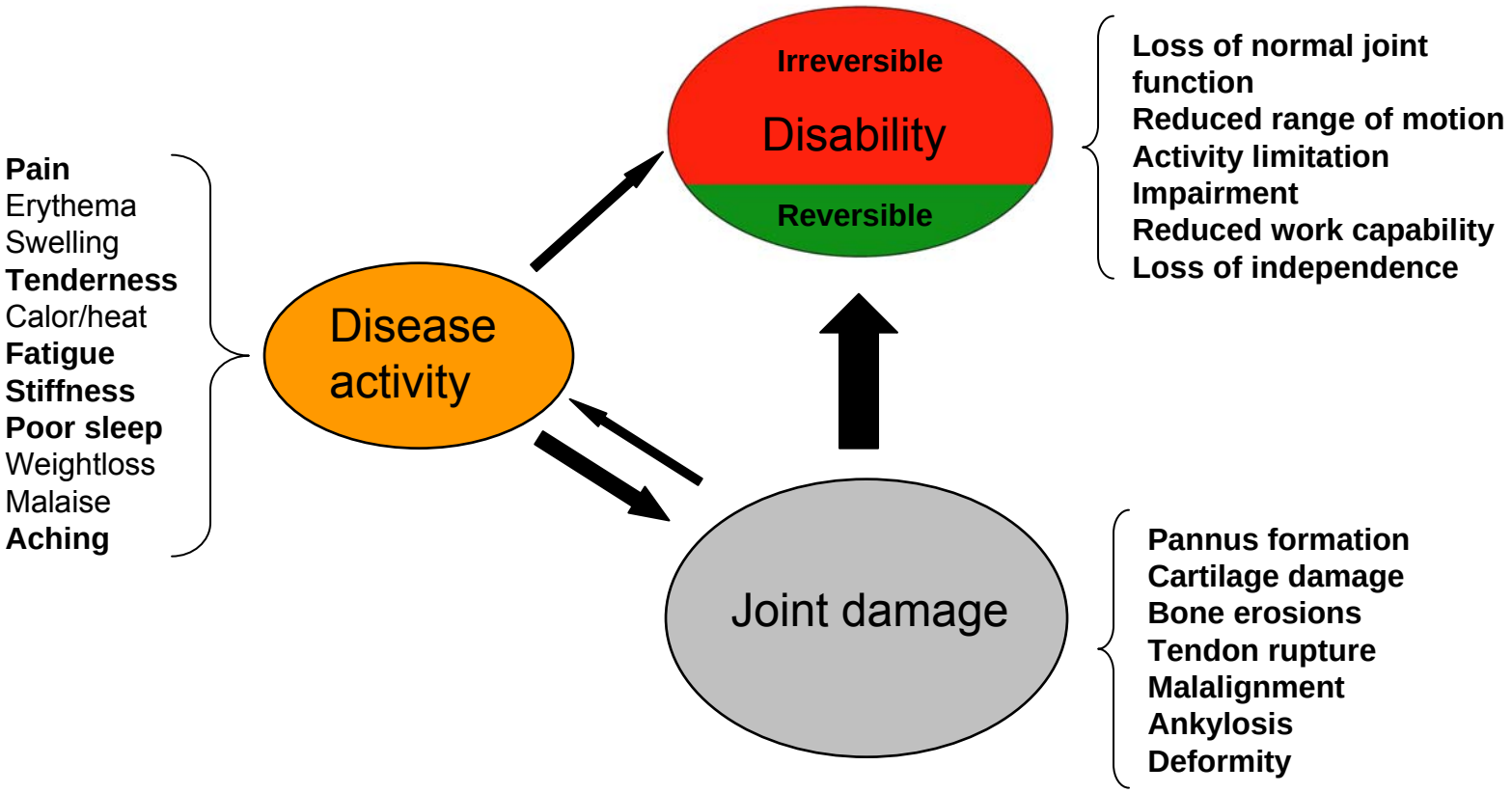
RA treatment strategy in 2011

- Early diagnosis
- Early use of synthetic disease modifying therapies (MTX)
- Identify a treatment target (remission)
- Monitor (tight control) and adjust disease-modifying therapy according to the target
- Add biological DMARD if target is not achieved
- Continue to monitor and adjust therapy as long as the target is not achieved

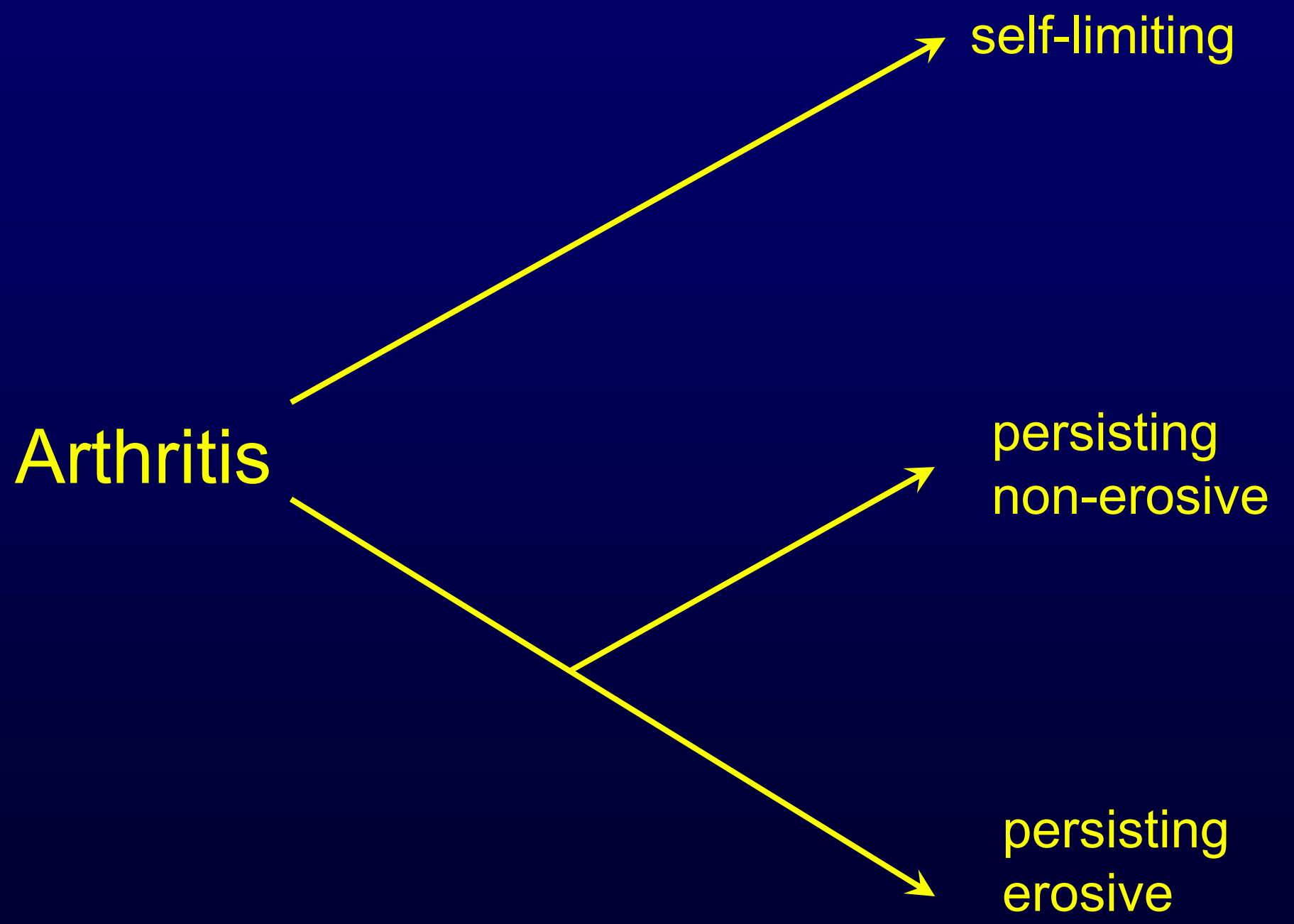
The link between disease activity, functional disability and structural joint damage in early rheumatoid arthritis



The link between disease activity, functional disability and structural joint damage in established/advanced rheumatoid arthritis



TAK ”Tidlig artritt klinikk”
NOR-VEAC


self-limiting
Arthritis
persisting
non-erosive
persisting
erosive

Objective
Norwegian very early arthritis clinic (NOR-VEAC)

- To study the disease spectrum and the 2-year disease course in patients with arthritis of <16 weeks duration
- To identify possible predictors of persistent and/or erosive arthritis
- To foster collaboration with the primary care / general practitioners

The Norwegian Very Early Arthritis Clinic (NOR-VEAC)

- Started in 2004
- Six rheumatology departments together serving approximately 1.7 million people
- Inclusion: 18-75 years, ≥1 swollen joint(s) of ≤16 weeks' duration
- Exclusion: Trauma, osteoarthritis, septic arthritis, crystal arthropathies

NOR-VEAC
Collaboration with GPs

- General practitioners were asked by letter invitation to refer all patients (18-75) with arthritis of ≤ 16 weeks duration
- The patients were promised a consultation within 14 days after referral
- Evening courses for general practitioners, focusing on recognition of the swollen joint and the importance of early referral to a rheumatology department

NOR-VEAC inclusion criteria: 18-75 years, ≥1 swollen joint(s) of ≤16 weeks' duration

Results 2004-2010:

- 1100 patients included
- Mean age 46 years, 56 % females (BeSt study age 54, 68 % females)
- Median duration of joint swelling 30 days
- RF+ 11 %, ACPA+ 14 %
- Mean DAS 28 4.0

J Rheumatol 2009;36:1401-6

Pattern of Joint Involvement and Other Disease Characteristics in 634 Patients with Arthritis of Less Than 16 Weeks' Duration

MARIA DAHL MJAAVATTEN, ANNE JULSRUD HAUGEN, KNUT HELGETVEIT, HALVOR NYGAARD, GÖRAN SIDENVALL, TILL UHLIG, and TORE KRISTIAN KVIEN

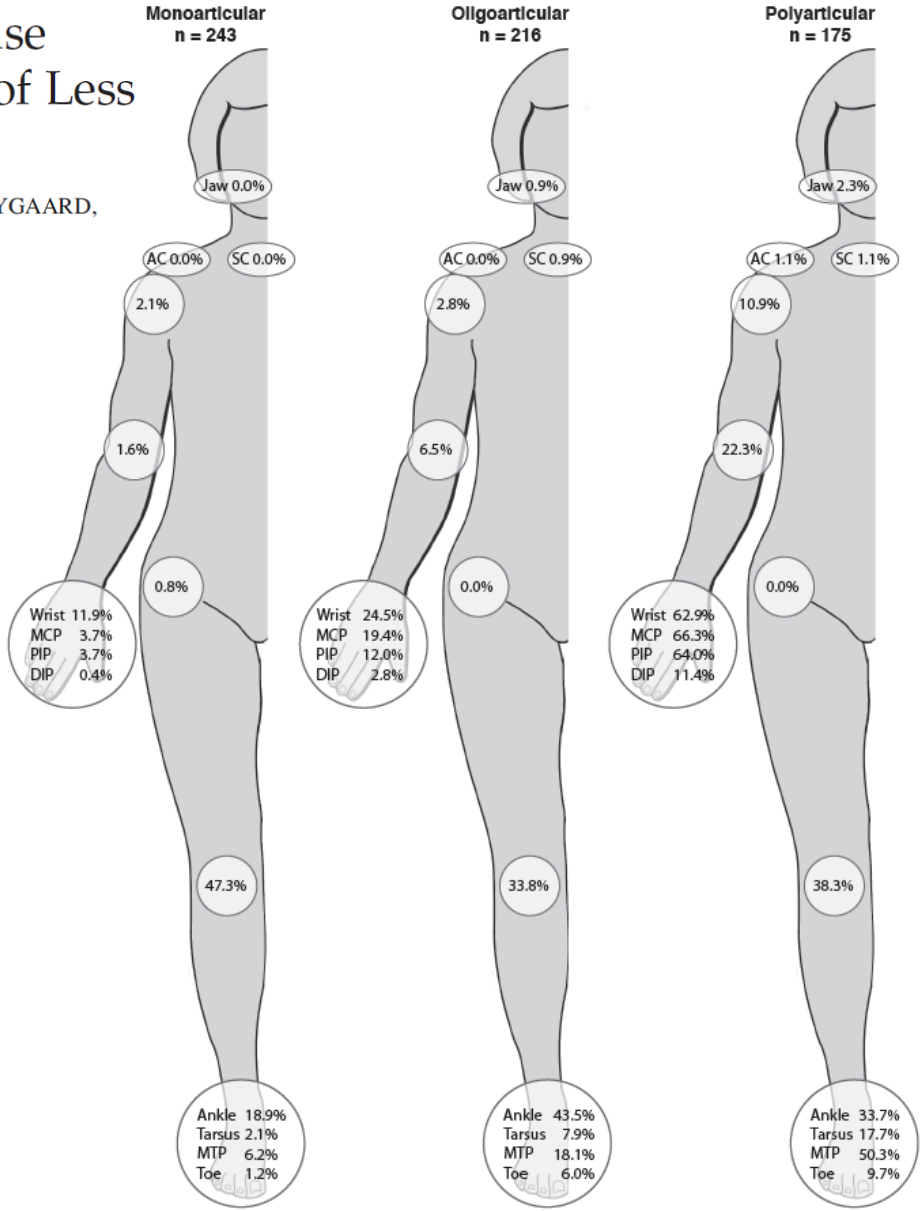
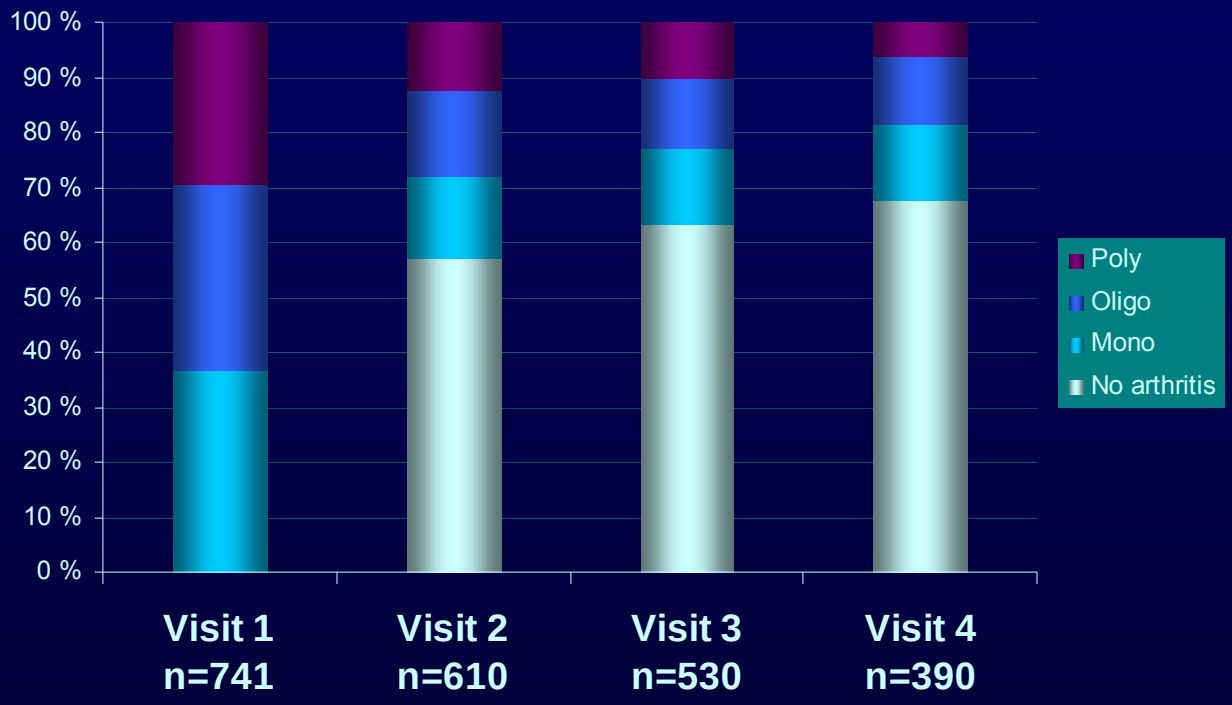


Figure 1. Distribution of swollen joints in patients with mono-, oligo-, and polyarthritis

Joint pattern distribution at different visits



ACR/EULAR classification criteria for RA 2010

Criteria

2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative

Daniel Aletaha,[1] Tuhina Neogi,[2] Alan J Silman,[3] Julia Funovits,[1] David T Felson,[2] Clifton O Bingham III,[4] Neal S Birnbaum,[5] Gerd R Burmester,[6] Vivian P Bykerk,[7] Marc D Cohen,[8] Bernard Combe,[9] Karen H Costenbader,[10] Maxime Dougados,[11] Paul Emery,[12] Gianfranco Ferraccioli,[13] Johanna MW Hazes,[14] Kathryn Hobbs,[15] Tom WJ Huizinga,[16] Arthur Kavanaugh,[17] Jonathan Kay,[18] Tore K Kvien,[19] Timothy Laing,[20] Philip Mease,[21] Henri A Ménard,[22] Larry W Moreland,[23] Raymond L Naden,[24] Theodore Pincus,[25] Josef S Smolen,[1] Ewa Stanislawska-Biernat,[26] Deborah Symmons,[27] Paul P Tak,[28] Katherine S Upchurch,[18] Jiří Vencovský,[29] Frederick Wolfe,[30] Gillian Hawker,[31]

Ann Rheum Dis 2010;69:1580-8

Candidate variables

- Joint counts / joint involvement
- Serology (RF and ACPA)
- Acute phase reactants

2010 ACR/EULAR classification criteria for RA

JOINTS (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0-3)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
SYMPTOM DURATION (0-1)	
<6 weeks	0
>=6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

A score ≥ 6 means patient is classifiable as rheumatoid arthritis

Aletaha et al *Ann Rheum Dis* 2010(9):69:1580-8

Research article

Open Access

Positive anti-citrullinated protein antibody status and small joint arthritis are consistent predictors of chronic disease in patients with very early arthritis: results from the NOR-VEAC cohort

Maria D Mjaavatten[1], Till Uhlig[1], Anne J Haugen[2], Halvor Nygaard[3], Göran Sidenvall[4], Knut Helgetveit[5] and Tore K Kvien[1]

[1]Department of Rheumatology, Diakonhjemmet Hospital, P.O. box 23 Vinderen, 0319 Oslo, Norway
[2]Department of Rheumatology, Østfold Hospital Trust, 1603 Fredrikstad, Norway
[3]Lillehammer Hospital for Rheumatic Diseases, Margrethe Grundtvigs vei 6, 2609 Lillehammer, Norway
[4]Department of Rheumatology, Innlandet Hospital, 2226 Kongsvinger, Norway
[5]Martina Hansen Hospital, P.O. box 23, 1306 Bærum Postal Terminal, Norway

Corresponding author: Maria D Mjaavatten, maria_mjaavatten@hotmail.com

Received: 12 May 2009 Revisions requested: 8 Jul 2009 Revisions received: 21 Sep 2009 Accepted: 1 Oct 2009 Published: 1 Oct 2009

Arthritis Research & Therapy 2009, **11**:R146 (doi:10.1186/ar2820)
This article is online at: http://arthritis-research.com/content/11/5/R146

Prediction of persistent synovitis, DMARD prescription and RA in multivariate logistic regression models (OR with 95% CI)

	Persistent synovitis N=98	DMARD start N=106	RA N=68
Age	1.01 (0.99-1.03)	0.99 (0.99-1.02)	1.04 (1.01-1.08)
Female gender	1.22 (0.69 (2.16)	0.99 (0.54-1.81)	1.24 (0.51-3.01)
ACPA positivity	3.17 (1.35-7.44)	5.62 (2.24-14.1)	19.3 (6.84-54.4)
IgM RF positivity	2.03 (0.80-5.14)	2.30 (0.83-6.41)	5.02 (1.47-17.1)
Small joint arthritis	1.90 (1.04-3.46)	3.45 (1.79-6.65)	3.45 (1.21-9.90)
HAQ	1.66 (1.06-2.59)	1.70 (1.09-2.68)	-
28-TJC	-	1.06 (1.00-1.12)	1.09 (1.02-1.16)
CRP (mg/l)	0.99 (0.98-1.00)	-	-

Mjaavatten et al. *Arthritis Res Ther*. 2009;11(5):R146

Mjaavatten *et al. Arthritis Research & Therapy* 2010, **12**:R76
http://arthritis-research.com/content/12/3/R76

arthritis research&therapy

RESEARCH ARTICLE Open Access

The likelihood of persistent arthritis increases with the level of anti-citrullinated peptide antibody and immunoglobulin M rheumatoid factor: a longitudinal study of 376 patients with very early undifferentiated arthritis

Maria D Mjaavatten*[1], Désirée van der Heijde[1,2], Till Uhlig[1], Anne J Haugen[3], Halvor Nygaard[4], Göran Sidenvall[5], Knut Helgetveit[6] and Tore K Kvien[1]

Univariate logistic regression for persistent arthritis with anti-CCP/IgM RF according to level

Anti-CCP (units/ml)	OR (95 % C.I.)	LR+	LR-
≤25	1.0	ref	ref
>25-100	4.4 (1.6-12.5)	4.1 (1.5-11.0)	0.9 (0.9-1.0)
>100-250	9.4 (2.1-42.9)	8.7 (2.0-38.2)	0.9 (0.8-1.0)
>250	13.6 (4.0-46.0)	11.4 (3.5-37.0)	0.8 (0.8-0.9)
IgM RF (units/ml)			
≤25	1.0	ref	ref
>25-75	4.6 (2.0-10.6)	4.0 (1.9-8.7)	0.9 (0.8-0.9)
>75	19.2 (4.5-82.5)	16.2 (3.9-67.2)	0.8 (0.8-0.9)

Mjaavatten et al Arthritis Res Ther 2010;12(3):R76

Objective

To determine the proportion of patients who switch antibody (ACPA and/or RF) status during the first year of follow up in patients with recent-onset arthritis

Extended report

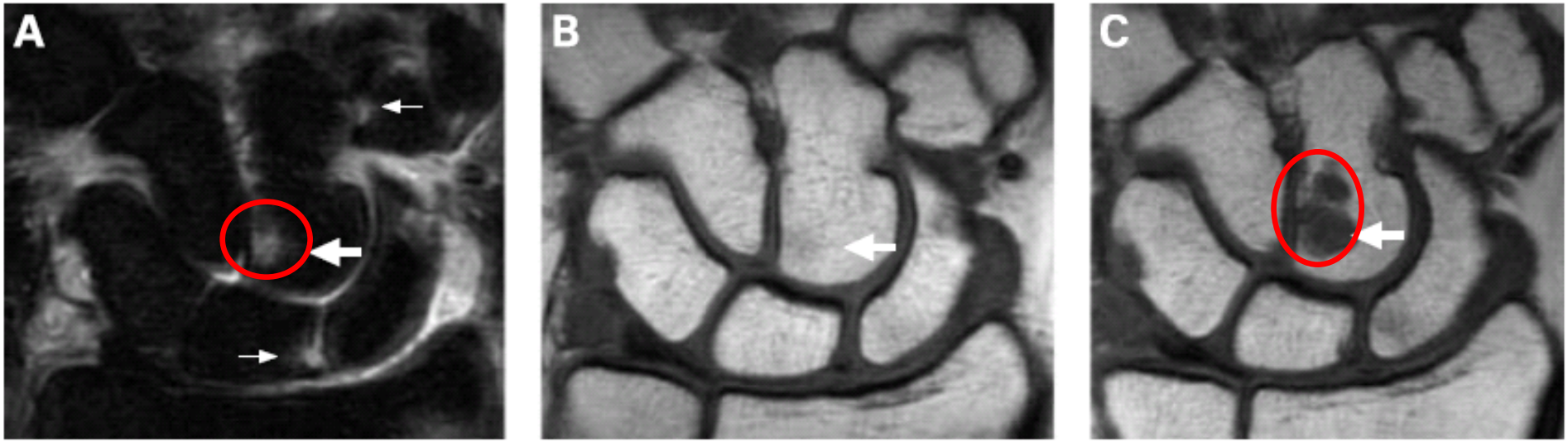
[1] Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway; [2] Faculty of Medicine, University of Oslo, Norway; [3] Department of Rheumatology, Copenhagen University Hospitals at Hvidovre and Herlev, Copenhagen, Denmark; [4] Department of Radiology, Diakonhjemmet Hospital, Oslo, Norway

Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression

E A Haavardsholm,[1,2] P Bøyesen,[1,2] M Østergaard,[3] A Schildvold,[4] T K Kvien[1,2]

Ann Rheum Dis 2008;67:794-800

Bone marrow edema was an independent predictor of erosive progression, both on CR and MRI



Baseline Baseline 12 months

Figure 2 Magnetic resonance imaging (MRI) of the wrist, at baseline (A, B) and 1-year follow-up (C). (A) Baseline coronal STIR image showing bone marrow in the capitate (thick arrow) and the lunate and trapezoid (thin arrows). (B) Baseline T1-weighted image without MRI erosion in the capitate (arrow). (C) T1-weighted image at 1-year follow-up, showing erosive progression in the capitate (arrow). Erosive progression was also seen in the trapezoid and the lunate, even though not optimally displayed in the presented slices.

Haavardsholm et al. *Ann Rheum Dis* 2008;67:794-800.

EDITOR'S CHOICE

Treating rheumatoid arthritis to target: recommendations of an international task force

Josef S Smolen,[1,2] Daniel Aletaha,[1] Johannes W J Bijlsma,[3] Ferdinand C Breedveld,[4] Dimitrios Boumpas,[5] Gerd Burmester,[6] Bernard Combe,[7] Maurizio Cutolo,[8] Maarten de Wit,[9] Maxime Dougados,[10] Paul Emery,[11] Alan Gibofsky,[12] Juan Jesus Gomez-Reino,[13] Boulos Haraoui,[14] Joachim Kalden,[15] Edw[illegible] [16] [17] Iain McInnes,[18] Emilio Martin-Mola,[19] Carlomaurizi[illegible] Desirée van der Heijde,[4] for the T2T Expert Comm[illegible]

ARD 2010
69:631-37

ARD 2010
69:629-30

'Treat to target': moving targets from hypertension, hyperlipidaemia and diabetes to rheumatoid arthritis

Dan Atar,[1,2] Kåre Inge Birkeland,[2,3] Till Uhlig[4]

Evidence for treating rheumatoid arthritis to target: results of a systematic literature search

Monika Schoels,[1] Rachel Knevel,[2] Daniel Aletaha,[3] Johannes W J Bijlsma,[4] Ferdinand C Breedveld,[2] Dimitrios T Boumpas,[5] Gerd Burmester,[6] Bernard Combe,[7] Maurizio Cutolo,[8] Maxime Dougados,[9] Paul Emery,[10] Desirée van der Heijde,[2] Tom W J Huizinga,[2] Joachim Kalden,[11] Edward C Keystone,[12] Tore K Kvien,[13] Emilio Martin-Mola,[14] Carlomaurizio Montecucco,[15] Maarten de Wit,[16] Josef S Smolen[1,3]

ARD 2010
69:638-43

Remission cutpoints

- DAS <1.6 (range 0-9.9)
- DAS28 <2.6 (range 0-9.1)
- SDAI ≤3.3 (range 0-86)
- CDAI ≤2.8 (range 0-76)
- RAPID3 ≤1 (range 0-10)
- ACR70 improvement

Content of remission indices

	TJC	SJC	Pat global	SR	CPR	MD global	Phys. funct	Pain
Disease activity score (DAS28)	X	X	X	X				
Clinical disease activity index (CDAI)	X	X	X			X		
Simplified disease activity index (SDAI)	X	X	X		X	X		
Routine assessment of patient index data (RAPID3)			X				X	X

American College of Rheumatology/European League Against Rheumatism Provisional Definition of Remission in Rheumatoid Arthritis for Clinical Trials

David T Felson,[1,2] Josef S Smolen,[3] George Wells,[4] Bin Zhang,[5] Lilian H D van Tuyl,[1] Julia Funovits,[6] Daniel Aletaha,[6] Cornelia F Allaart,[7] Joan Bathon,[8*] Stefano Bombardieri,[9] Peter Brooks,[10] Andrew Brown,[11] Marco Matucci-Cerinic,[12] Hyon Choi,[4] Bernard Combe,[13] Maarten de Wit,[14] Maxime Dougados,[15] Paul Emery,[16] Daniel Furst,[17] Juan Gomez-Reino,[18] Gillian Hawker,[19] Edward Keystone,[20] Dinesh Khanna,[17] John Kirwan,[21] Tore K. Kvien,[22] Robert Landewé,[23] Joachim Listing,[24] Kaleb Michaud,[25] Emilio Martin-Mola,[26] Pamela Montie,[27] Theodore Pincus,[28] Pamela Richards,[29] Jeffrey N Siegel,[30†] Lee S Simon,[31] Tuulikki Sokka,[32] Vibeke Strand,[33] Peter Tugwell,[3] Alan Tyndall,[34] Desirée van der Heijde,[7] Suzan Verstappen,[35] Barbara White,[36] Frederick Wolfe,[37,38] Angela Zink,[24] and Maarten Boers[5]

Ann Rheum Dis 2011;70:404-13

New ACR/EULAR remission criteria

- Boolean definition:
  - Swollen joints ≤1
  - Tender joints ≤1
  - C reactive protein ≤1 mg/dl (≤10 mg/l)
  - Patient global (≤1) on 10 point scale*

    *"Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?"
- or SDAI ≤3.3

Felson DT et al. Ann Rheum Dis 2011;70:404-13

New remission criteria for RA: 'modern times' in rheumatology—not a silent film, rather a 3D movie

Lennart T H Jacobsson,[1] Merete Lund Hetland[2]

Ann Rheum Dis 2011;70:401-3

NOR-DMARD





General aim:

To study safety and effectiveness of various DMARD regimens in clinical practice

Background

- 5 rheumatology departments (Oslo, Lillehammer, Tromsø, Drammen, Trondheim)
- Start December 2000 (Drammen and Trondheim from 2002)
- Covers >1.4 million inhabitants, or ~30% of the Norwegian population
- All DMARD prescriptions in adult (>18 years old) patients with inflammatory arthropathies
- As of May 2011: about 11 000 prescriptions included

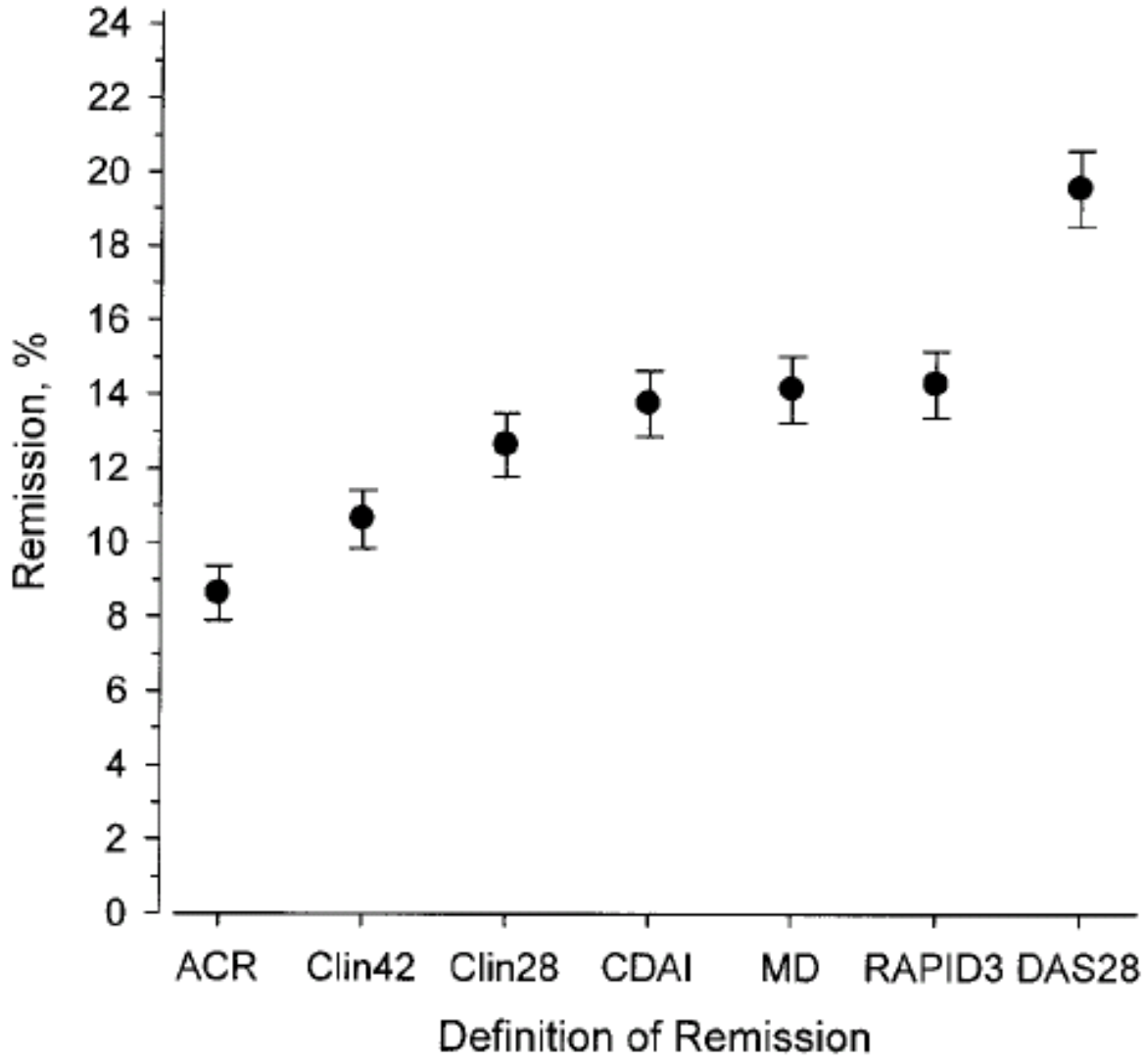
NOR-DMARD vs. most other European registries

- Includes all inflammatory arthropathies – main groups: RA, PsA, AS, JIA, UA
- Includes all DMARD treatments – not only biologics

Organization – NOR-DMARD

- In principle all patients are included
  - Completeness ~85%
- Based on informed consent
- Full or part time research nurses in all centres
- Integrated in regular clinical practice
- Registration at baseline, follow-up 3, 6, 12 months and then yearly

Performance of remission criteria in QUEST



Sokka T et al. Arthritis Rheum 2008;58:2642-51

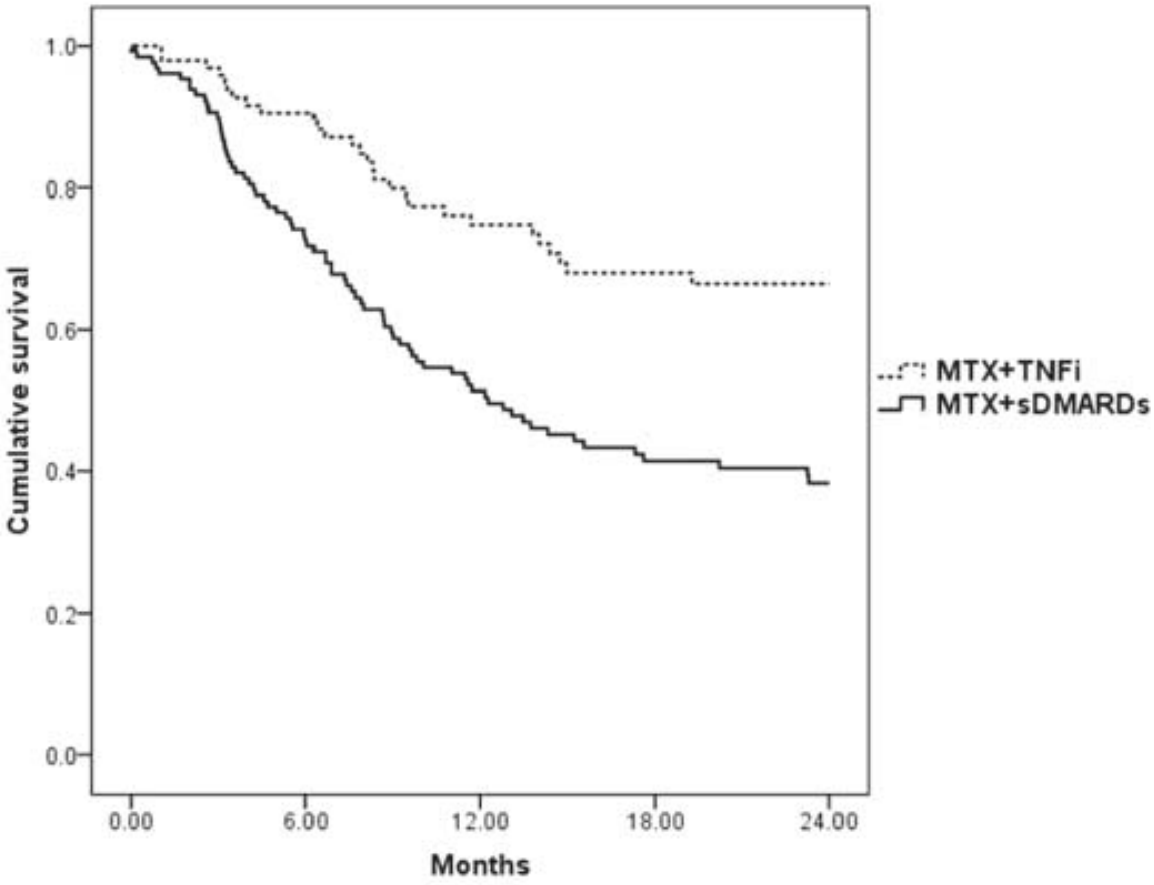
Treatment strategies in patients with rheumatoid arthritis for whom methotrexate monotherapy has failed: data from the NOR-DMARD register

Elisabeth Lie,[1] Désirée van der Heijde,[1,2] Till Uhlig,[1] Knut Mikkelsen,[3] Synøve Kalstad,[4] Cecilie Kaufmann,[5] Erik Rødevand,[6] Tore K Kvien[1]

Table 3 Remission and response rates and changes in disease activity measures after 3 and 6 months of the first combination therapy

	3 Months				6 Months			
	MTX+TNFi (n=80)	MTX+sDMARDs (n=105)	p Value*	p Value†	MTX+TNFi (n=68)	MTX+sDMARDs (n=81)	p Value*	p Value†
DAS28<2.6 (n (%))	20 (29.0)	11 (11.6)	0.005	0.02	19 (34.5)	9 (12.9)	0.004	0.02
SDAI≤3.3 (n (%))	12 (16.4)	4 (4.3)	0.009	0.03	13 (22.0)	6 (8.3)	0.03	0.15
DAS28≤3.2 (n (%))	30 (43.5)	25 (26.3)	0.02	0.03	30 (54.5)	20 (28.6)	0.003	0.02
SDAI≤11 (n (%))	36 (49.3)	28 (30.1)	0.01	0.02	39 (66.1)	21 (29.2)	<0.001	0.001
EULAR good response (n (%))	24 (36.4)	14 (15.6)	0.003	0.02	21 (39.6)	14 (20.9)	0.03	0.10
DAS28 (mean (SD))	−1.61 (1.41)	−0.85 (1.09)	<0.001	0.005	−1.91 (1.46)	−1.03 (1.38)	0.01	0.04
SDAI (mean (SD))	−15.4 (14.6)	−8.0 (12.0)	0.001	0.01	−16.5 (14.5)	−10.0 (14.2)	0.01	0.22
MHAQ score (0–3) (mean (SD))	−0.41 (0.56)	−0.19 (0.39)	0.003	0.03	−0.48 (0.48)	−0.27 (0.38)	0.003	0.08
28-SJC (mean (SD))	−4.6 (6.0)	−2.0 (4.8)	0.002	0.04	−4.9 (6.4)	−2.7 (5.7)	0.03	0.50
28-TJC (mean (SD))	−4.6 (6.8)	−2.7 (6.3)	0.05	0.17	−5.2 (6.5)	−3.0 (6.8)	0.05	0.19
ESR (mm/h, (median (IQR)))	−7.5 (−18.25 to 0.25)	−4 (−14 to 0)	0.34	0.72	−9 (−27.5 to −1.25)	−6 (−15 to 0)	0.10	0.44
CRP (mg/l, (median (IQR)))	−6 (−26 to 0)	−2 (−10 to 1.5)	0.03	0.90	−6 (−27.5 to −0.5)	−1.5 (−20.5 to 0)	0.08	0.78
PhGA VAS (mean (SD))	−22.6 (23.0)	−12.8 (19.8)	0.002	0.08	−26.1 (24.9)	−15.1 (19.9)	0.003	0.31
PGA VAS (mean (SD))	−23.7 (28.5)	−12.3 (23.7)	0.004	0.006	−27.5 (25.4)	−14.4 (25.8)	0.003	0.03
Pain VAS (mean (SD))	−22.0 (30.1)	−11.9 (24.1)	0.01	0.01	−24.9 (26.4)	−18.1 (22.1)	0.09	0.16
Fatigue VAS (mean (SD))	−12.8 (31.4)	−5.6 (24.4)	0.09	0.50	−18.5 (26.9)	−8.8 (25.1)	0.03	0.25
SF-6D (mean (SD))	0.09 (0.13)	0.06 (0.09)	0.06	0.21	0.13 (0.13)	0.07 (0.12)	0.002	0.04
SF-36 PCS (mean (SD))	7.5 (10.6)	4.3 (7.8)	0.03	0.05	10.2 (9.2)	4.5 (9.2)	<0.001	0.003
SF-36 MCS (mean (SD))	3.6 (11.1)	0.5 (10.6)	0.07	0.31	3.6 (11.8)	1.7 (11.8)	0.35	0.51

*Unadjusted analyses (χ^2 test, Independent samples t test or Mann–Whitney U test were applied as appropriate).
†Analyses with adjustment for propensity score quintile (analysis of covariance for continuous outcomes, logistic regression for dichotomous outcomes).
28-SJC and 28-TJC, 28-swollen and tender joint counts, respectively; CRP, C-reactive protein; DAS28, Disease Activity Score 28; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; MCS, mental components summary; MHAQ, Modified Health Assessment Questionnaire; MTX, methotrexate; PCS, physical components summary; PGA, Patient's global assessment; PhGA, Physician's global assessment; SDAI, Simplified Disease Activity Index; sDMARD, synthetic-disease modifying antirheumatic drug; SF-36, Short-Form Health Survey; TNFi, tumour necrosis factor inhibitor; VAS, Visual analogue scale (0–100 mm).



Number of patients at risk:

Months	0	3	6	12	18	24
MTX+TNFi	98	93	82	56	47	37
MTX+sDMARDs	129	115	91	60	43	36

Figure 2 Kaplan–Meier plots over 2-year retention to therapy. The table shows the numbers of patients at risk at different time points during follow-up. Log rank test for 2-year drug survival: $p<0.001$. MTX, methotrexate; sDMARD, synthetic disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor.

ARD 2011

Clinical remission in NOR-DMARD

- 5788 patients with RA started with a synthetic (n=3875) or biological DMARD (n=1913)
- Age was mean (SD) 55.3 (29.9) yrs, disease duration was 8.2 (9.6) yrs, 73.3% of patients were females.
- Applied definitions for clinical remission at 3 and 6 months DMARD treatment
- Assessed subsequent changes in physical function until 1 year (MHAQ non-progression)

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Clinical remission in NOR-DMARD

	DAS28	SDAI	CDAI	RAPID 3	ACR/ EULAR BOOL	ACR/ EULAR	ACR/ EULAR PRAC
Remission 3 months (%)	**19.1**	**7.6**	**8.1**	**17.0**	**6.9**	**9.3**	**8.1**
MHAQ non-progression 3-12 months	65.7	63.9	64.9	65.2	64.2	63.6	65.6
Remission 6 months (%)	**24.7**	**10.5**	**11.3**	**19.8**	**9.0**	**12.3**	**11.0**
MHAQ non-progression 6-12 months	69.6	73.5	73.6	69.8	74.9	72.6	73.7

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Conclusions

- Early diagnosis and treatment with DMARDs are essential in RA
- Early arthritis clinics can be an important tool for early diagnosis and treatment
- Algorithms can assist in the prediction of persistent arthritis – anti-CCP and small joint involvement seem to be particularly important
- Remission may be achieved in RA patients, especially early in the disease and in patients with moderate disease activity