# ARTRITE REUMATOIDE: diagnosi precoce e early arthritis clinic

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# EARLY SYMPTOMS OF RHEUMATOID ARTHRITIS

BY

N. EGELIUS, N. G. HÄVERMARK, and ERIC JONSSON

*Stockholm, Sweden*

Ann Rheum Dis. 1949 September; 8(3): 217–219.

" we consider it justifiable to suspect early rheumatoid arthritis even when the symptoms are relatively uncharacteristic"

# LONG-TERM RESULTS IN EARLY CASES OF RHEUMATOID ARTHRITIS TREATED WITH EITHER CORTISONE OR ASPIRIN

A THIRD REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, A.C.T.H., AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

"…only patients with a disease duration of not less than three and not more than nine months were included…"

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"…the proportion of patients in remission at three and half years was 23%…"

"… the difference between complete remission and partial remission is far from clear and almost not uniformely applied in different centres…"

## "Early, Curable Stage" of Rheumatoid Arthritis

London W.1. FRANCIS BACH.

…Dr Todd says our fault is not the failure to give treatment, but the giving of too much treatment. "steroids, chloroquine, gold, and phenilbutazone are all dangerous drugs which should be reserved for the severely afflicted but which are too often given to patients with minor disease"..

## "Early, Curable Stage" of Rheumatoid Arthritis

London W.1. FRANCIS BACH.

… when we see an outpatient for the first time, we do not know if this patient is suffering from a "*minor disease*" or will in five years be "*severely affected*" and be suitable for treatment with "*dangerous drugs*" – a stage at which these drugs may be dangerous but will almost certainly be ineffectual in preventing disability..

*British Journal of Rheumatology* 1991;**30**:241–244

# EDITORIALS

## WHY EARLY ARTHRITIS CLINICS?

P. EMERY, A. GOUGH
*Department of Rheumatology, University of Birmingham, Queen Elizabeth and Selly Oak Hospitals*

We would suggest that patients with inflammatory arthritis deserve to be seen by a rheumatologist as a matter of urgency. Rheumatoid arthritis remains the commonest cause of inflammatory disabling disease and is potentially reversible, whilst untreated it rapidly produces joint destruction. It represents the biggest challenge and opportunity for rheumatologists in the next decade.

# The importance of early diagnosis

*Data of multiple observational cohorts and clinical trials indicate that treatment initiation in the first 3 months of RA is particularly effective at controlling arthritis and results in a better outcome.*

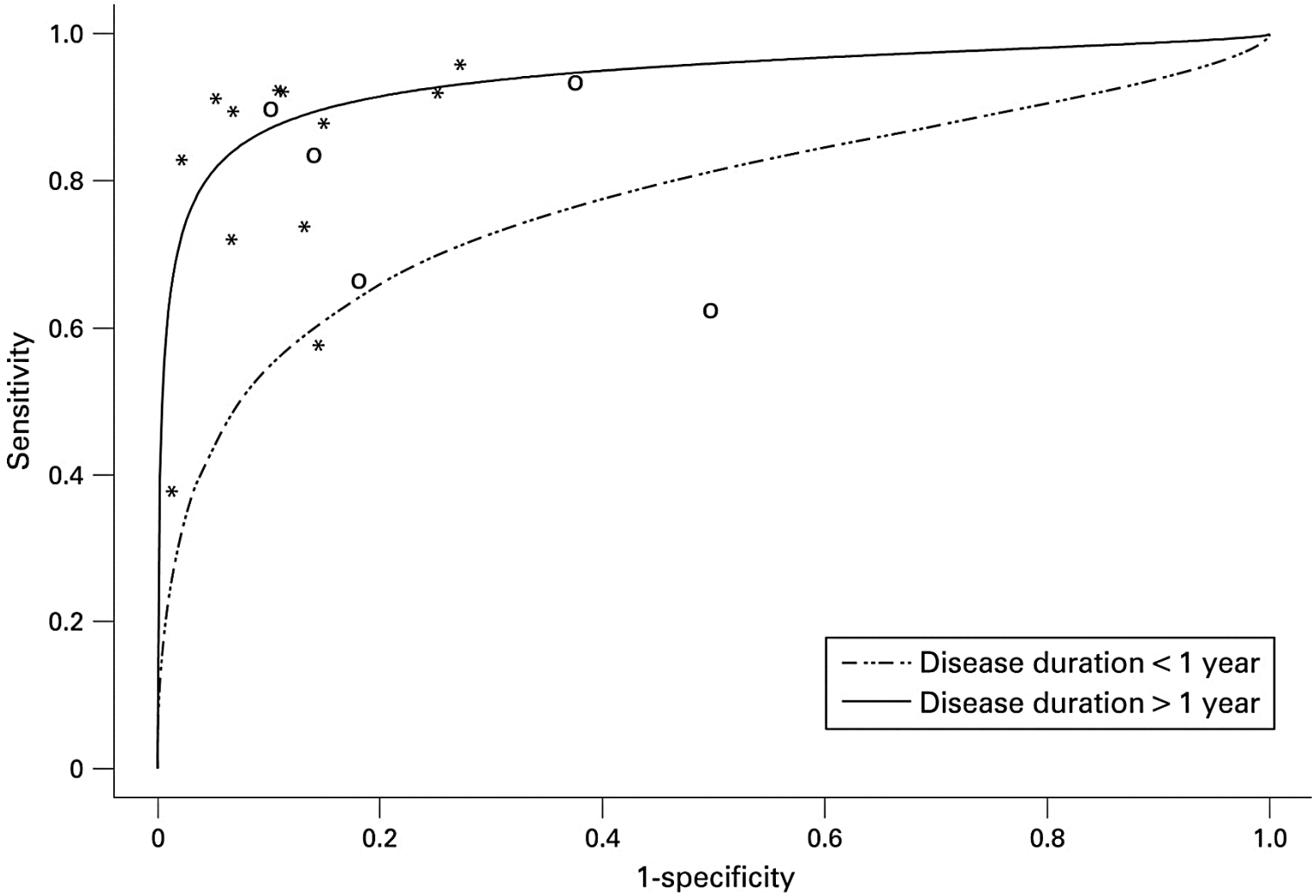
# 1987 Revised ACR criteria – list format

1. morning stiffness in and around joints lasting at least 1 hour before maximal improvement;
2. soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician;
3. swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints;
4. symmetric swelling (arthritis);
5. rheumatoid nodules;
6. the presence of rheumatoid factor;
7. radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

*Criteria 1 through 4 must have been present for at least 6 weeks.*

*Rheumatoid arthritis is defined by the presence of 4 or more criteria, and no further qualifications (classic, definite, or probable) or list of exclusions are required*.

# 1987 Revised ACR criteria – accuracy in early disease




*Banal F et al. Ann Rheum Dis 2009; 68:1184-91*

Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

# 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 M. W. Hazes,[14] Kathryn Hobbs,[15] Tom W. J. 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] and Gillian Hawker[31]

# 2010 EULAR/ACR criteria – list format

| | Score |
|---|---|
| Target population (Who should be tested?): Patients who | |
| 1) have at least 1 joint with definite clinical synovitis (swelling)* | |
| 2) with the synovitis not better explained by another disease† | |
| Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡ | |
| A. Joint involvement§ | |
| 1 large joint¶ | 0 |
| 2–10 large joints | 1 |
| 1–3 small joints (with or without involvement of large joints)# | 2 |
| 4–10 small joints (with or without involvement of large joints) | 3 |
| >10 joints (at least 1 small joint)** | 5 |
| B. Serology (at least 1 test result is needed for classification)†† | |
| Negative RF *and* negative ACPA | 0 |
| Low-positive RF *or* low-positive ACPA | 2 |
| High-positive RF *or* high-positive ACPA | 3 |
| C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡ | |
| Normal CRP *and* normal ESR | 0 |
| Abnormal CRP *or* abnormal ESR | 1 |
| D. Duration of symptoms§§ | |
| <6 weeks | 0 |
| ≥6 weeks | 1 |

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# Polyarticular Arthritis

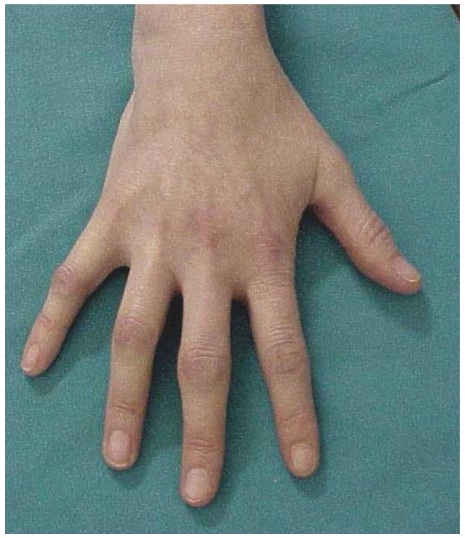
Not only is the evaluation of chronic polyarthritis the most common intellectual exercise facing the Rheumatologist, but it is also one of the most rewarding.

There are few areas left in Medicine where the bedside skills of the physician are so important, and few areas that share the excitement of being able to use one's experience and intellectual abilities to the benefit of patients

John Sergent in: Kelley et al. *Textbook of Rheumatology*, Chapter 27
Third Edition, Saunders Company 1989

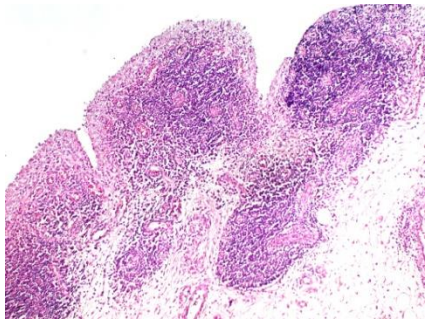
# Early RA mimicking disorders

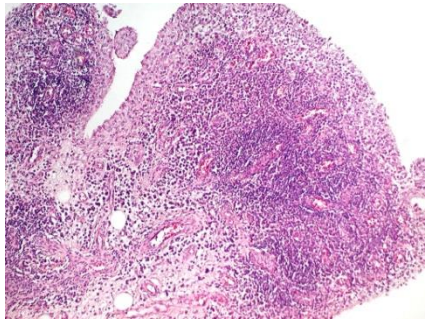
- **Inflammatory arthropaties**
  - psoritic arthropathy and seronegative enthesitis-arthritis
  - reactive arthritis
  - viral arthritis
  - CPPD cristal arthritis
  - polyarticular gouty arthritis
  - paraneoplastic arthritis
- **Connective tissue diseases**
  - SLE
  - UCTDs
  - vasculitides
  - Anti-synthetase syndrome
- **Others**
  - sarcoidosis
  - polymyalgia reumatica



# Early clinical RA = chronic immunologic disease

**Early RA**





**Long-standing RA**

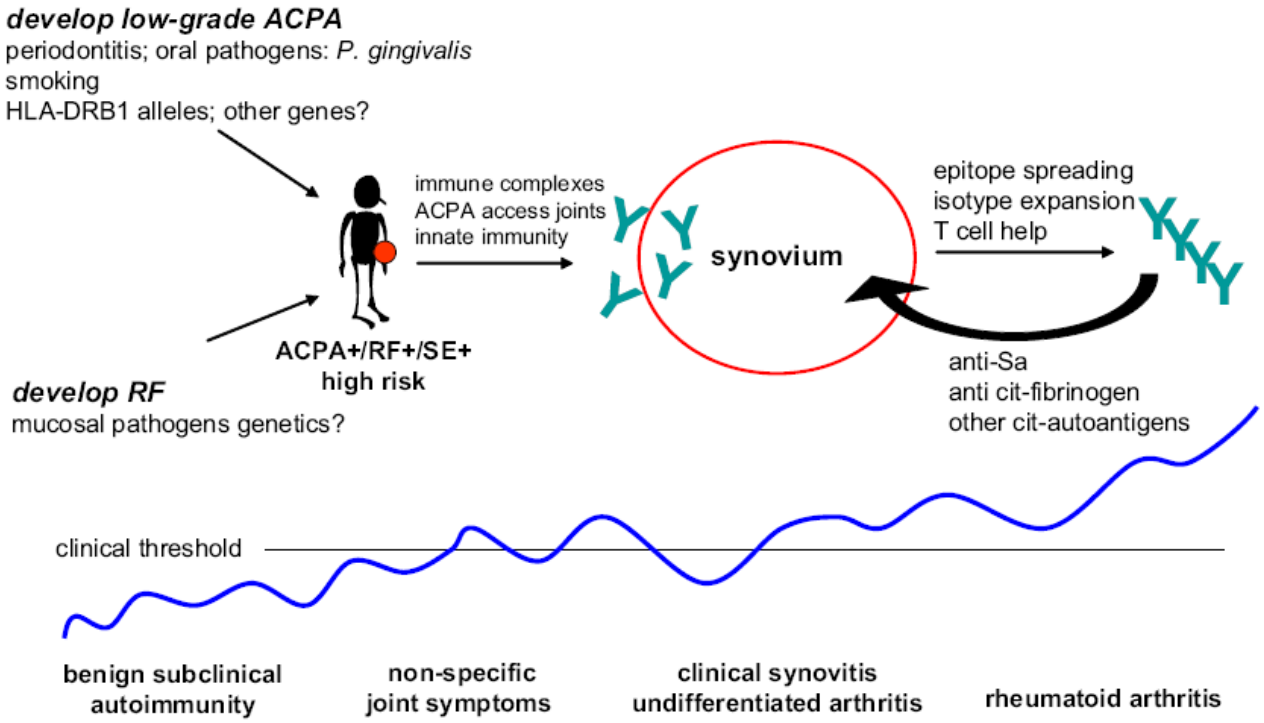
Rheumatology Laboratory
IRCCS Policlinico San Matteo Foundation, Pavia, Italy

**Histological scores in patients with early (E) and long-standing (L) rheumatoid arthritis (RA)**

| | Group I | | | | | | | | | | Group II | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Histological feature | L-01 | L-04 | L-02 | E-01 | E-10 | E-04 | L-03 | E-06 | E-12 | E-09 | E-03 | E-02 | E-08 | E-07 | E-05 | E-11 |
| Proliferation of synovial cells | 3 | 2 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 2 | 1 |
| | 1.80 ± 0.63 (1.67 ± 0.52) | | | | | | | | | | 1.33 ± 0.52 | | | | | |
| Typical palisading | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | 3 | 1 | 1 | 2 | 2 | 2 | 0 |
| | 2.30 ± 0.68*(2.00 ± 0.63) | | | | | | | | | | 1.33 ± 0.82 | | | | | |
| Non-foreign-body giant cells | 2 | 3 | 3 | 1 | 2 | 1 | 1 | 1 | 2 | 1 | 1 | 3 | 1 | 2 | 0 | 0 |
| | 1.70 ± 0.82 (1.33 ± 0.52) | | | | | | | | | | 1.17 ± 0.48 | | | | | |
| Lymphoid cell infiltration | 3 | 1 | 3 | 0 | 2 | 1 | 2 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1.60 ± 0.97† (1.17 ± 0.75*) | | | | | | | | | | 0.00 ± 0.00 | | | | | |
| Plasma cell infiltration | 3 | 3 | 3 | 0 | 3 | 2 | 3 | 1 | 3 | 3 | 0 | 0 | 1 | 0 | 0 | 0 |
| | 2.40 ± 1.08† (2.00 ± 1.27*) | | | | | | | | | | 0.17 ± 0.41 | | | | | |
| Neovascularization | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 3 | 3 | 3 | 2 | 2 | 1 | 3 |
| | 2.20 ± 0.42 (2.17 ± 0.41) | | | | | | | | | | 2.33 ± 0.82 | | | | | |
| Mesenchymoid transformation | 1 | 1 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.80 ± 1.03 (0.50 ± 1.23) | | | | | | | | | | 0.00 ± 0.00 | | | | | |
| Fibrinoid necrosis | 1 | 3 | 2 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 0 | 0 | 1 | 0 | 1 | 0 |
| | 1.00 ± 1.05 (0.50 ± 0.84) | | | | | | | | | | 0.33 ± 0.52 | | | | | |
| Total | 18 | 18 | 19 | 6 | 12 | 10 | 15 | 8 | 13 | 19 | 6 | 8 | 9 | 7 | 6 | 4 |
| | 13.80 ± 4.76† (11.33 ± 4.37*) | | | | | | | | | | 6.67 ± 1.75 | | | | | |

*Tsubaki T, et al. Arthritis Res Ther 2005.*

# How early is early?




H. El-Gabalawy / Best Practice & Research Clinical Rheumatology 23 (2009) 49–58

**Fig. 1.** Conceptual framework for evolution of rheumatoid arthritis (RA) autoantibodies and disease onset. ACPA, anti-citrullinated protein antibody; RF, or rheumatoid factor; SE, shared epitope.

| Systemic autoimmunity associated with RA | Symptoms without clinical arthritis | Unclassified arthritis | RA |
|---|---|---|---|

*Gerlag D et al. Ann Rheum Dis 2012;71:638-41.*

# Benefits of early diagnosis (and DMARD treatment institution) for response to therapy

| | |
|---|---|
| Anderson et al, A&R 2000 | Metanalysis demonstrating that RA pts with a shorter disease duration respond better to similar therapies, as compared with patients with longer-term disease. |
| Lard et al, Am J Med 2001 | Initiation of treatment at a median of 15 days after diagnosis results in improved disease activity at 2 yrs, as compared with treatment initiated a median of 123 days after diagnosis |
| Mottonen et al, A&R 2002 | Delay of initiation of therapy 4 months after the onset of symptoms decreases the ability for a single drug to induce remission |
| Nell et al, Rheumatology 2004 | Pts with a median duration of 3 months have improved outcomes with similar therapies when compared with pts with a median disease duration of 12 months |
| Van der Woude et al, A&R 2009 | Sustained drug-free remission is significantly associated with shorter duration of symptoms at time of initiation of therapy |
| Van der Linden et al, A&R 2010 | Treatment within 3 months of symptom onset is associated with increased chance of DMARD-free remission |

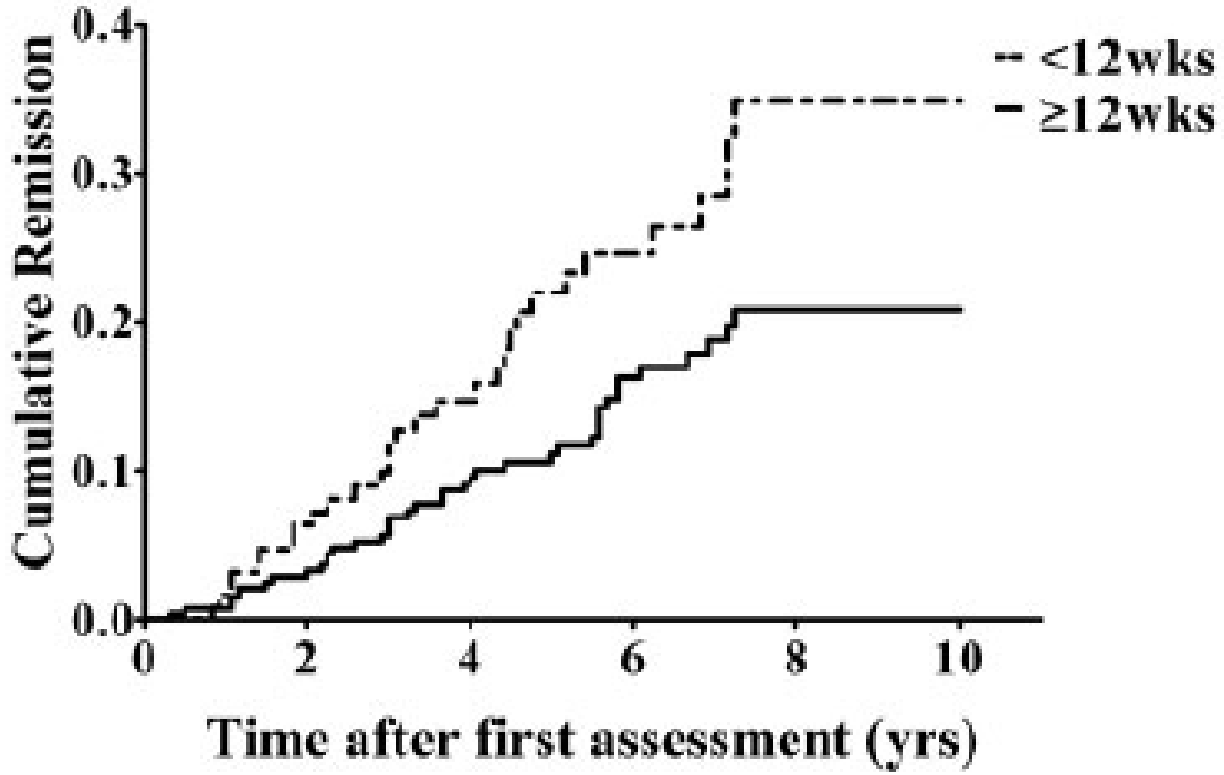
# Benefits of early diagnosis (and DMARD treatment institution) for response to therapy: remission

**Table 4** Model predicting 12-month DAS28 remission in the follow-up cohort of 481 early RA patients with moderate–high disease activity at baseline

| Variables | OR (95% CI) |
|---|---|
| DAS28 T0, <5.1=1 | 1.54 (0.94 to 2.51) |
| HAQ T0, <1.5=1 | 1.29 (0.75 to 2.23) |
| VERA, yes=1 | **2.03 (1.25 to 3.30)** |
| Anti-CCP+, yes=1 | 1.39 (0.94 to 2.07) |
| Erosions T0, yes=1 | 0.47 (0.29 to 1.08) |
| DMARD within 3 months from disease onset, yes=1 | **1.65 (1.06 to 2.55)** |
| Hosmer–Lemeshow test | p=0.59 |

*Gremese E et al. Ann Rheum Dis 2012, doi: 10.1136/annrheumdis-2012-201456*

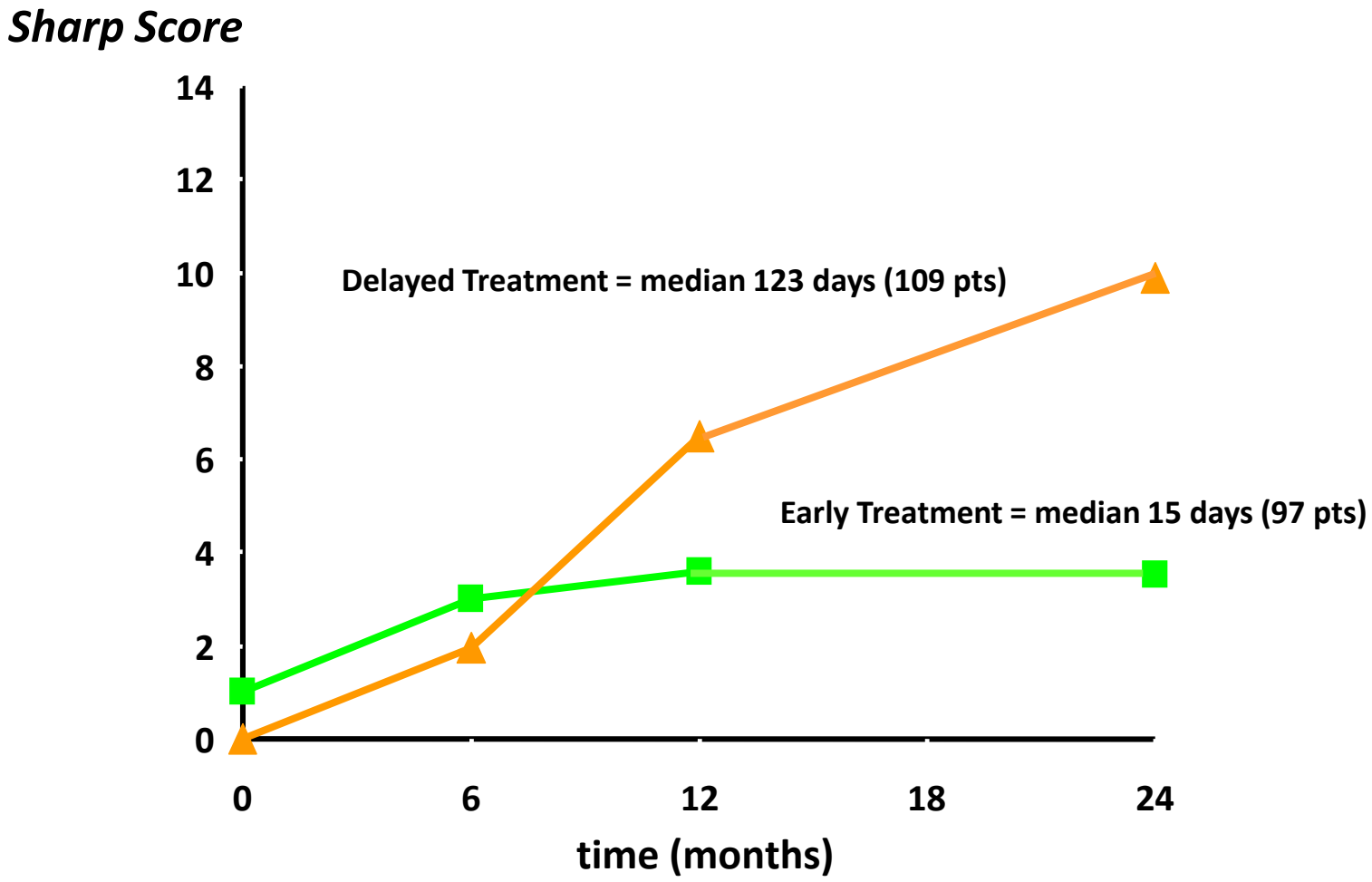
# Benefits of early diagnosis (and DMARD treatment institution) for response to therapy: drug-free remission




**remission: persistent absence of synovitis for at least 1 year after the cessation of DMARD therapy**

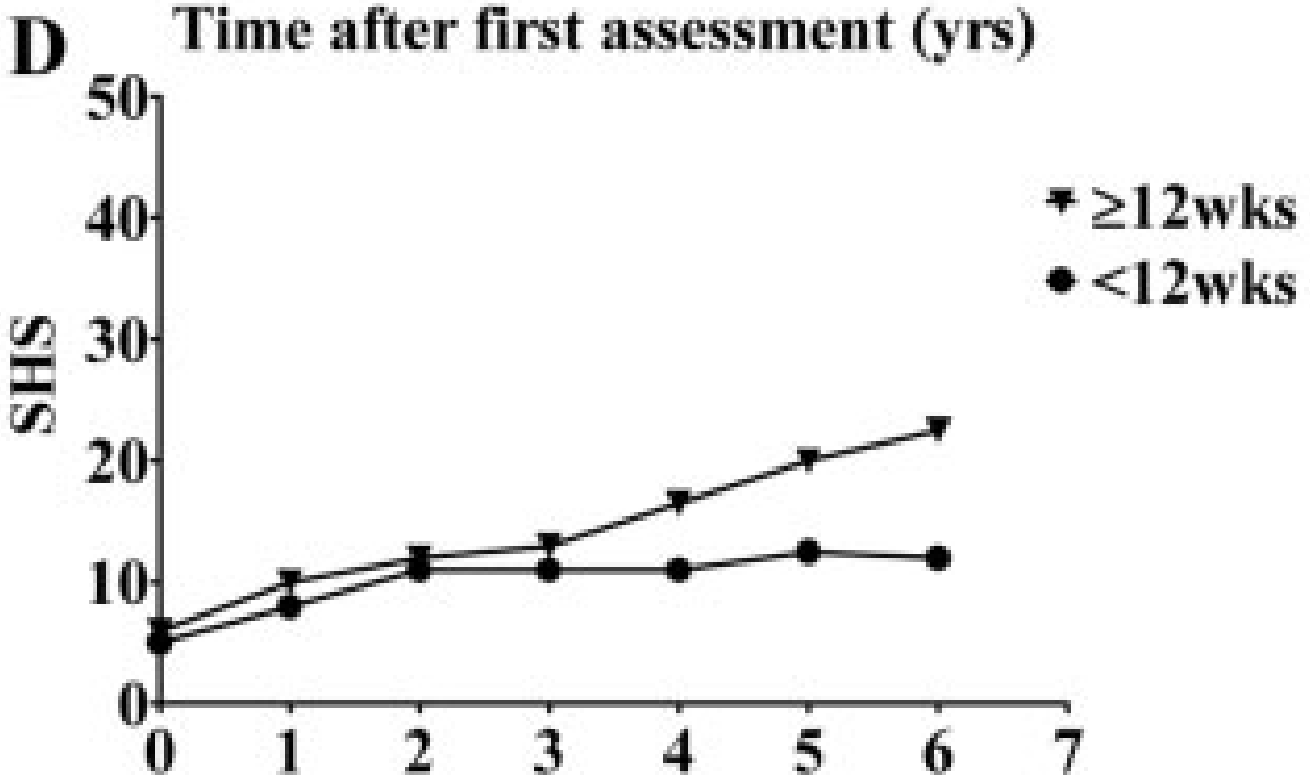
*van der Linden MP et al. Arthritis Rheum 2010;62:3537-46.*

# Benefits of early diagnosis (and DMARD treatment institution) for radiographic progression




*Lard LR et al. Am J Med 2001;111:446-51.*

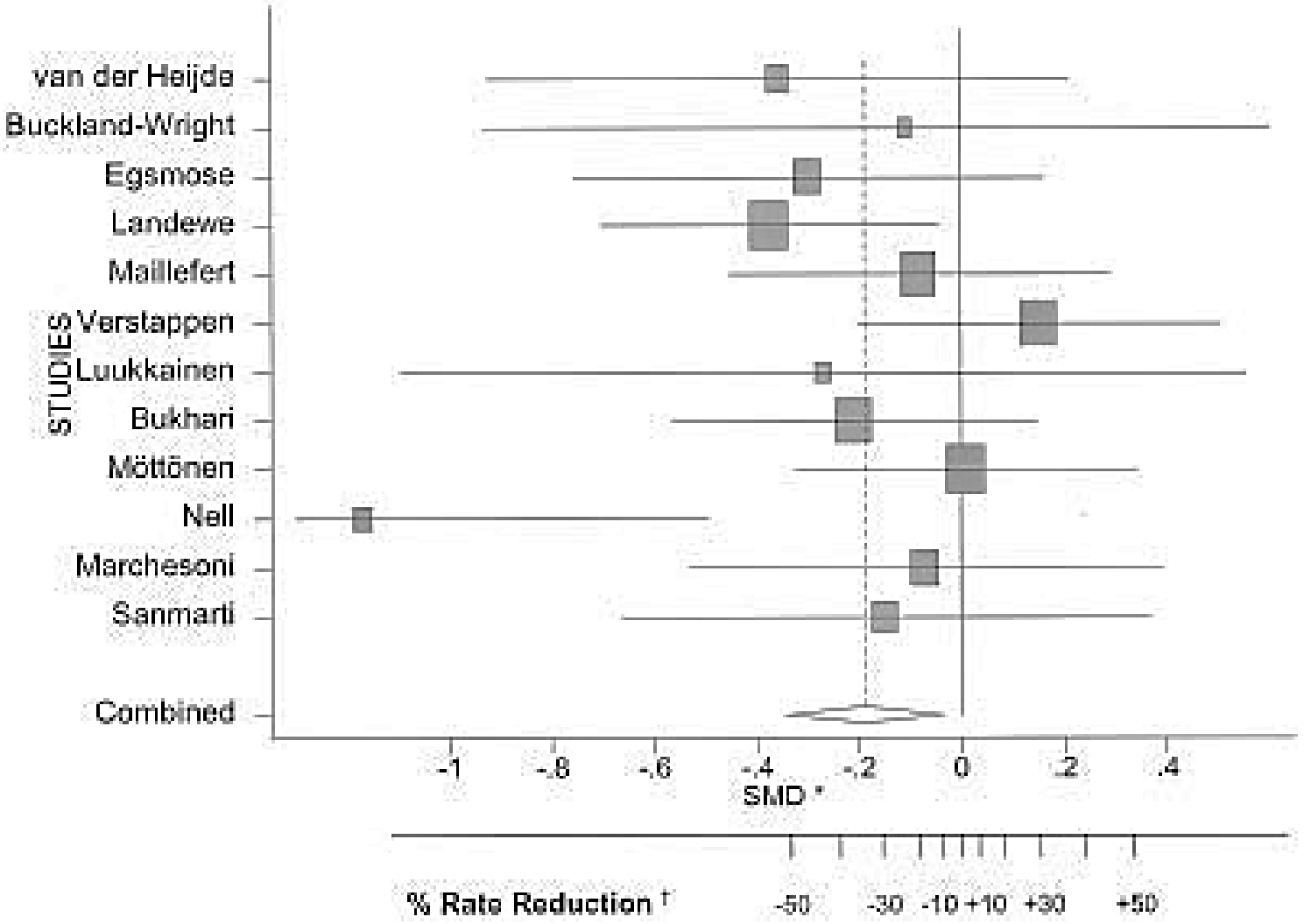
# Benefits of early diagnosis (and DMARD treatment institution) for radiographic progression




**1999–2006, prompt treatment with either sulfasalazine or methotrexate**

*van der Linden MP et al. Arthritis Rheum 2010;62:3537-46.*

# Benefits of early diagnosis (and DMARD treatment institution) for radiographic progression (long-term)




*Finckh A et al. Arthritis Rheum 2006;55:864-72.*

# Benefits of early diagnosis (and DMARD treatment institution)

Early treatment knocks disability progression down and improves work ability

*Puolakka K, et al. Arthritis Rheum 2005;52:36*

Early treatment decreases mortality rate

*Symmons DPM et al. J Rheumatol 1998;25:1072-7.*

Early treatment reduces the cardiovascular risk factors

*Georgiadis AN, et al. Semin Arthritis Rheum 2008*

Early treatment is cost-effective since it slightly increase direct costs but significantly decreases indirect costs

*Korthals-de Bos I, et al. J Rheumatol 2004;31:1709-16*

# Is RA diagnosed early?

Despite increased recognition of the benefits of early treatment there remains considerable delay between symptom onset and the initiation of treatment.

Delays in assessment by rheumatologists reflect a composite of delays on the part of:

(1) the patient seeking medical advice;
(2) the initial healthcare professional (HCP; typically a general practitioner) seeing the patient once an appointment has been sought;
(3) the initial HCP referring to a rheumatologist;
(4) the rheumatologist seeing the patient following a referral.

# Is RA diagnosed early?

| | Berlin | Birmingham | Heraklion | Lund | Prague | Stockholm | Umeå | Vienna | Warsaw | Zurich |
|---|---|---|---|---|---|---|---|---|---|---|
| Total number of patients | 50 | 50 | 42 | 48 | 50 | 55 | 50 | 38 | 50 | 49 |
| Age (years) median (IQR) | 44 (35–59) | 55 (44–69) | 53 (43–62) | 58 (45–68) | 56 (40–60) | 59 (44–68) | 55 (42–67) | 56 (47–66) | 55 (47–62) | 53 (36–62) |
| Gender (female), n (%) | 35 (70) | 33 (66) | 36 (86) | 35 (73) | 35 (70) | 39 (71) | 36 (72) | 29 (76) | 41 (82) | 37 (76) |
| Level of delay (weeks) median (IQR) | | | | | | | | | | |
| Delay 1 | 2 (1–8) | 12 (3–64)* | 22 (8–72) | 8 (4–8) | 8 (2–12) | 4 (2–8) | 8 (2–17) | 2 (1–10) | 4 (1–8) | 8 (4–13) |
| Delay 2† | 2 (1–4) | 1 (<1–1)* | 12 (6–63) | 2 (1–2) | <1 (<1–2) | 1 (<1–2) | 1 (<1–2) | <1 (<1–1)* | 2 (1–8) | 1 (1–2) |
| Delay 3‡ | 10 (3–23) | 2 (1–5)* | 3 (<1–4) | 8 (4–12) | 10 (3–52) | 2 (1–8) | 8 (2–20) | 8 (2–26) | 12 (2–48) | 8 (4–15) |
| Delay 4 | 11 (4–14) | 4 (2–6) | 4 (<1–8) | 3 (2–4) | 4 (2–8) | 3 (2–4) | 4 (2–5) | 1 (1–2) | 4 (1–8) | 2 (1–3) |
| Total delay (weeks) median (IQR)§ | 27 (19–43) | 21 (13–63)¶ | 38 (16–192) | 22 (15–32) | 25 (12–77) | 16 (9–27) | 25 (14–53) | 16 (7–65)* | 35 (14–74) | 20 (13–36) |
| Patients seen ≤12 weeks after symptom onset, n (%)§ | 5 (10) | 9 (19) | 6 (14) | 4 (8) | 14 (28) | 23 (42) | 7 (14) | 14 (38) | 11 (22) | 11 (22) |

Median delay 24 weeks

Median **patient delay**: Heraklion, Birmingham 22, 12 weeks; Vienna, Berlin, Warsaw 2-6 weeks

Median **GP delay**: Heraklion, Birmingham 3, 2 weeks; Vienna, Berlin, Warsaw 8-12 weeks

*Raza K et al. Ann Rheum Dis 2011;70:1822-5.*

Leiden, median delay 18.4 weeks (**patient delay** 3.3 weeks, **GP delay** 15.1)

*van der Linden MP et al. Arthritis Rheum 2010;62:3537-46.*

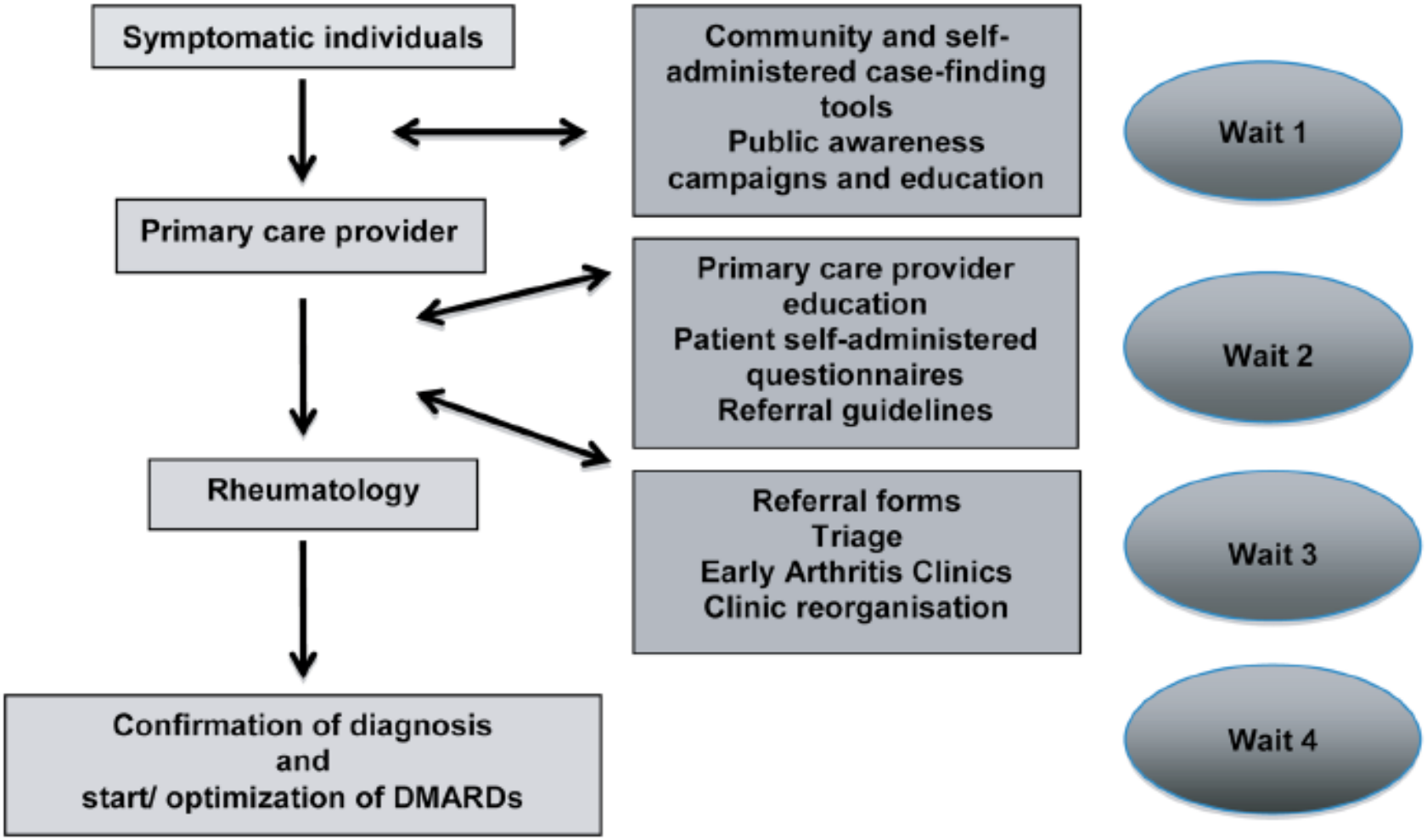
# Is RA diagnosed early?

Reasons for seeking/postponing medical help in patients with arthralgia

| | | Patient delay | | Arthritis at examination | |
|---|---|---|---|---|---|
| | All arthralgia patients N=612 | <4 weeks N=242 | >4 weeks N=245 | Present N=272 | Absent N=340 |
| **Reasons for seeking medical help: Because…** | | | | | |
| The symptoms suddenly occurred | 27.9 | 47.5 | 18.0* | 34.2 | 22.9* |
| The symptoms were getting worse | 65.7 | 60.3 | 69.4* | 64.7 | 66.5 |
| More symptoms occurred | 37.4 | 29.3 | 39.2* | 35.7 | 38.8 |
| I worried about what could be wrong | 42.0 | 43.8 | 43.3 | 43.8 | 40.6 |
| I worried I might have had a joint inflammation | 36.1 | 36.4 | 33.9 | 34.9 | 37.1 |
| I worried I might have had a joint inflammation and I heard/read that you have to act quickly | 14.4 | 14.0 | 13.9 | 14.0 | 14.7 |
| Due to my symptoms, I was unable to do things | 35.1 | 40.9 | 28.6* | 37.5 | 33.2 |
| I wanted to ask for a painkiller | 15.8 | 16.9 | 12.2 | 16.2 | 15.6 |
| My family/friends thought I should go | 22.2 | 22.3 | 21.6 | 26.1 | 19.1* |
| **Reasons for postponing seeking medical help: Because…** | | | | | |
| I was unable to go sooner | 2.0 | 2.9 | 2.0 | 1.8 | 2.1 |
| I wanted to wait and see | 43.0 | 39.7 | 47.3 | 41.2 | 44.4 |
| The doctor could not see me sooner | 1.1 | 1.2 | 1.6 | 1.1 | 1.2 |
| It seemed like it was getting better | 7.5 | 4.1 | 11.4* | 7.0 | 7.9 |
| I thought it would go away by itself | 39.4 | 32.6 | 48.2* | 37.9 | 40.6 |
| I thought nothing could be done about it | 6.4 | 1.7 | 7.3* | 5.5 | 7.1 |
| I thought I wouldn't be taken seriously | 3.4 | 0.8 | 3.7* | 3.3 | 3.5 |
| It didn't seem serious | 12.4 | 7.0 | 16.3* | 11.4 | 13.2 |
| I was afraid it might have been serious | 2.6 | 1.7 | 3.7 | 3.3 | 2.1 |
| I asked somebody else to look at it first | 3.9 | 1.7 | 4.1 | 3.3 | 4.4 |

*van Nies JAB et al. Ann Rheum Dis. 2013;72:1302-7.*

# How can early diagnosis be improved?




*Villeneuve E et al. Ann Rheum Dis 2012.*

# How can early diagnosis be improved?

**Strategies from patients at symptom onset to primary care**

Community case-finding strategies

Questionnaire (Connective Tissue Disease Screening Questionnaire) + autoantibody testing

*Deane KD et al. Arthritis Rheum 2009;61:1642-9.*

Self-adiministered hand test

*Eberhardt K et al. Br J Rheumatol 1988;27:457-61.*

Public awareness programmes

Internet and website information

# How can early diagnosis be improved?

**Strategies from primary care to rheumatology referral**

PCP and health professional education programmes

Patient self-adiministered questionnaires

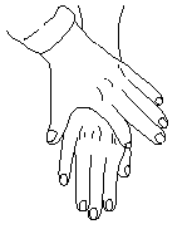
Referral guidelines

- **Several models have been used to facilitate the initial evaluation of patients with early arthritis.**
- **Every rheumatologists has the potential to facilitate early referral**
- **The challenge is to find the model that works best for each**

**Regardless of the model, the goal should be rapid consultation (within 2 weeks) and a process that is easiest for the GP to comply with**

*Cush JJ. Rheum Dis Clin N Am, 2005*

# *Pavia EAC*



**GPs**

**Referral criteria**

**E-mail referral**
**Fax referral**
**Phone referral**

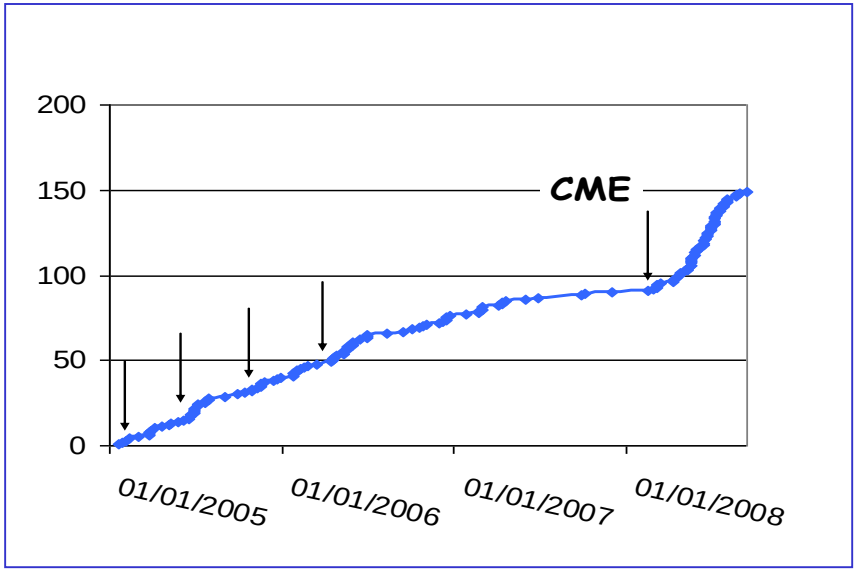
**CME**

**referral**

**general population**

## *Referral criteria*

- ≥ 3 swollen joints
- Positive squeeze test (MCP, MTP)
- Morning stiffness > 30 min



# How can early diagnosis be improved?

**Strategies from rheumatology referral to rheumatology assessment**

Triage of referrals

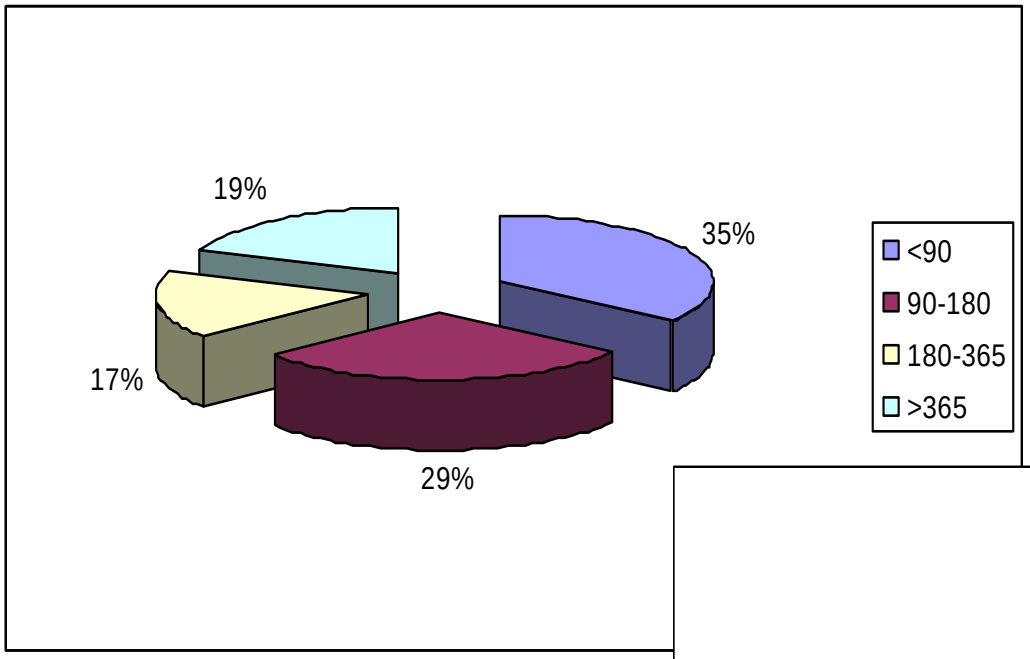
Referral forms

Triage clinics

Rapid access services

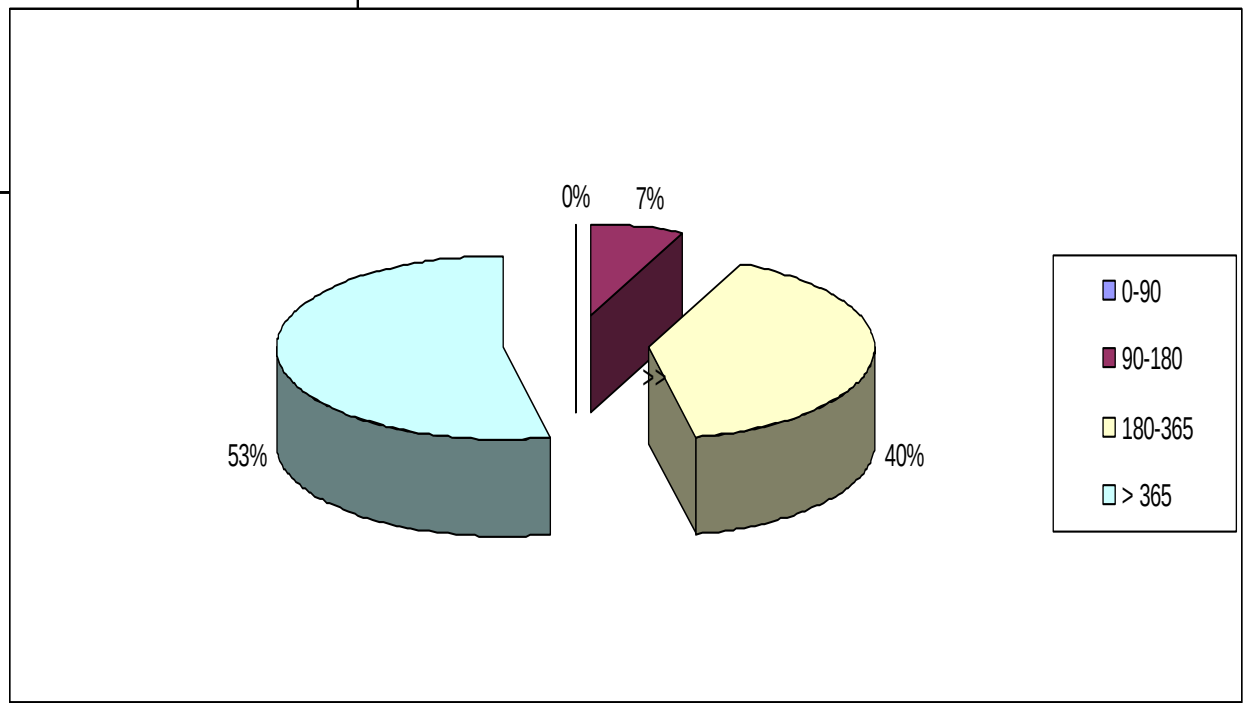
Early arthritis clinics

# Time from first symptom to diagnosis (days)




EAC

Routine outpt clinic



# Beyond EACs

## Early Arthritis Recognition Clinic (EARC)

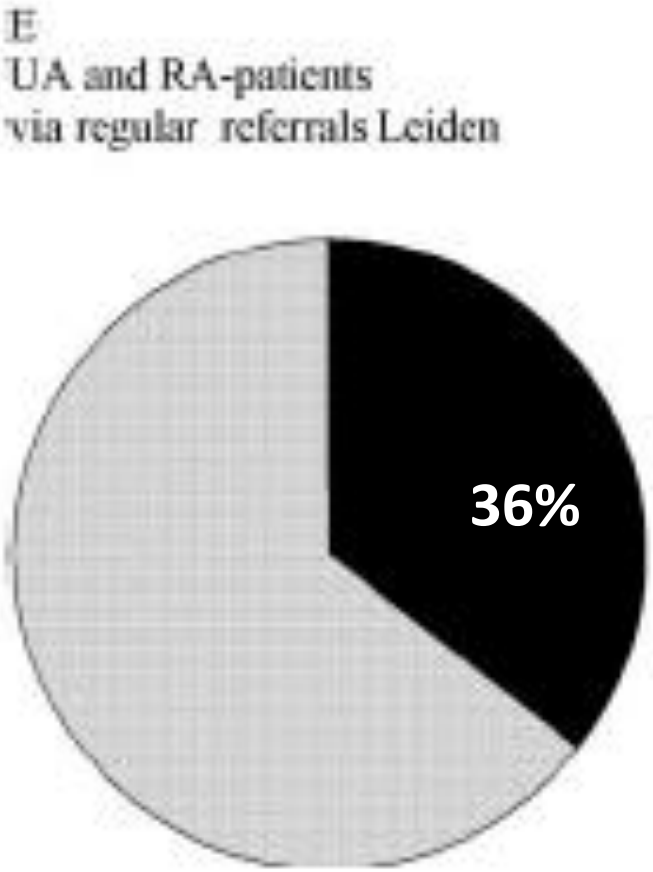
Started in September 2010 in Leiden and in October 2010 in Groningen, the Netherlands.

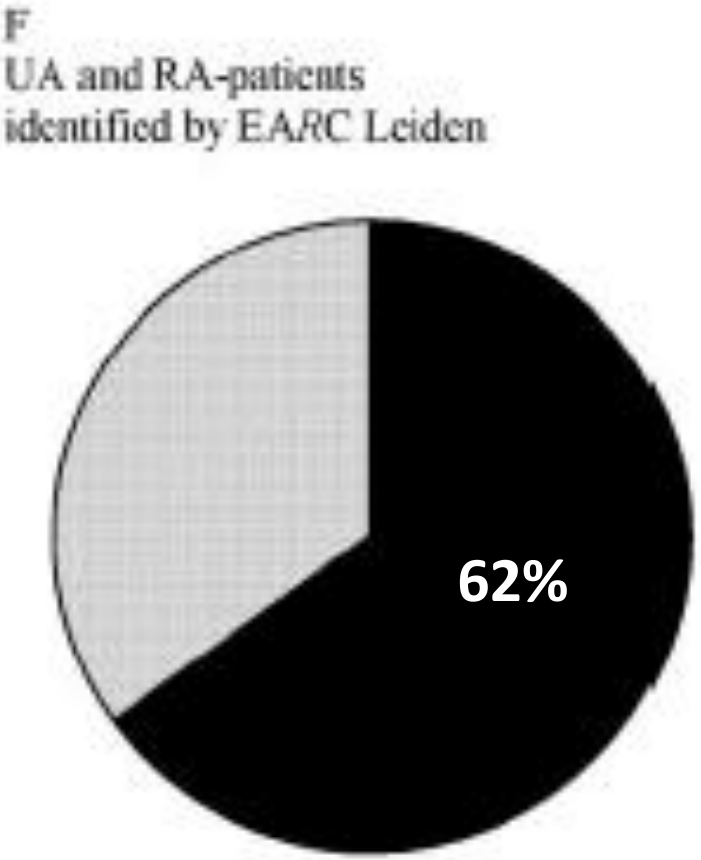
Educational campaign among regional GPs (articles in GP-oriented journals, lectures and discussions at periodic trainings of GPs and correspondence to GPs). No campaign at the level of the general public.

GPs are advised to send any patients for which they have a clinical suspicion of arthritis, instead of applying a ‘wait-and-see’ approach.

At the EARC patients complete a questionnaire about their joint symptoms, their reasons for seeking medical help and a HAQ. Hereafter, they are seen by an experienced rheumatologist who performs a full joint examination. In case arthritis is present, patients visit the general outpatient clinic, within 1 week time for further examinations, inclusion in the EAC and appropriate treatment.

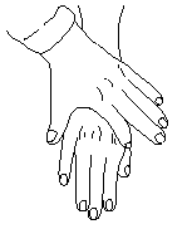
**proportion of pts seen by a rheumatologist within 12 weeks from symptoms' onset**




*Van Nies JAB et al. Ann Rheum Dis 2013;72:1295-301.*

# *Pavia EAC*



**GPs**

**Referral criteria**

**E-mail referral**
**Fax referral**
**Phone referral**

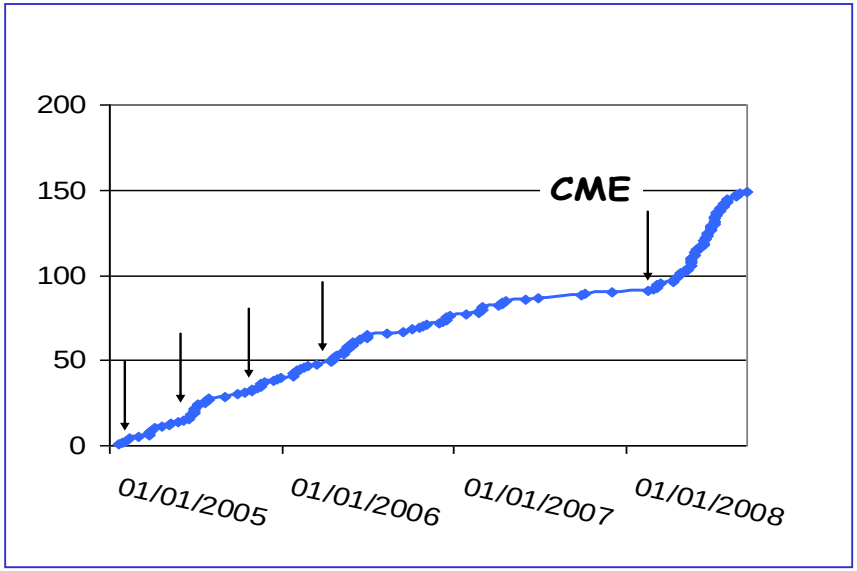
**CME**

**referral**

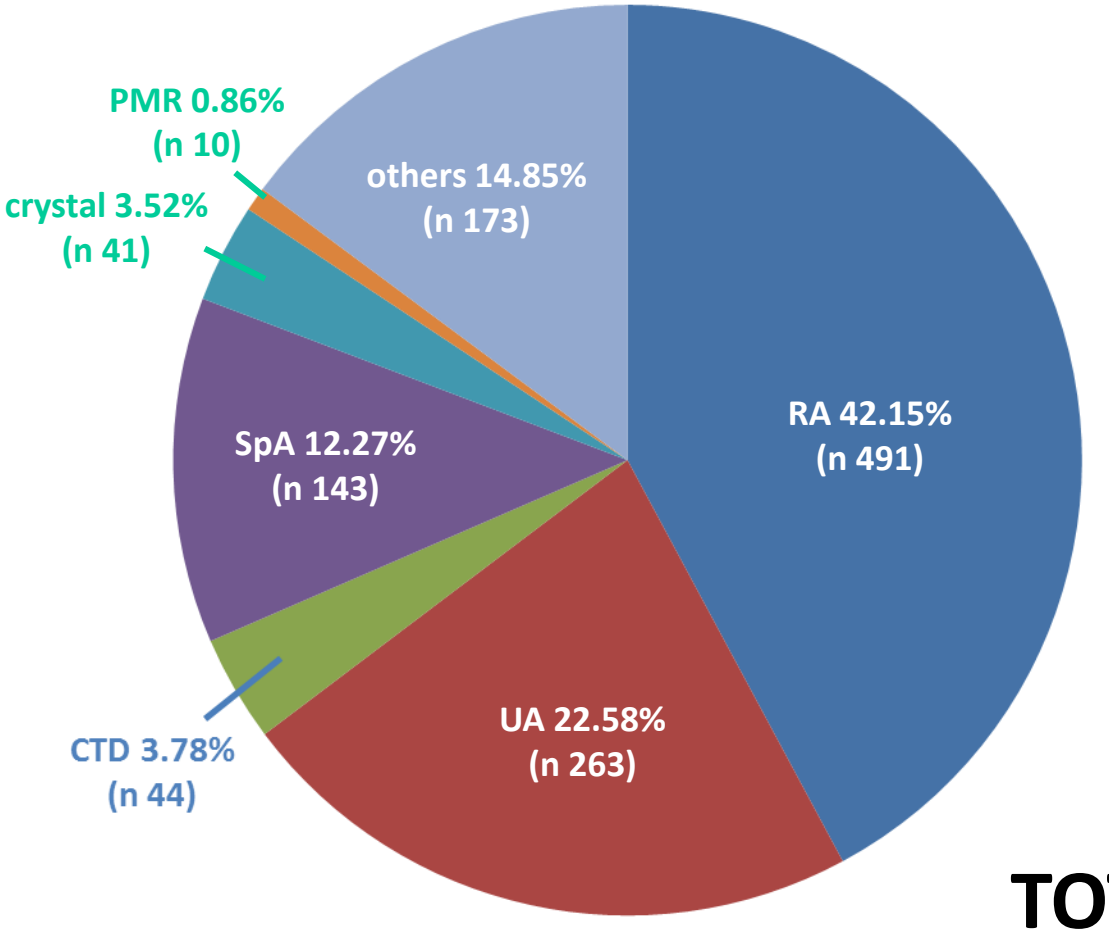
**general population**

## *Referral criteria*

- ≥ 3 swollen joints
- Positive squeeze test (MCP, MTP)
- Morning stiffness > 30 min



# T0: diagnosis




**TOT**

**1.165**

# RA treatment protocol

Tight control: bi-monthly in the first 6 months; 3-monthly from T6 to T36; 6-monthly from T36

DAS28 driven

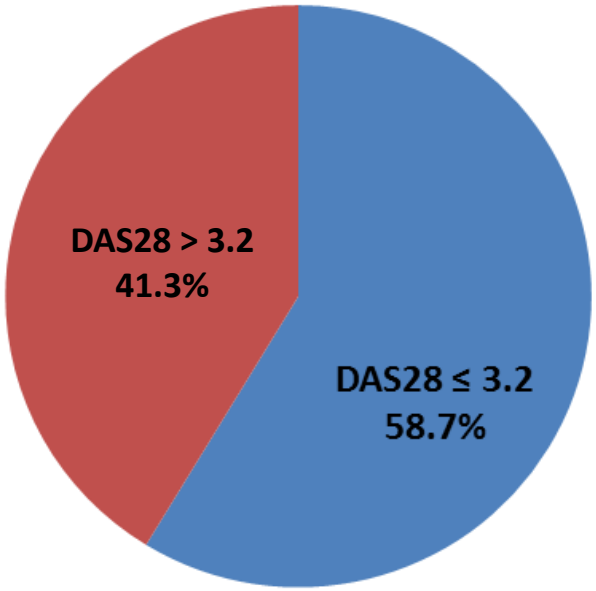
Treatment target: LDA (DAS28 ≤ 3.2)

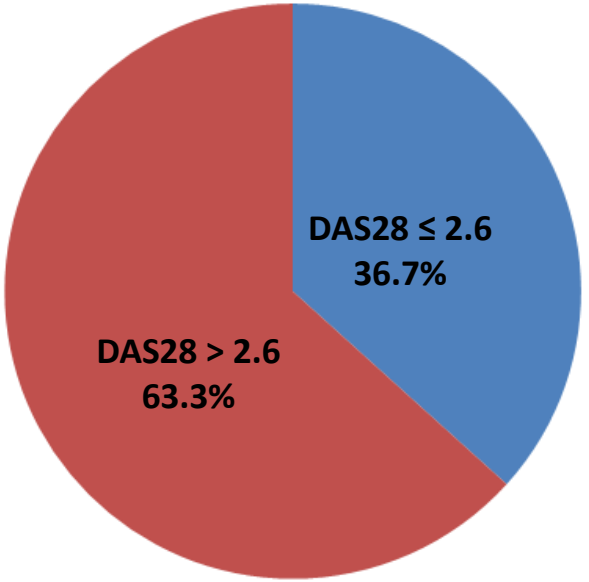
MTX 15 mg/wk ------ MTX 25 mg/wk. From T6, if DAS28 > 3.2: (a) DAS28 > 5.1, add biologic DMARD; (b) 5.1 ≤ DAS28 > 3.2 and poor prognostic factors*, add biologic DMARD; (c) 5.1 ≤ DAS28 > 3.2 without poor prognostic factors, add SSZ 1 g

GCs (in all unless contraindicated): Lodotra 5 mg/d from T0 to T12, 2 mg/d from T12 to T15, then stop

* poor prognostic factors: RF and/or ACPA positivity, early erosive disease, PD-positive synovitis in ≥ 3 joints

# RA: 12 months clinical follow-up




The Future
NEXT EXIT

- MORE DATA ON GENETIC SUSCEPTIBILITY
- MORE DATA ON PRECLINICAL IMMUNOLOGICAL ABNORMALITIES
- MORE DATA ON PRECLINICAL DISEASE IN ANIMAL MODELS

IDENTIFICATION OF PATIENTS AT RISK OF DEVELOPING RA

**DISEASE PREVENTION IN HIGH-RISK INDIVIDUALS ?**