Defining Remission in Rheumatoid Arthritis

Part 1:

Why is a new remission definition in rheumatoid arthritis needed?

Background

- Increasing numbers of patients reach remission
- Abundance of remission definitions
  - 'strict' definitions: American Rheumatism Association (Pinals); SDAI/CDAI
  - 'loose' definitions: DAS/DAS28; mARA; SJC0/TJC0/ESR10; MDA

→Need for a uniform definition

(RA trials, practice)

Etymology

- *Remittere* (L):
  to send back; to decrease; to relax...
- *Remission*
  - (med dictionary): an abatement or lessening of the manifestations of a disease
  - (Wiki): the state of absence of disease activity in patients with a chronic illness, with the possibility of return of disease activity

Concept: Key Points

- Remission is a state, not change or transition
- Absence of disease activity

Concept: Remission

- Related but not identical to remission:
  - *Cure:* disease does not return
  - *Arrest:* disease progression is stopped
  - *Intermission:* period of no activity between two periods of active disease
- Remission is antithetical to the following:
  - *Relapse:* return of disease activity
  - *Flare:* substantial increase of disease activity

Current Definitions: American Rheumatism Association*

- 5 or more must be fulfilled for at least 2 consecutive months:
  - Morning stiffness not exceeding 15 minutes
  - No fatigue
  - No joint pain (by history)
  - No joint tenderness or pain on motion
  - No soft tissue swelling in joints or tendon sheaths
  - ESR (W) < 30 mm/h (f); < 20 mm/h (m)

** Pinals RS, et al. Arthritis Rheum 1981;24:1308-15.*

ARA (Pinals)

- 3 groups of RA patients classified according to the rheumatologist:
  - complete remission
  - partial remission
  - active disease
- Sensitivity 72%;
  Specificity 90% (against partial remission)

Problems with ARA (Pinals) Definition

- Depends on measures not widely assessed now in RA trials:
  - Morning stiffness (absent in many patients with active RA)
  - Tendon sheath swelling
- Very strict definition
  - Attainment very rare in RA trials
  - Thus unrealistic target for treatment success
- Many unvalidated modifications in use

DAS/DAS 28
Threshold for Remission*

- DAS: Ritchie joint index and 44 swollen joint ct
- DAS28: 28 tender & swollen joint count
- ESR/CRP versions
- Both use a 'general health' VAS (0-100)

- DAS28 remission: < 2.6
- DAS remission: < 1.6

** Fransen J et al. Rheumatology 2004;43:1252-5.*

DAS/DAS28 Remission

- Validation against ARA (Pinals) criteria in Nijmegen data, moderately active disease
- Modified ARA (Pinals) criteria used:
  - Fatigue not assessed
  - Remission defined as 4 out of 5 remaining criteria
- Sensitivity and specificity against modified ARA (Pinals) 87%

SDAI/CDAI Remission

- SDAI = (28TJC) + (28SJC) + MDGA + PtGA + CRP*
- CDAI = (28TJC) + (28SJC) + MDGA + PtGA*
- SDAI remission ≤ 3.3**
- CDAI remission ≤ 2.8**
- Developed in patient profile exercise and validated in observational datasets

* *Smolen JS et al. Rheumatology. 2003;42:244*

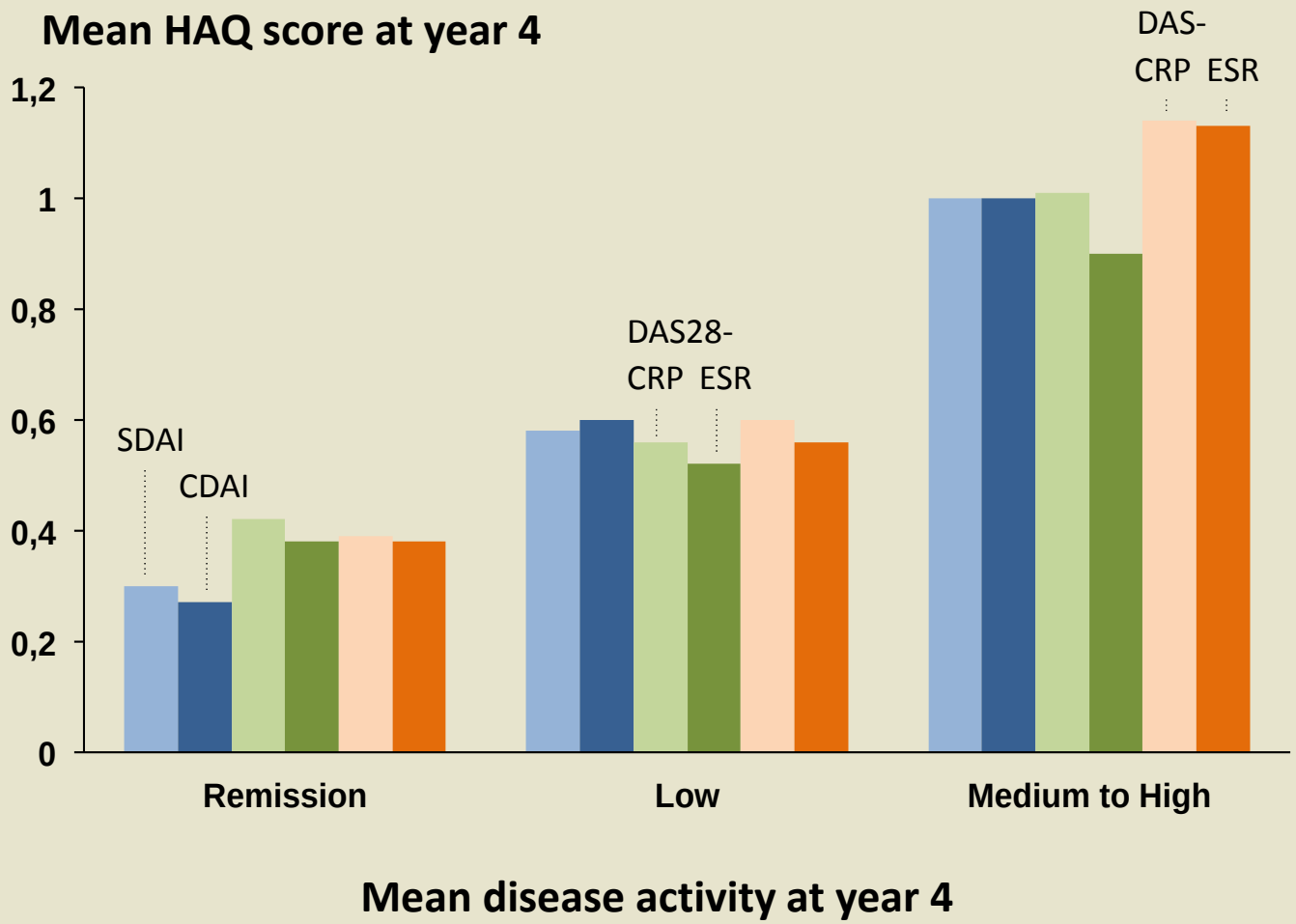
** *Aletaha D et al. Arthritis Rheum. 2005;52:2625*

Other Definitions of Remission and Related States

- PAS and RAPID3:* both based solely on patient reported outcomes
- Minimal Disease Activity:** developed at OMERACT, based on core set measures
- Yet other definitions exist, both for remission and minimal disease activity

** Wolfe F et al. J Rheumatol 2005;32:2410-5.*
*** Wells GA et al. J Rheumatol 2005;32:2016-24.*

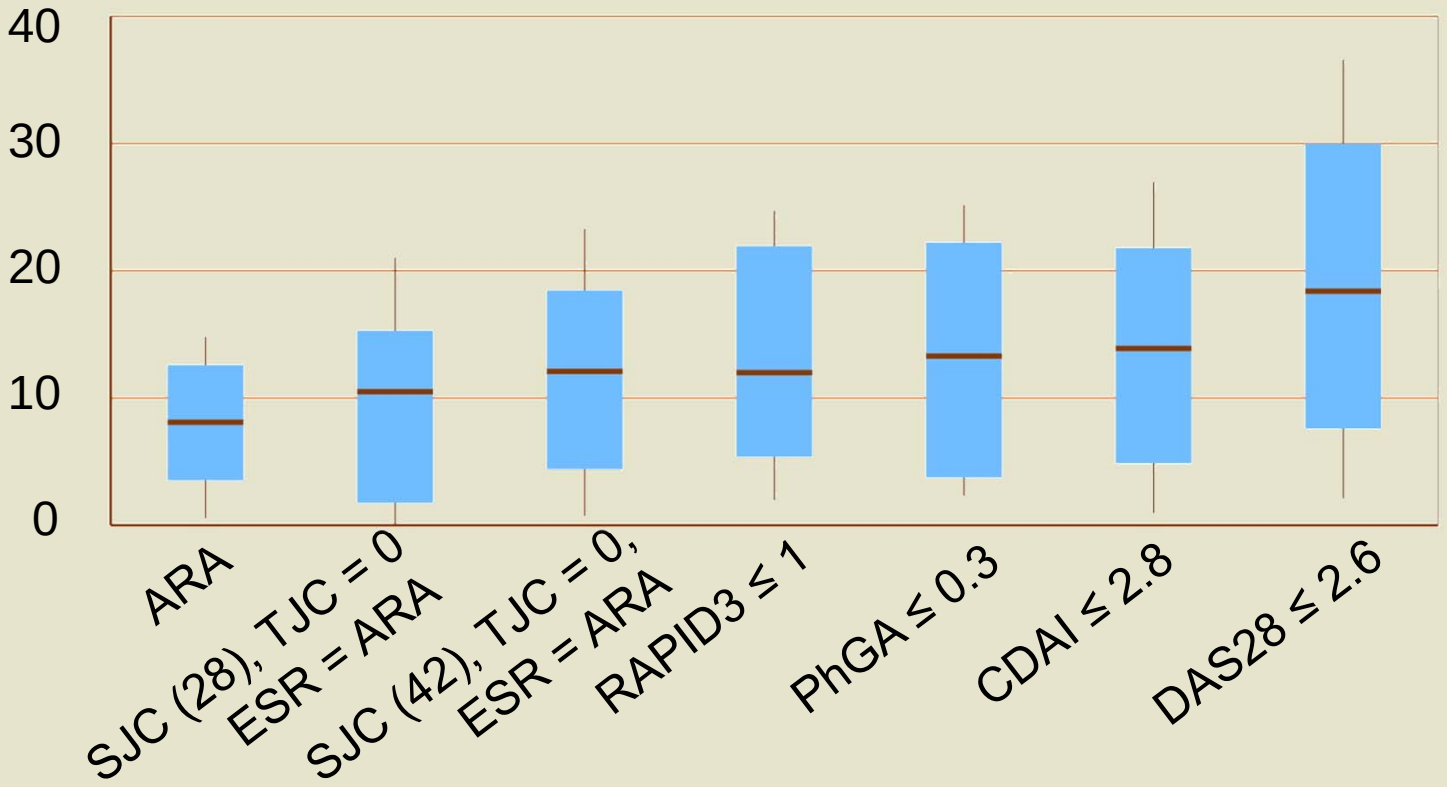
Another Reason to Define Remission: Associated with Best Functional Outcome (BeSt Data)



Koevoets et al. Arthritis Rheum 2009; 60 Suppl 10:957.

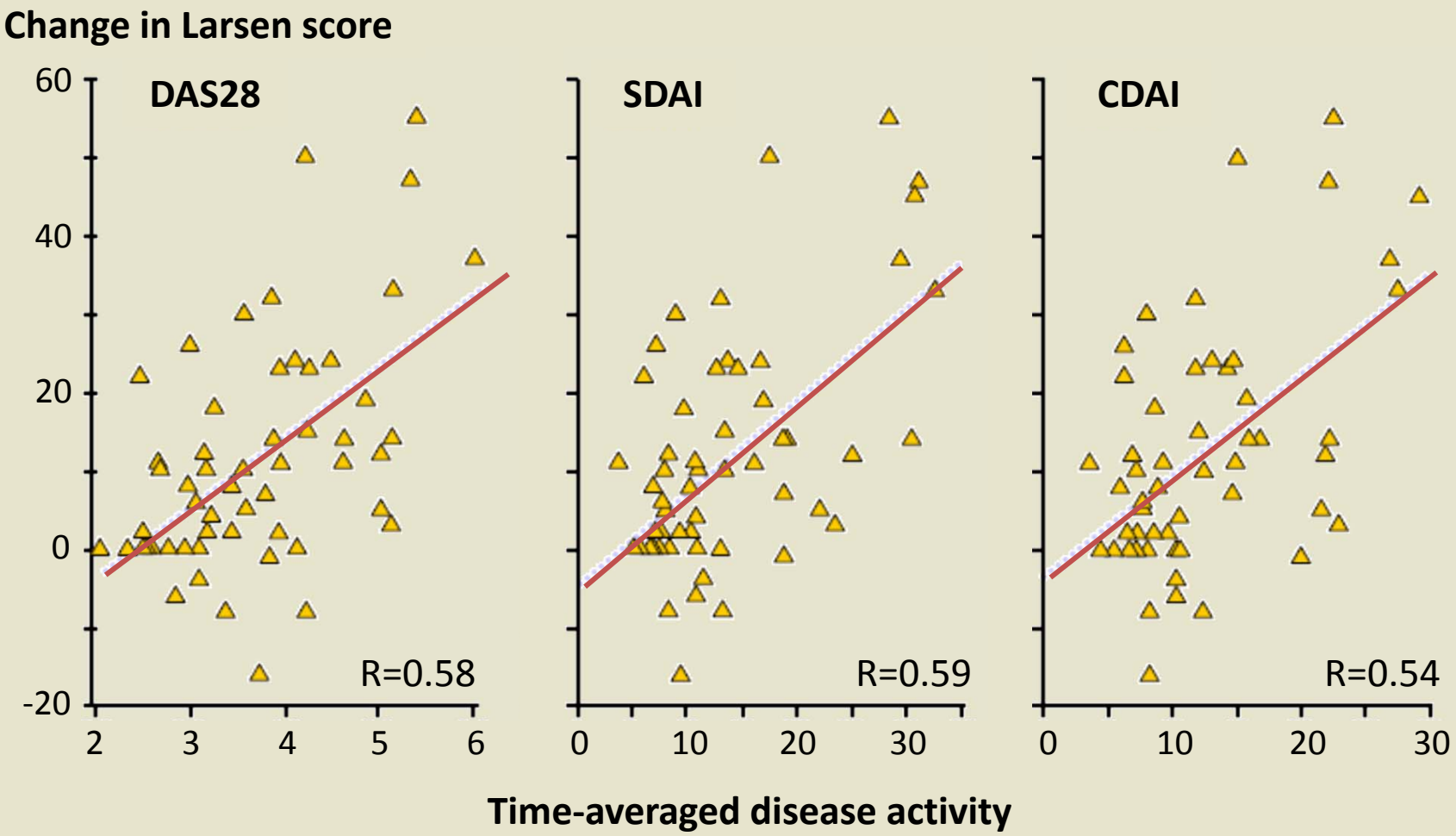
How Strict Are Current Definitions? Prevalence of Remission in QUEST-RA*

- Survey of RA patients in 24 countries



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

Levels of RA Disease Activity Measures Are Associated With X-ray Progression



Aletaha et al. Arthritis Res Ther. 2005;7:R796-806.

Background: Conclusion

- 'Strict' and 'loose' definitions of RA remission
  - ARA (Pinals), CDAI/SDAI, PAS/RAPID3 - 'strict'
  - Modified ARA, DAS28 - 'loose'
- No definition universally used
- Variability in how each definition is operationalized
- Remission leads to better RA outcomes
- Agreement on need for uniform definition(s)

ACR/EULAR 2011 Provisional Definition of Rheumatoid Arthritis Remission:

How was it developed
and how will it work?

Who was involved?

- A broad Parent Committee, including representatives of ACR, EULAR and OMERACT, set out goals, defined the tasks, evaluated interim analyses
  - RA trialists/clinicians + patient experts
- A smaller Working Committee carried out the analyses and presented findings to the Parent Committee

Outline of Approach

- Charge from committee
- Survey committee members on threshold for remission
- Address whether patient reported outcomes should be included
- Create possible definitions of remission
- Test possible definitions
  - Predictive validity
  - Face validity
- Decide on definition(s) of remission
- Address remaining concerns

Where did the data come from?

- Actual data from large, multicenter RA trials of 2nd line drugs/biologics
- Appreciation to:
  - Amgen, Abbott, Wyeth and others who shared data
- Industry had no role in criteria development process

ACR/EULAR Committee Requirements (1)

The definition should:

- be stringent
  - little, if any, residual active disease
- include at least the following core set measures
  - tender + swollen joint counts, acute phase reactant
- not include physical function
  - affected by disease duration
  - outcome used for validation
- not include presence or absence of treatment
- not include duration of remission

ACR/EULAR Committee Requirements (2)

The definition should further:

- predict good outcome
  - later lack of x-ray damage and stable good function
- be defined for trials
  - subsequent modification for clinical practice
- pass the OMERACT Filter*
  - Truth: unbiased and relevant
  - Discrimination: discriminate between relevant states
  - Feasibility: easy to apply and to interpret

* *Boers M et al. J Rheumatol 1998;25:198-9.*

Core Set for RA Clinical Trials*

- Patient global assessment of disease activity
- Physician/Assessor global assessment of disease activity
- Pain
- Tender joint count (TJC)
- Swollen joint count (SJC)
- Physical disability
- Acute phase reactant

**Felson et al, Arthritis Rheum 1993;36:729-40;*
Boers et al, J Rheumatol 1994;21(suppl 41):86-9.

Step 1: What cut points of core set measures are compatible with remission?

- Survey of 27 Committee members, including patients
- Asked to choose threshold for remission…
  - If a variable was the only measure used
  - If all other measures pointed to remission

→RESULTS: thresholds for remission for most core set measures cluster around values of 1

What would be the threshold for remission if _____ was the only measure used?

	Mean (s.d.)	Median	80th percentile
TJC28	1.1 (1.3)	1	2
SJC28	0.5 (0.9)	0	1
CRP (mg/dL)	0.9 (0.4)	1	1
Pain (0-10 scale)	1.3 (0.7)	1	2
Physician Global Assessment (0-10)	1.0 (0.9)	1	1
Patient Global Assessment (0-10)	1.2 (0.8)	1	2

What would be the threshold for remission if all other measures pointed to remission?

	Mean (s.d.)	Median	80th percentile
TJC28	2.6 (2.0)	1	4
SJC28	1.3 (1.3)	1	2
CRP (mg/dL)	1.1 (0.6)	1	1.5
Pain (0-10 scale)	2.4 (1.3)	2	3
Physician Global Assessment (0-10)	1.6 (1.0)	2	2
Patient Global Assessment (0-10)	2.2 (1.3)	2	3

Step 2: Should patient reported outcomes be included?

- PRO's: patient global; pain
- Analysis of 4 large multicenter trials of TNF inhibitors + MTX vs. MTX alone
- What outcomes best identified the efficacy of the biologic/MTX combination?
  - Whatever outcomes had the most stringent p value discriminating comb. vs. MTX were the best outcomes
  - If PRO's discriminate comb. vs. MTX, they detect effect of treatment as well/better than non-PRO's

How do PRO's rank among 7 core set outcome measures? Analysis of 4 trials

	Patient Global Assessment	Patient Pain
Trial #1	1st	
Trial #2	4th	
Trial #3		2nd
Trial #4	not in top 4	

PRO's help identify effective treatments. At least one should be included in the definition of remission.

Step 3: What candidate definitions of remission should be tested?

- Boolean Definitions
  - Depend on meeting a (low) level in each of a series of separate disease activity measures
- Index Definitions: DAS28, SDAI
  - An index is a formula combining several measures
  - Definitions depend on meeting a (low) level in the index

Tested Definitions: Boolean

- TJC28, SJC28, CRP* all ≤ 1
- TJC28, SJC28, CRP, PatientGA* (PtGA) all ≤1
- TJC28, SJC28, CRP, Pain all ≤1
- TJC28, SJC28, CRP, PhysicianGA (PhGA), PtGA all ≤1
- TJC28, SJC28, CRP, PhGA, Pain all ≤1
- TJC28, SJC28, CRP, PtGA, Pain all ≤1
- TJC28, SJC28, CRP, PhGA, PtGA, Pain all ≤1

**GA: 0-10 scale; CRP: mg/dl*

Indexes Tested

- **DAS28**

  = 0.56*√(TJC28) + 0.28*√(SJC28)
  + 0.36*Ln(CRP*10 + 1) + 0.014*PtGA (0-100 scale)
  + 0.96

  – Levels tested: DAS28 < 2.6; DAS28 < 2.0

- **SDAI** (Simplified Disease Activity Index)

  = TJC28 + SJC28 + PtGA (0-10 scale) + PhGA (0-10) + CRP (mg/dL)

  – Level tested: SDAI $\leq$ 3.3

Step 4: Predictive Validity
Comparing the Candidate Definitions

- Does remission predict later good outcome?
- Remission at month 6 should predict good outcome for x-ray and HAQ between 12 and 24 months:
  - X-ray - **good outcome**:
    change ≤ 0 in modSharp or Sharp-vdH score
  - Function - **good outcome**:
    change ≤ 0 in HAQ and HAQ score ≤ 0.5

Validity of Candidate Remission Definitions: Predicting a Good Outcome for X-ray

	Percent in Remission with Good Outcome	Percent NOT in Remission with Good Outcome	Positive Likelihood Ratio	P Value
TJC28, SJC28, CRP ≤ 1	69%	50%	2.0	0.01
+ PtGA ≤1	77%	51%	2.9	0.006
+ Pain ≤1	74%	51%	2.6	0.01
+ PhGA and PtGA ≤1	77%	51%	2.9	0.01
+ PhGA and Pain ≤1	77%	51%	2.9	0.01
+ PtGA and Pain ≤1	76%	51%	2.8	0.001
+ PhGA, PtGA and Pain ≤1	76%	51%	2.8	0.02

Validity of Index Remission Definitions: Predicting a Good Outcome for X-ray

	Percent in Remission with Good Outcome	Percent NOT in Remission with Good Outcome	Positive Likelihood Ratio	P Value
TJC28, SJC28, CRP, PtGA ≤1	77%	51%	2.9	0.006
I N D E X E S				
DAS28<2.6	60%	59%	1.0	0.93
DAS28<2.0	70%	59%	1.6	0.48
SDAI≤3.3	77%	50%	3.0	0.003

Validity of Candidate Remission Definitions: Predicting a Good Outcome for Both X-ray and HAQ

	Percent in Remission with Good Outcome	Percent NOT in Remission with Good Outcome	Positive Likelihood Ratio	P Value
TJC28, SJC28, CRP ≤ 1	46%	17%	3.2	<.0001
+ PtGA ≤1	66%	17%	7.2	<.0001
+ Pain ≤1	60%	17%	5.7	<.0001
+ PhGA and PtGA ≤1	68%	17%	8.0	<.0001
+ PhGA and Pain ≤1	64%	18%	6.7	<.0001
+ PtGA and Pain ≤1	64%	17%	6.8	<.0001
+ PhGA, PtGA and Pain ≤1	67%	18%	7.5	<.0001

Validity of Index Remission Definitions: Predicting a Good Outcome for Both X-ray and HAQ

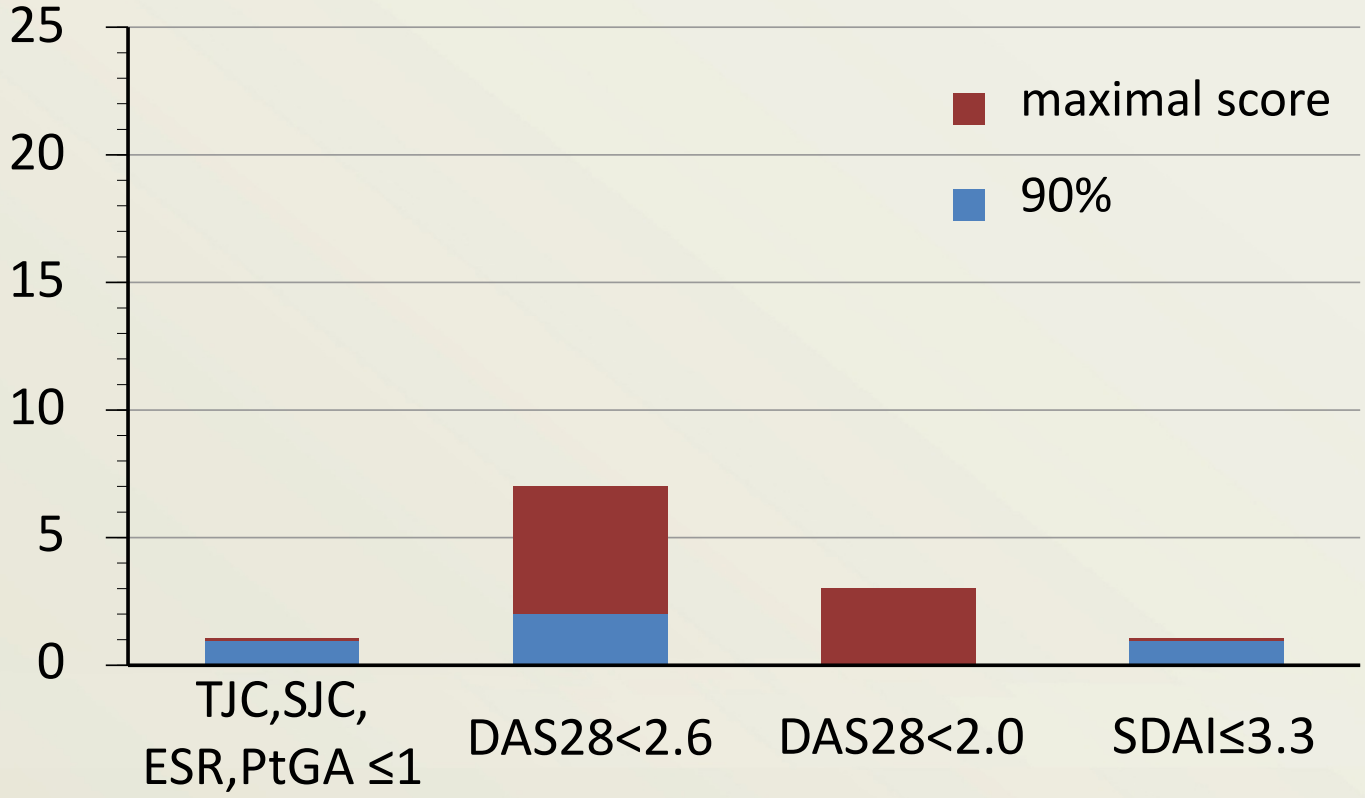
	Percent in Remission with Good Outcome	Percent NOT in Remission with Good Outcome	Positive Likelihood Ratio	P Value
TJC28, SJC28, CRP, PtGA ≤1	66%	17%	7.2	<.0001
I N D E X E S				
DAS28<2.6	38%	18%	2.2	0.01
DAS28<2.0	56%	20%	4.5	0.01
SDAI≤3.3	56%	17%	4.8	<.0001

Predictive Validity Analyses

- **Boolean definitions** with SJC, TJC, CRP and patient reported outcome(s) have similar predictive validity

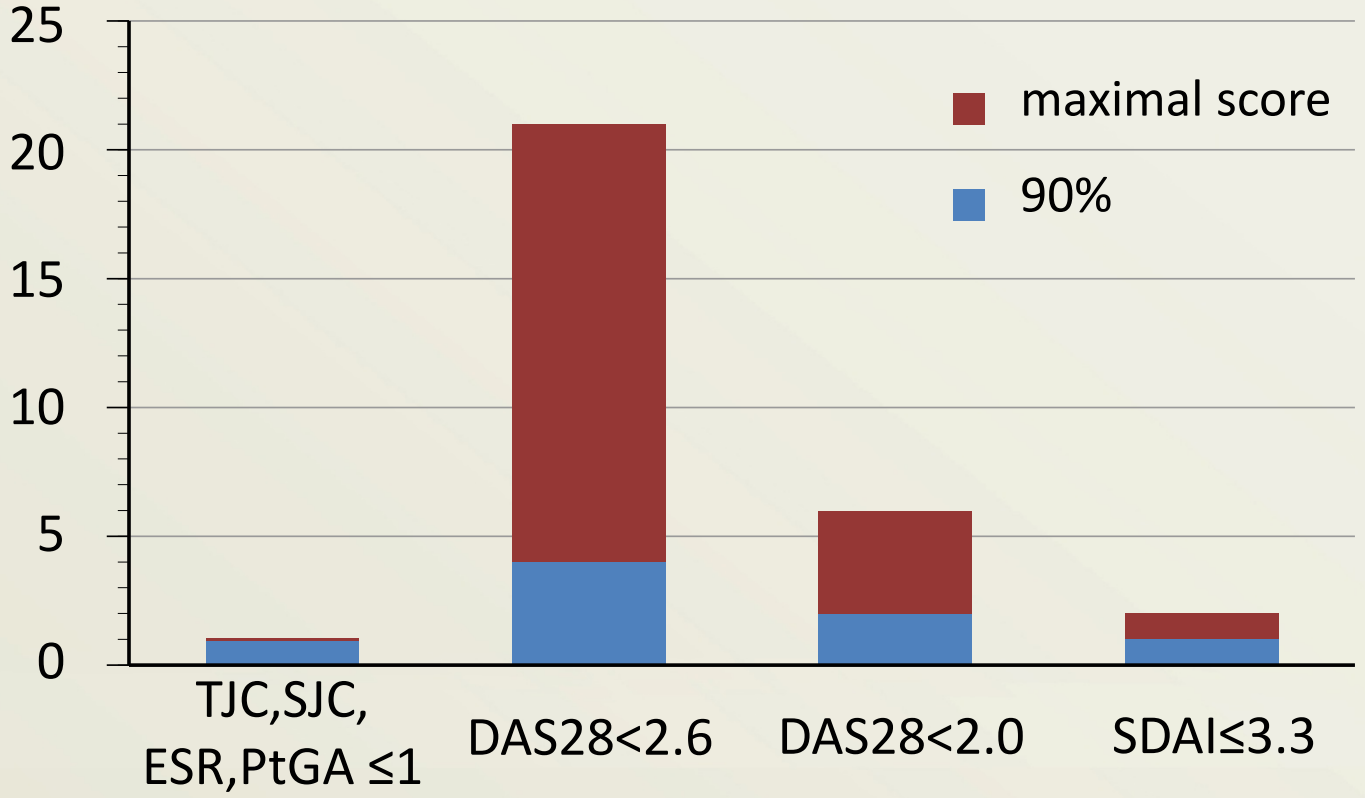
- **Indexes** did not perform the same:
  - DAS28 < 2.6 did not predict later good outcome as well as DAS < 2.0 or SDAI $\leq$ 3.3
  - DAS28 < 2.0 did not predict x-ray outcome well and was achieved rarely (<1/3 as often as other index thresholds)
  - Possible explanation: in DAS28, TJC is strongly weighted; TJC predicts X-ray less well than SJC

Step 5: Face Validity
If you meet the remission definition, do you always have a low tender joint count?



Step 5: Face Validity

If you meet the remission definition, do you always have a low swollen joint count?



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Summary of Face Validity Analyses

- **Boolean definitions** required low SJC and TJC by definition
  - not more than 1 of both possible
- **For Indexes:**
  - SDAI
    - Maximum of 2 active joints possible (same for CDAI)
      - CRP in SDAI to be set to 0.5 if lower
    - Maximum of 2 active joints seen in analyses
  - DAS28
    - SJC and TJC of 3-6 active joints were not rare
    - These are incompatible with remission

Step 6:
Committee Decision on Definition

- Committee meeting October 2009
- Split into two groups to discuss data –
  Same consensus achieved in both groups:
  One Boolean definition, one index definition
- Select one of these as outcome in each trial
- Report both

ACR/EULAR 2011 Provisional Definitions of Remission for Clinical Trials

- **Boolean Based Definition**
  At any time point, a patient must satisfy all of the following:
  - Tender Joint Count ≤1
  - Swollen Joint Count ≤1
  - CRP ≤1 mg/dL
  - Patient Global Assessment ≤1 (on a 0-10 scale)
- **Index Based Definition**
  At any time point, a patient must have SDAI ≤3.3

Global Assessment: How to Word the Question

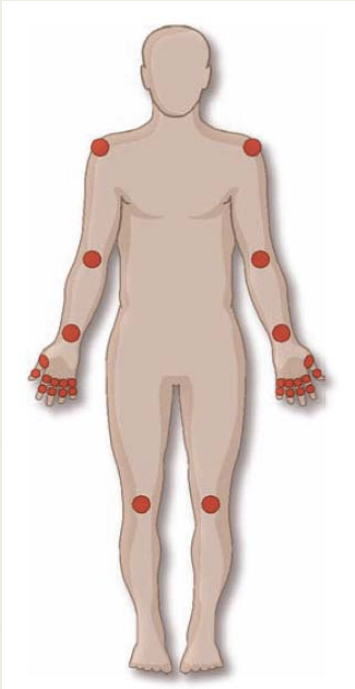
- The following wording and response categories should be used for global assessment:
  Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?
- Verbal anchors for the response are ‘very well’ and ‘very poor’

Percentage Achieving Remission in Recent Trials by Definition

Remission definition	DMARD monotherapy (n=380)	Biological monotherapy (n=520)	Combination Therapy (n=330)	Total (n=1230)
TJC,SJC,CRP ≤ 1 + PtGA ≤ 1	9	7	22	12
+ PtGA, pain ≤ 1	8	6	20	12
+ PtGA, PhGA ≤ 1	8	7	20	10
+ PhGA, pain ≤ 1	8	6	20	10
+ PtGA, PhGA,pain ≤ 1	7	6	18	9
DAS28 <2.6	19	17	35	21
DAS28 < 2.0	5	8	24	10
SDAI ≤ 3.3	10	8	26	14

Concern 1:
28 Joints Used to Define Remission vs. Full Joint Count

28 joints counted →



What if foot/ankle joints active? Should patient be in remission?

In Patients with 28 Joint Count ≤ 1

- <10% had active ankles/feet
- In these, PtGA was often high, thus:
  - would not meet criteria for remission anyway
- How many not in remission when full joint counts used (i.e., 'false positive' for remission)?
- Compare drop in % remission in 2 trials:
  - Trial 1: from 6% (28 jt count) → 4% (full jt count)
  - Trial 2: from 14% → 9%
  - Yet, similar % of good outcome in remission:
    - 80-90% in full jt count remission
    - 1-4% less when only in 28 jt count remission

Recommendation for Joint Counts

- The new ACR/EULAR criteria do not *require* inclusion of ankles and forefeet in the assessment of remission but *recommend* that these joints are also included in the examination

- Investigators should always report which joints were examined

Concern 2:
What value of ESR corresponds to CRP = 1?

- In men with RA, CRP value of 1mg/dl corresponds roughly to 20mm/hour*

- In women with RA, CRP value of 1mg/dl corresponds roughly to 30mm/hour*

**Wolfe, J Rheumatol 24: 1477-1485, 1997*

Other Concerns: Elements for the future?

- Fatigue
  - Could not be studied because trial datasets contained no information on it
  - Part of the research agenda

Other Concerns: Elements for the future?

- Fatigue
- Imaging
  - Need a clinical definition of remission now
  - Imaging standards not yet developed
  - Given high rate of synovitis in clinically inactive RA joints, not clear that a 'no synovitis' threshold on imaging could be achievable at present

Conclusion for Defining Remission in Trials

- New Definition of Remission in RA
  - Stringent
  - Achievable
  - Should be major outcome for trials
  - Variants on these definitions may be utilized in practice settings

Assessing RA Remission in Practice

- Acute Phase Reactant often unavailable during patient visit
- Can we suggest a definition of remission without Acute Phase Reactant?

- All data sets used to derive remission definition were from trials, not practice
- Trials are different from practice
  - Trials include only selected patients
    - high disease activity, otherwise comparatively healthy
  - Long term follow-up in trials is selective

Validity of Definitions without ESR/CRP: Predicting a Good Outcome for Both X-ray and HAQ

	Percent in Remission with Good Outcome	Percent NOT in remission with Good Outcome	Positive Likelihood Ratio	P Value
TJC28, SJC28, CRP + PtGA ≤1	66%	17%	7.2	<.0001
SDAI≤3.3	56%	17%	4.8	<.0001
DEFINITIONS WITHOUT ACUTE PHASE REACTANTS				
TJC28, SJC28, PtGA ≤ 1	66%	16%	7.2	<.0001
CDAI≤2.8*	63%	16%	6.4	<.0001

**CDAI = sum of (TJC, SJC, Patient Global (0-10), Physician Global (0-10))*

Defining Remission in Practice

- Definitions without Acute Phase Reactants perform comparably to those with them and could be used in practice:
  - TJC, SJC, Patient Global all $\leq$ 1
  - CDAI $\leq$ 2.8
- Remission definitions for practice are best defined using data from practice settings

ACR-EULAR 2011 Definition of Remission

For clinical trials

- Boolean
  - SJC, TJS, PtGA, CRP all ≤1
- Index-based
  - SDAI ≤3.3

SDAI=SJC+TJC+PhGA+PtGA+ CRP (mg/dl)

For clinical practice

- Boolean
  - SJC, TJC, PtGA all ≤1
- Index-based
  - CDAI ≤2.8

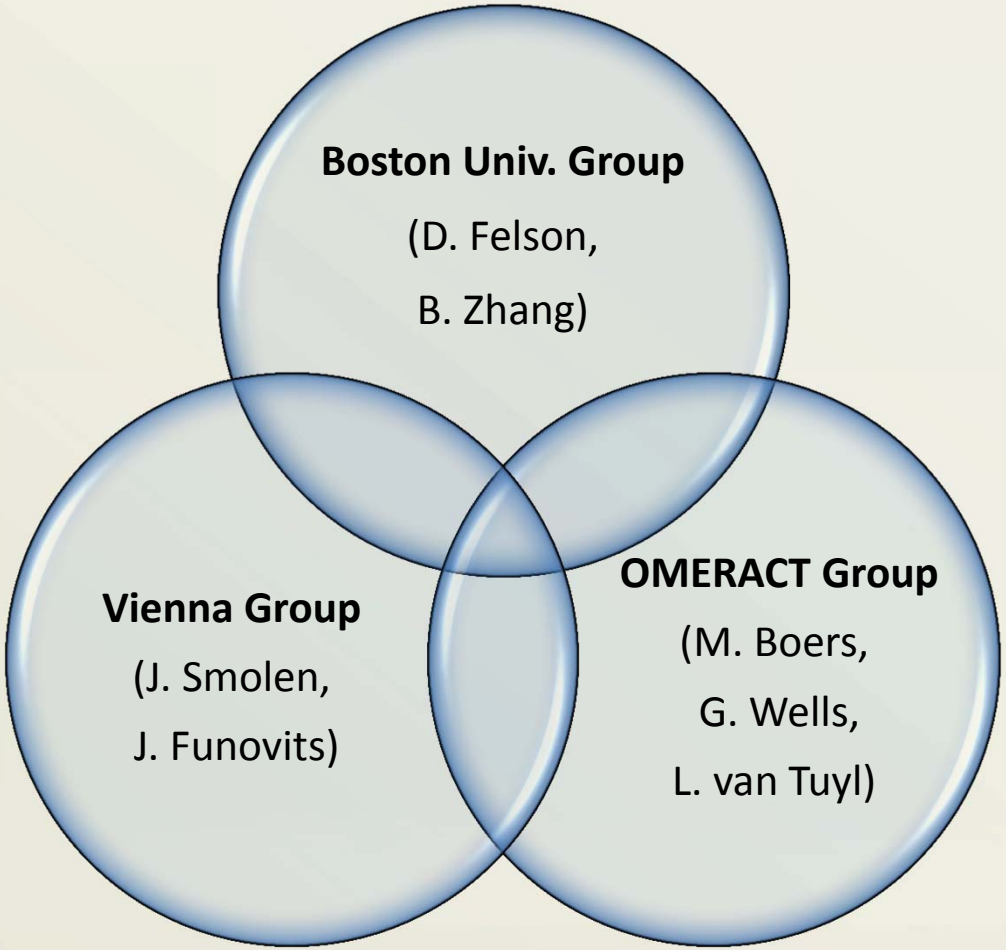
CDAI=SJC+TJC+PhGA+PtGA

Conclusion about Defining Remission in Practice

- Remission predicts the best clinical, functional and structural outcomes

- ACR/EULAR definitions of remission were developed using trial data and need to be validated for use in practice settings

Working Committee on RA Remission



The Parent ACR/EULAR Committee

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