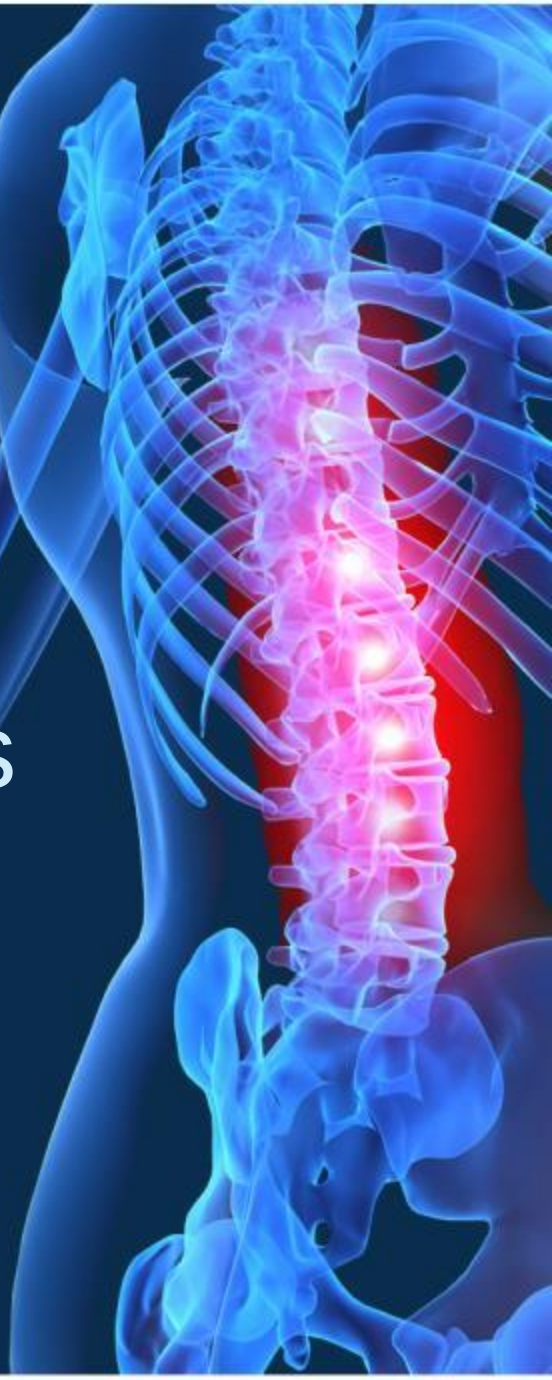
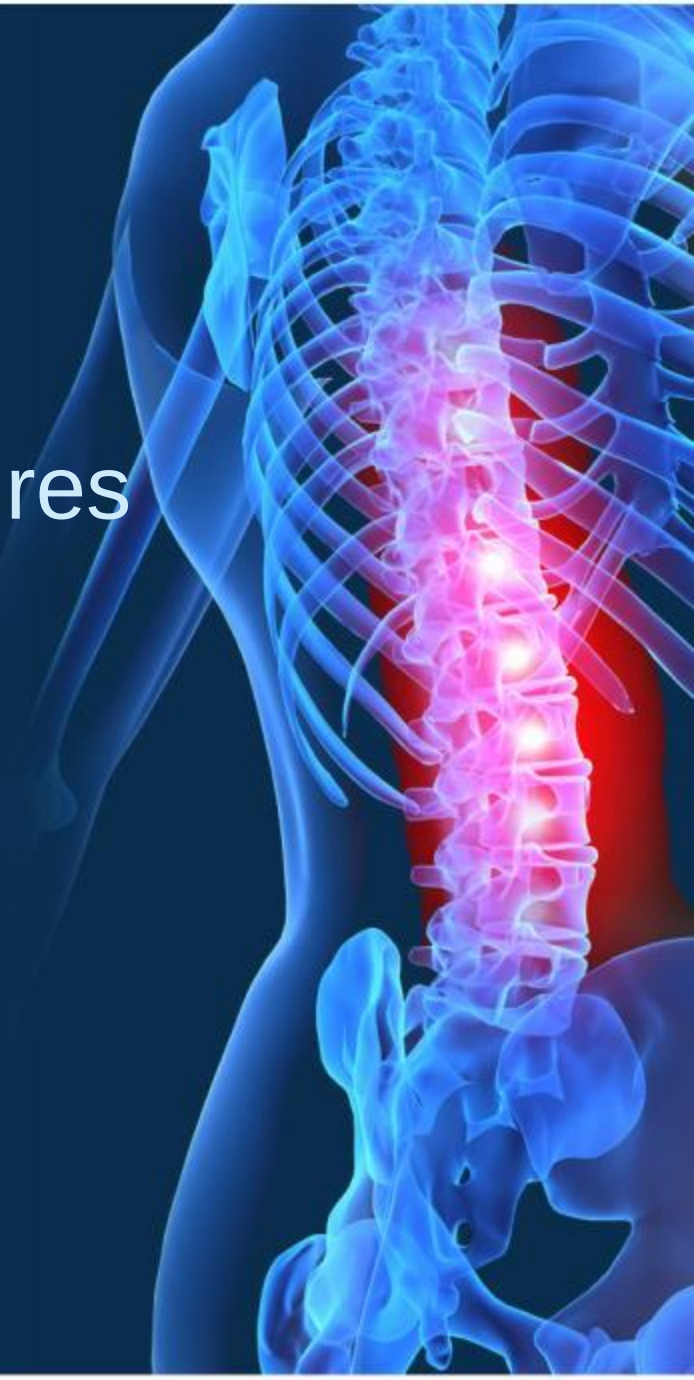
Annual Rheumatology & Therapeutics Review for Organizations & Societies



Objective Outcome Measures and Treat-to-Target in Rheumatoid Arthritis and Spondyloarthritis



RA and Spondyloarthritis

- Outcome Measures
- Treat-to-Target

Outcome Measures

Outcome Measures

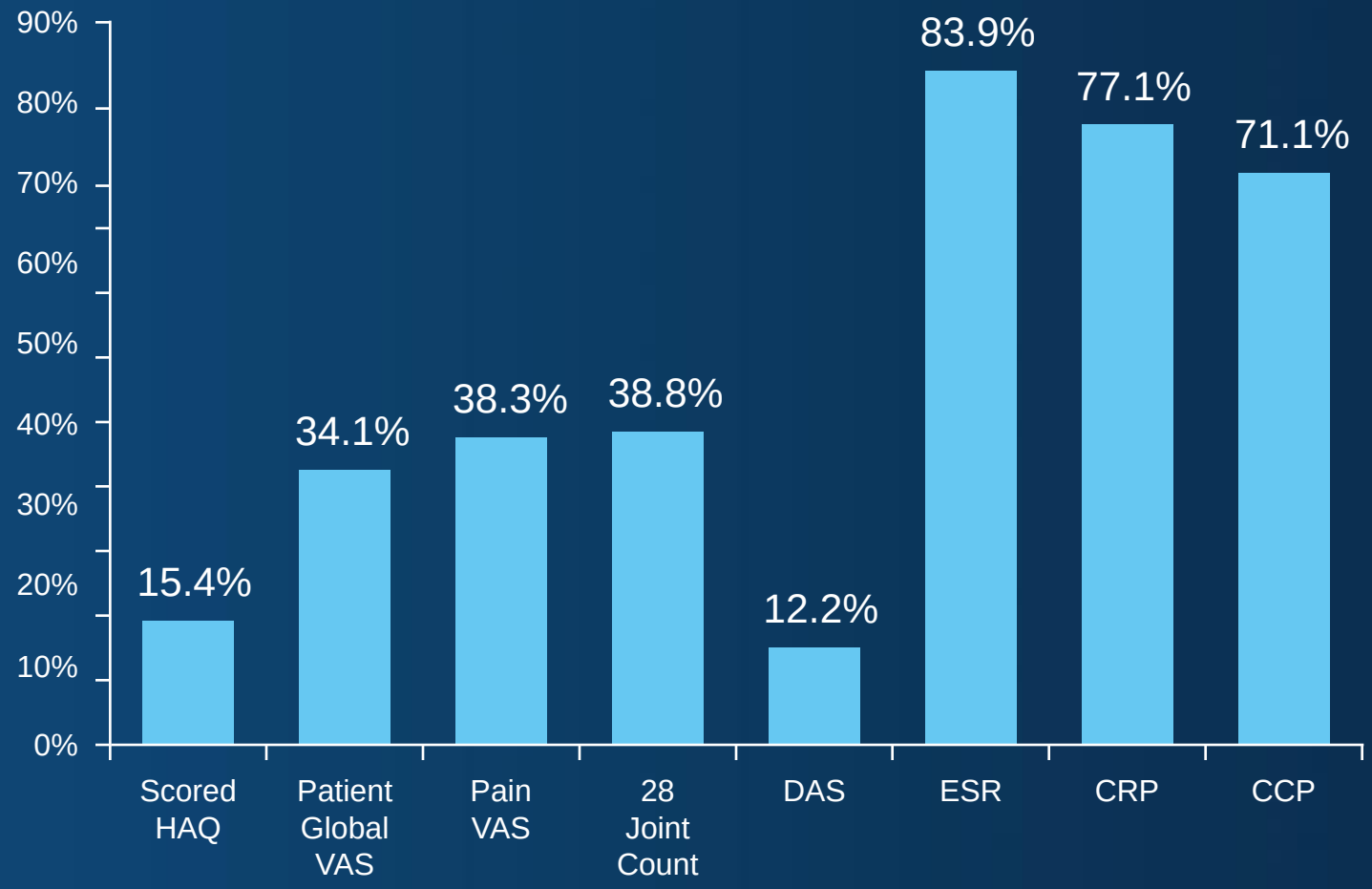
- Traditionally, rheumatologists have used subjective and intuitive methods to assess disease activity in RA
- In the last decade, with the advent of clinical trials and increasingly diverse outcome measures to choose from, some rheumatologists have begun to utilize these instruments
- In many European countries, objective outcome measures are mandated prior to drug approval
- Insurance companies in the United States have begun to request objective outcome measures to justify drug approval

What We CAN Measure

- Gestalt: is not standardized nor quantified: unable to compare visit to visit
- Formal joint counts
- Patient global assessment*
- Physician global assessment
- HAQ/MDHAQ*
- Laboratory values: ESR/CRP, RA, ACP/CCP
- Categorical outcomes measures
  - ACR 20, 50, 70*
- Continuous measurement tools
  - DAS*
  - SDAI*
  - CDAI*
  - GAS*
  - MDHAQ + SF36*
  - RAPID*
- Imaging results

*Is or contains patient-reported outcome measures.

What We DO Measure



Surveymonkey 2008. Courtesy — Jack Cush, MD.

Outcome Measures: The Debate

- Rationale for using objective outcome measures
  - Published studies demonstrating benefit
  - Treatment targets in other disease states – Hemoglobin A1C in diabetes
  - A more scientific/objective approach to treating a disease
  - Integration of outcome measures with EMR's
  - Patient outcomes and/or quality improvement goals

Bakker MF et al. *Ann Rheum Dis*. 2007;3:iii56-60; Grigor C et al. *Lancet*. 2004;364:263-9.

Outcome Measures: The Debate

- Rationale for not using objective outcome measures
  - Perceived increase in time requirement
  - Lack of consensus on which instruments to use
  - Does use of these instruments in daily practice as opposed to clinical trials truly result in better patient outcomes?

Clinical Components of Composite Measures

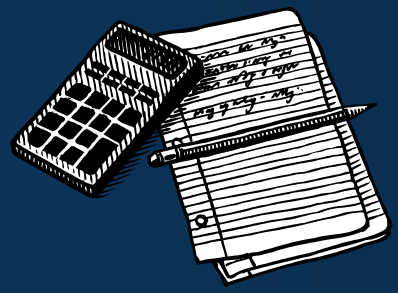
Outcome Measures in RA

	ACR20/ 50/70	DAS28	SDAI	CDAI	GAS	ERAM	RADAI	RADARA	RAPID
Patient function	+				+			+	+
Patient pain	+		+		+				+
Patient global	+	+	+	+		+	+		+
MD global	+		+	+		+			
# Tender joints	+	+	+	+	+		+	+	
# Swollen joints	+	+	+	+		+		+	
ESR or CRP	+	+	+						

Cush JJ. Presented at: 2005 ACR Annual Scientific Meeting; November 12-17, 2005; San Diego, CA. Abstract 1854.
Sesin CA, et al. *Semin Arthritis Rheum*. 2005;35(3):185-196. Makinen H, et al. *Clin Exp Rheumatol*. 2006;24(6 suppl 43):S22-S28.
Yazici Y. *Bull NYU Hosp Jt Dis*. 2007;65(suppl 1):S25-S28. Call S, et al. Presented at: 2007 ACR Annual Scientific Meeting; Boston, MA. Abstract 425. Fransen J, et al. *Rheumatol*. 2000;39(3):321-327.

Composite Measures Used as Outcomes in RA Clinical Trials

- ACR 20/50/70 Response
  - ≥20/50/70% improvement in swollen and tender joint counts with concomitant improvement (≥20/50/70%) in at least 3 of the following 5 measures:
    - Patient's Global Assessment (VAS 0-10)
    - Physician's Global Assessment (VAS 0-10)
    - Patient's Assessment of Pain (VAS 0-10)
    - Acute-Phase Reactant (ESR or CRP)
    - Functional Disability (HAQ)



- DAS28
  - Tender joint count (0-28)
  - Swollen joint count (0-28)
  - ESR or CRP levels
  - General health assessment (VAS – 0-100)

Felson DT, et al. *Arthritis Rheum*. 1998;41(9):1564-1570. van Gestel AM, et al. *Arthritis Rheum*. 1998;41(10):1845-1850.

Continuous Measures: Disease Activity Indices

SDAI*

- TJC (0-28)
- SJC (0-28)
- Patient Global Assessment (0-10)
- Physician Global Assessment (0-10)
- CRP (mg/dL)

CDAI*

- TJC (0-28)
- SJC (0-28)
- Patient Global Assessment (0-10)
- Physician Global Assessment (0-10)
- Eliminates ESR/CRP

*Both are highly correlated with DAS28, ACR20/50/70, and HAQ

Aletaha D, et al. *Clin Exp Rheumatol*. 2005;23(suppl 39):S100-S108.

RAPID3

- MDHAQ (0-10)
- Patient pain VAS (0-10)
- Patient global assessment VAS (0-10)

1. Please check (x) the ONE best answer for your abilities at this time:

OVER THE PAST WEEK, were you able to:	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
Dress yourself, including typing shoelaces and doing buttons?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of bed?	☐ 0	☐ 1	☐ 2	☐ 3
Lift a full cup or glass to your mouth?	☐ 0	☐ 1	☐ 2	☐ 3
Walk outdoors on flat ground?	☐ 0	☐ 1	☐ 2	☐ 3
Wash and dry your entire body?	☐ 0	☐ 1	☐ 2	☐ 3
Bend down to pick up clothing from the floor?	☐ 0	☐ 1	☐ 2	☐ 3
Turn regular faucets on and off?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of a car, bus, train, or airplane?	☐ 0	☐ 1	☐ 2	☐ 3
Walk two miles?	☐ 0	☐ 1	☐ 2	☐ 3
Participate in sports and games as you would like?	☐ 0	☐ 1	☐ 2	☐ 3

2. How much pain have you had because of your condition OVER THE PAST WEEK? Please indicate below how severe your pain has been:

NO PAIN ○ PAIN AS BAD AS IT COULD BE

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

3. Considering all the ways in which illness and health conditions may af fect you at this time, please indicate below how you are doing:

VERY WELL ○ VERY POORLY

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

FN ☐

1=0.3 16=5.3
2=0.7 17=5.7
3=1.0 18=6.0
4=1.3 19=6.3
5=1.7 20=6.7
6=2.0 21=7.0
7=2.3 22=7.3
8=2.7 23=7.7
9=3.0 24=8.0
10=3.3 25=8.3
11=3.7 26=8.7
12=4.0 27=9.0
13=4.3 28=9.3
14=4.7 29=9.7
15=5.0 30=10

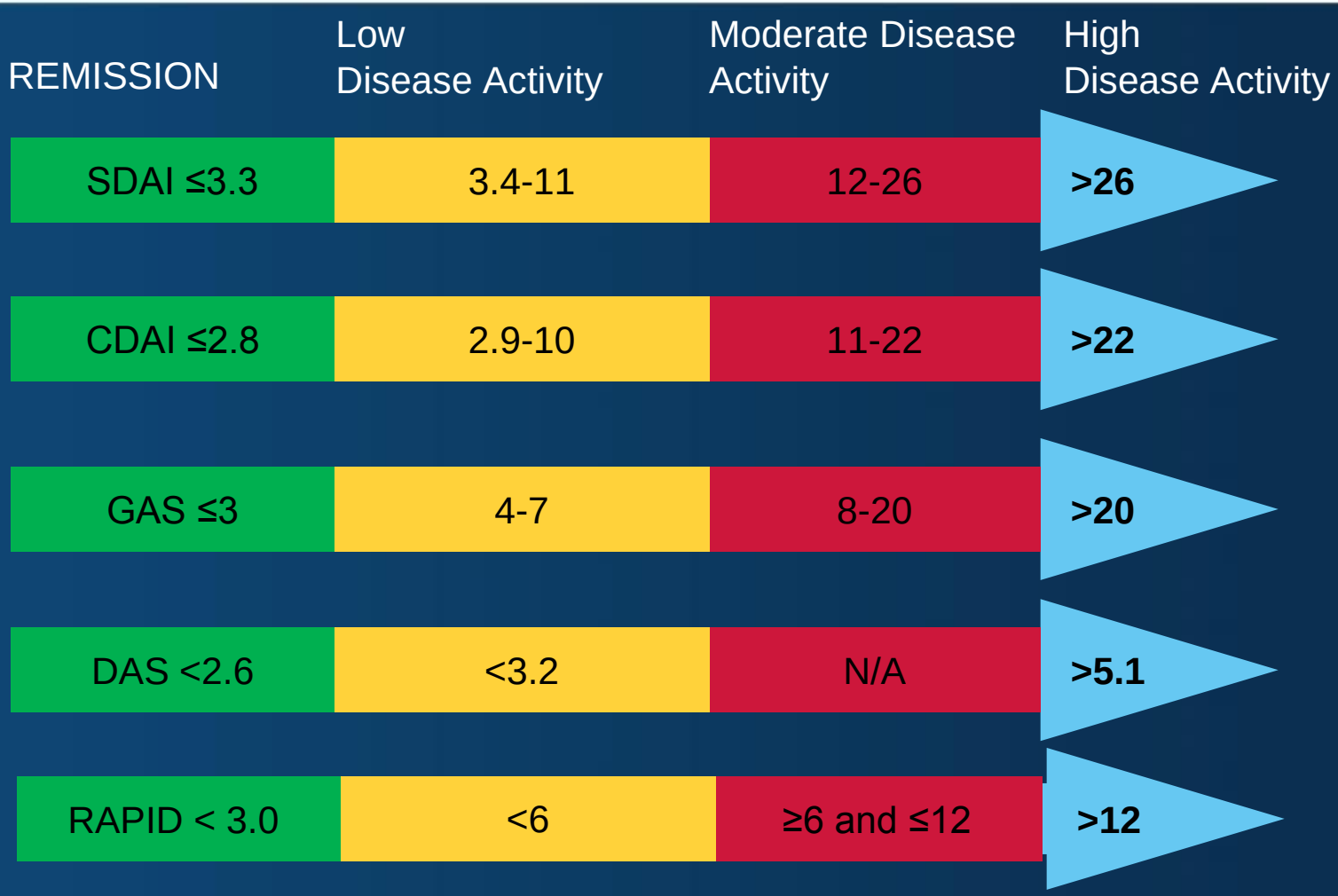
PN ☐

PTGL ☐

RAPID ☐ (0-30)

Pincus T, et al. *Clin Exp Rheumatol*. 2006; 24(16 suppl 43):S60-S73. Pincus T, et al. *J Rheum*. 2006;33:448-454.

Clinical Measurements Tools to Guide Treatment Decisions



Aletaha D, et al. *Clin Exp Rheumatol*. 2005;23(suppl 39):S100-S108. Cush JJ. Presented at: 2005 ACR Annual Scientific Meeting; November 12-17, 2005; San Diego, CA. Abstract 1854.

Limitations of Composite Measurement Tools

- Accuracy of clinical joint assessments
  - Tender joint counts in context of fibromyalgia (FM), nodal osteoarthritis (OA)
  - “swollen joints” — fibrous thickening vs. synovitis
- Patient global and assessment questions
  - Woefully inadequate to address RA inflammatory activity currently
    - Frequently accounts for comorbid symptoms (headache, back pain)
    - Includes nonreversible functional impairment
      - Adds to scoring of measures which are used to make clinical treatment decisions
- HAQ/MDHAQ — allows for irreversible disability (floor effect)
- Acute phase reactants
  - Even if current measurements available — not always reflective of underlying disease activity

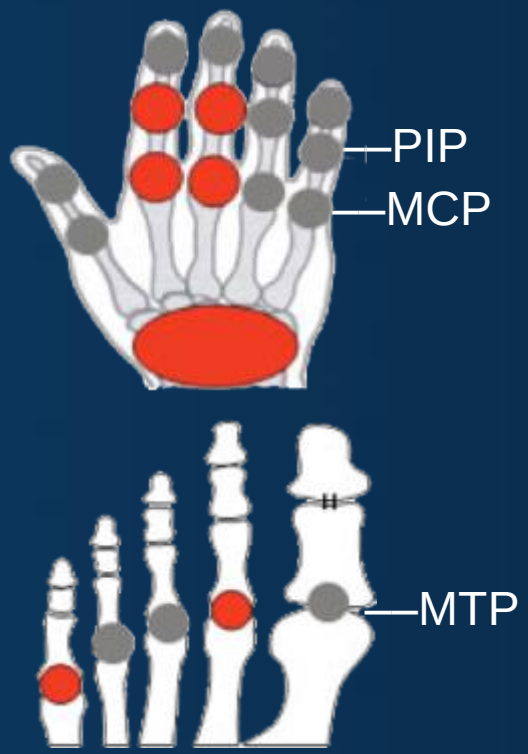
Ultrasound in Daily Practice

- "German US7 score" (G7), a new standardized US score based on 7 joints of the clinically dominant hand and foot
- Synovitis and synovial/tenosynovial vascularity were scored semiquantitatively by Gray-scale (GS) and Power Doppler (PD) US
- 120 patients with RA were examined at baseline and after start or change of DMARD and/or TNF-a inhibitor therapy 3 and 6 mos later
- At 6 mos, GS and PD US scores decreased by 32% and 39%, respectively; DAS 28 also decreased significantly
- Conclusion: G7 Score reflected therapeutic response, and was found to be a viable tool for examining RA pts

Backhaus M et al. *Arthritis Rheum*. 2009 Sep 15;61:1194-201.

Ultrasound in Rheumatologic Practice (German US Score)

Paratenonitis/ Tenosynovitis Synovitis	Wrist	Fingers	Toes
	dorsal +PD palmar +PD ulnar +PD	**MCP II,III** palmar +PD dorsal only PD **PIP II,III** palmar +PD dorsal only PD	**MTP III,V** dorsal +PD
	dorsal +PD palmar +PD ulnar +PD	**MCP II,III** dorsal +PD palmar +PD	
Erosions		**MCP II,III** dorsal, palmar, **MCP II** radial **PIP II,III** dorsal, palmar	**MTP II,V** dorsal, plantar **MTP V** lateral
	1 joint	**4 joints**	**2 joints**
		7 joints	



Gray-scale US and power Doppler US - synovitis, tenosynovitis/ paratenonitis, and erosions from dorsal, palmar, and ulnar aspects of wrist, MCP, PIP and MTP joints

Backhaus M et al. *Arthritis Rheum.* 2009 Sep 15;61:1194-201.

Vectra™ DA Biomarkers: Categories and Primary Role

Biomarkerv	Biomarker Category	Primary Role
VCAM-1	Adhesion Molecules	Cellular influx and tissue expansion
EGF	Growth Factors	
VEGF-A		
IL-6	Cytokine-related Proteins	Local inflammation and destruction
TNF-RI		
MMP-1	Matrix Metalloproteinases	Cartilage degradation and joint damage
MMP-3		
YKL-40	Skeletal-related Proteins	Stromal activity & regulation (fibroblasts, chondrocytes, vascular cells)
Leptin	Hormones	Systemic Inflammatory Response
Resistin		
SAA	Acute Phase Proteins	
CRP		

Treat-to-Target
Fact, Fiction, Hypothesis?

Is Treat-to-Target (TTT) a Proven Strategy ?

- Can we equate RA with diabetes (DM), hypertension (HTN), hyperlipidemia?
  - Validity of outcome measure
  - Disease course
  - Symptomatic vs Asymptomatic
  - Safety of intervention
  - Cost of intervention
  - Monitoring of intervention

Is TTT a Proven Strategy ?

- Is there enough evidence from clinical trials?
  - TTT Strategy Trials
    - TICORA, CAMERA, Fransen, Symmons
  - Treatment Trials with a Target
    - BeST, FIN-RACo

Is TTT a Proven Strategy ?

- Barriers in Rheumatology
  - Many patients with RA are not being treated by a Rheumatologist
  - 35 to 60 % of patients w/ RA Dx are not being treated with a DMARD
  - Patients perspective on TTT – is it even discussed ?
  - Frequency of visits
  - Medication availability

Goals

Clinical

- Remission
- Reduce/prevent inflammation
- Alleviate pain resulting From inflammation
- Maximize QoL

Radiographic

- Inhibit joint damage

Functional

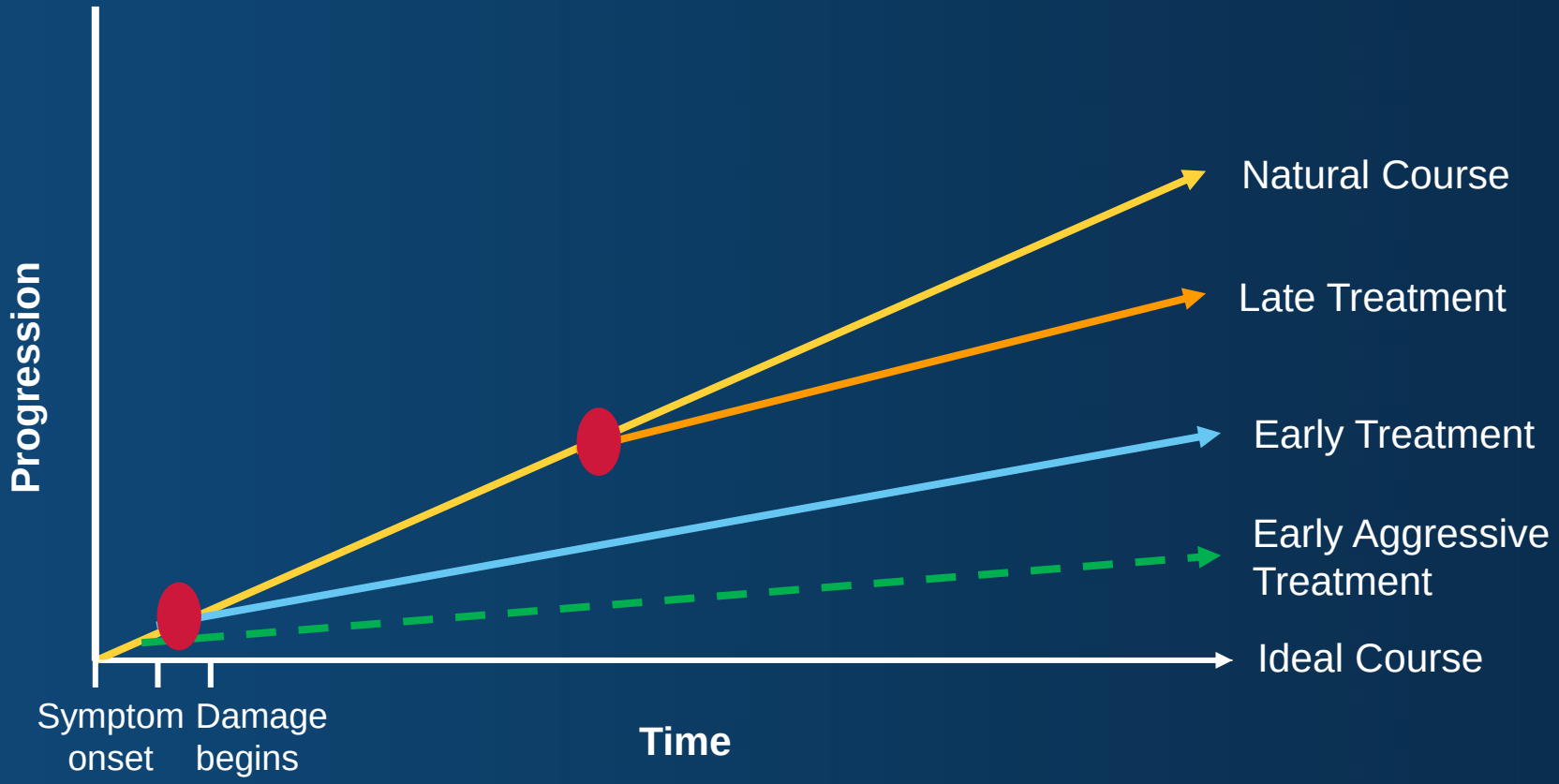
- Maintain function, capacity for work, and basic ADL and prevent disability
- Maximize QoL

“Window of Opportunity” – Early Intervention

- Early interventions can lead to greater improvement in clinical, radiographic and functional outcomes[1]
- Delay in diagnosis and treatment of RA common
  - Median time from symptom onset to rheumatology evaluation 24 weeks[2]
  - Delay in treatment results in functional deterioration[3]

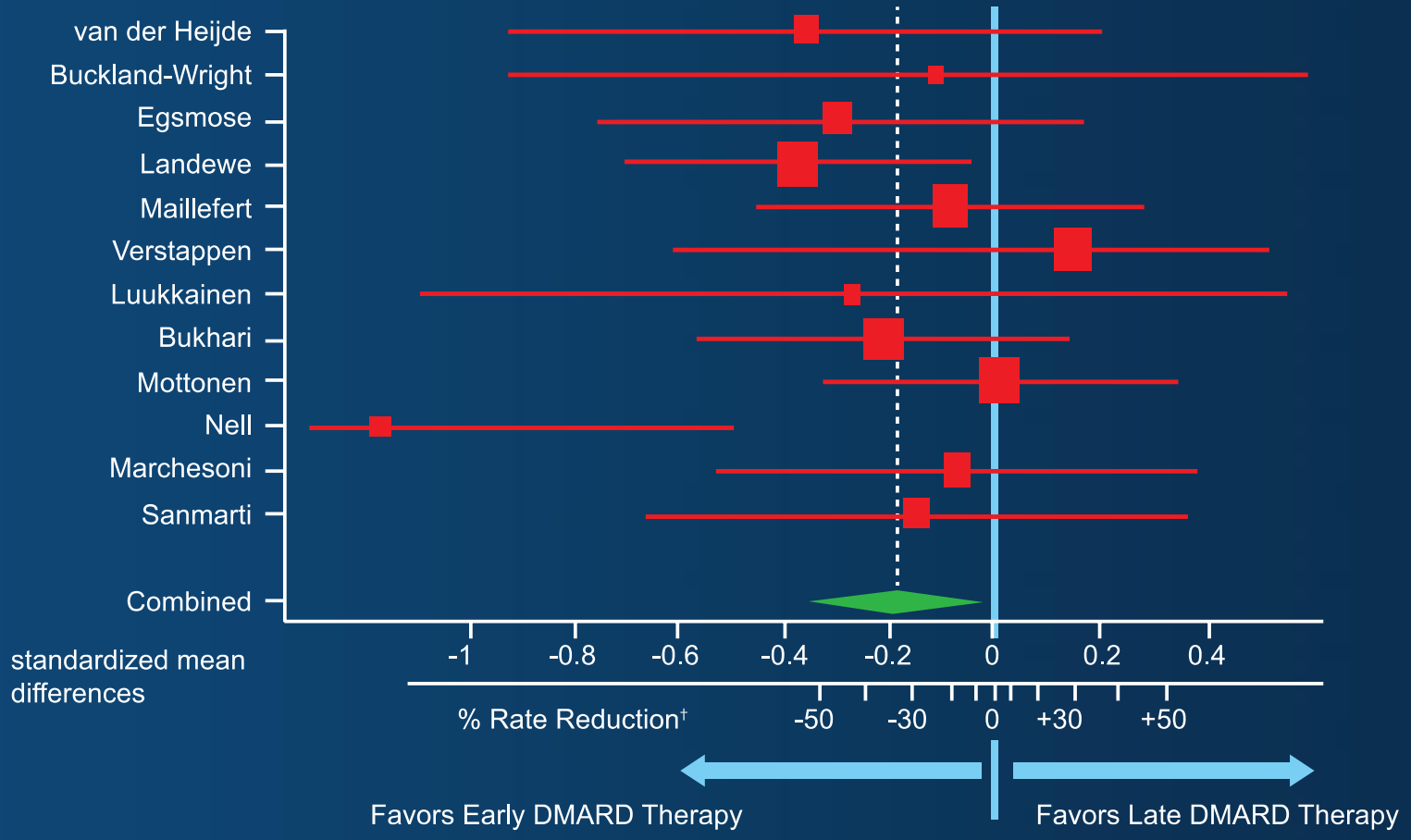
Resman-Targoff BH, et al. *Am J Manag Care*. 2010;16:S249-S258.
Raza K, et al. *Ann Rheum Dis*. 2011;70:1822-1825.
Emery P, et al. *Ann Rheum Dis*. 1995;54:944-947.

Natural Hx of Treated and Un-treated RA



Wolf, Breedveld FC, et al. *Ann Rheum Dis*. 2004;63:627-633.

Meta Analysis – Radiographic Progression < vs > 9 Mo



Finckh A, et al. Arthritis Rheum. 2006;55:864-872.

Concept and Background

- Really 3 concepts
  - Choose Measurement and Measure Consistently
  - Identify a Target or Targets
  - Utilization of the Measurement in a Defined Time Frame

TICORA / BeST / CAMERA

- TICORA, CAMERA and BeST 3 examples of studies that utilize sustained tight control aiming for lower disease activity

Bakker MF et al. *Ann Rheum Dis*. 2007;3:iii56-60; Grigor C et al. *Lancet*. 2004;364:263-9.

TICORA: Patient Criteria

- Inclusion criteria:
  - RA for <5 years (? not early RA)
  - Active disease, defined as DAS >2.4
  - Age between 18 and 75 years
- Exclusion criteria:
  - Previous combination DMARD treatment
- Two arms – Intensive Care vs Routine Care

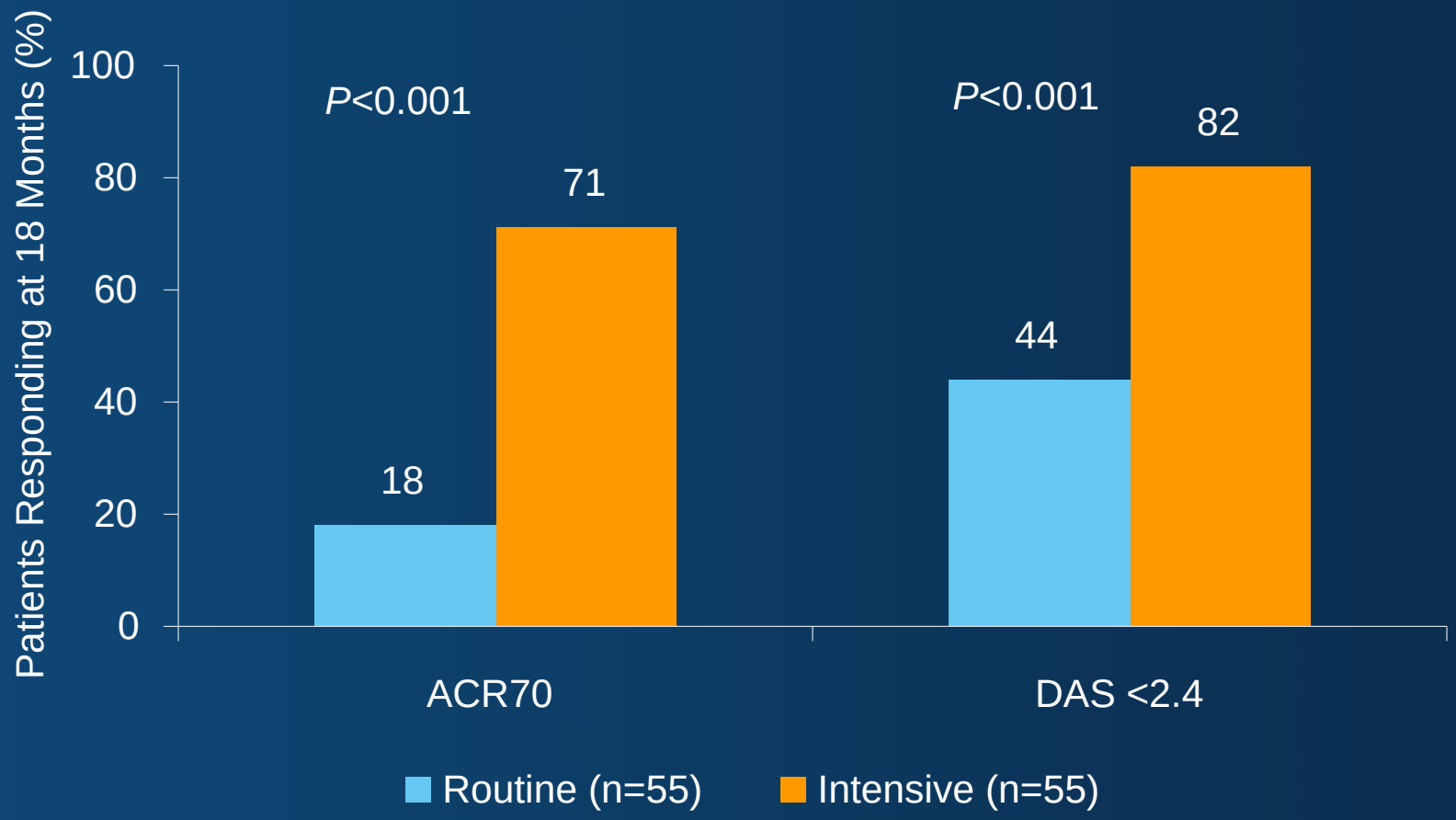
Grigor C et al. *Lancet*. 2004;364:263-269.

TICORA: Study Design

- Intensive treatment arm
  - Seen Q 1 month by the same rheumatologist
  - Swollen joints injected
  - Checked DAS and if >2.4, changed therapy as per protocol:
    - SSZ ➔ MTX + SSZ + HCQ ➔ ↑ MTX (up to 25 mg/wk); ↑ SSZ (up to 5 g/dose) ➔ ↑ add prednisolone 7.5 mg/dose ➔ switch to MTX + CSA
      ➔ switch to leflunomide
- Routine treatment arm
  - Seen Q 3 months in Rheum clinic
  - Injected joints and treated changes as per MD caring for the patient
  - No formal outcome measurement

Grigor C et al. *Lancet*. 2004;364:263-269.

DAS Remission / ACR 70 – 18 Months



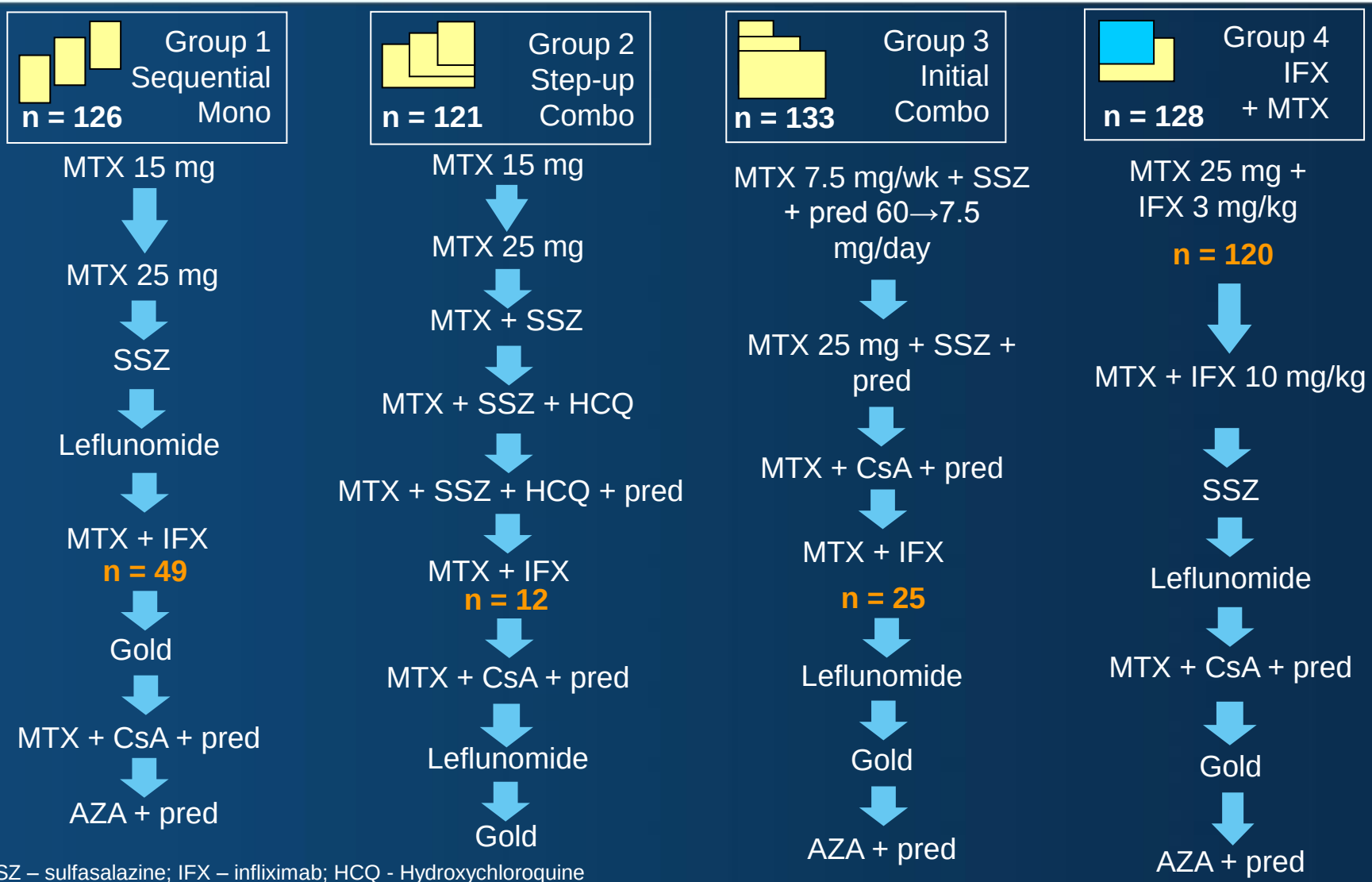
Grigor C et al. *Lancet*. 2004;364:263-269.

BeSt: Patient Population

- Multicenter, randomized clinical trial
- Inclusion criteria:
  - Active, early RA
  - ≥6 of 66 swollen joints
  - ≥6 of 68 tender joints
  - ESR ≥28 mm/hr or global health score of ≥20 mm
- Exclusion criteria:
  - Previous treatment with DMARD
  - Concomitant treatment with experimental drug

Goekoop-Ruiterman YPM et al. *Arthritis Rheum*. 2005;52:3381-3390.

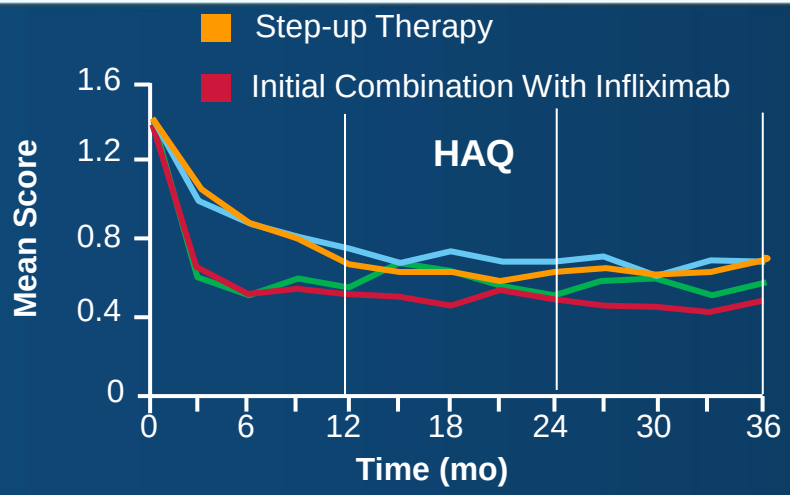
BeSt Study Design

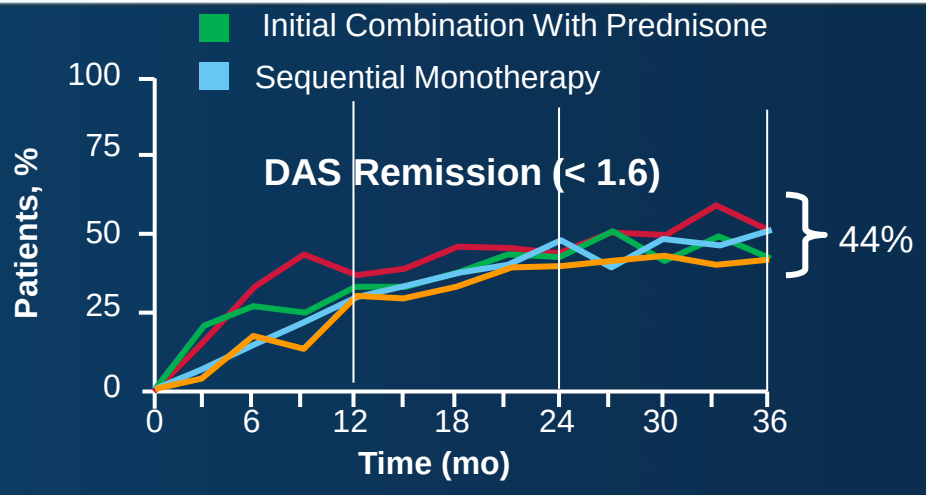


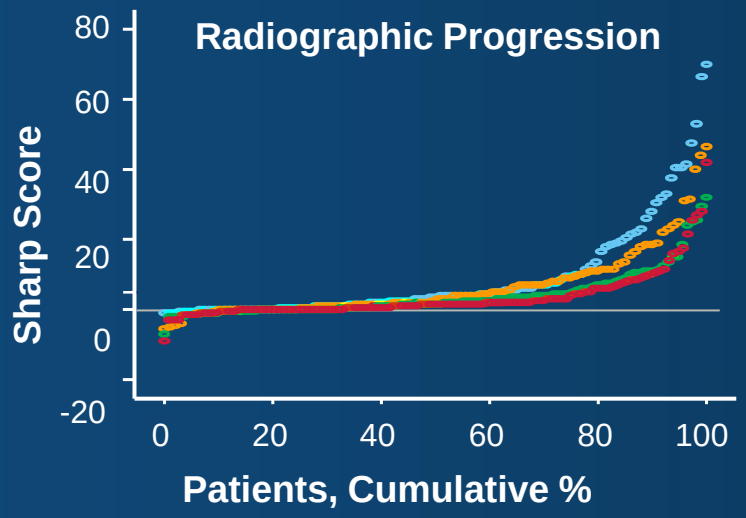
SSZ – sulfasalazine; IFX – infliximab; HCQ - Hydroxychloroquine

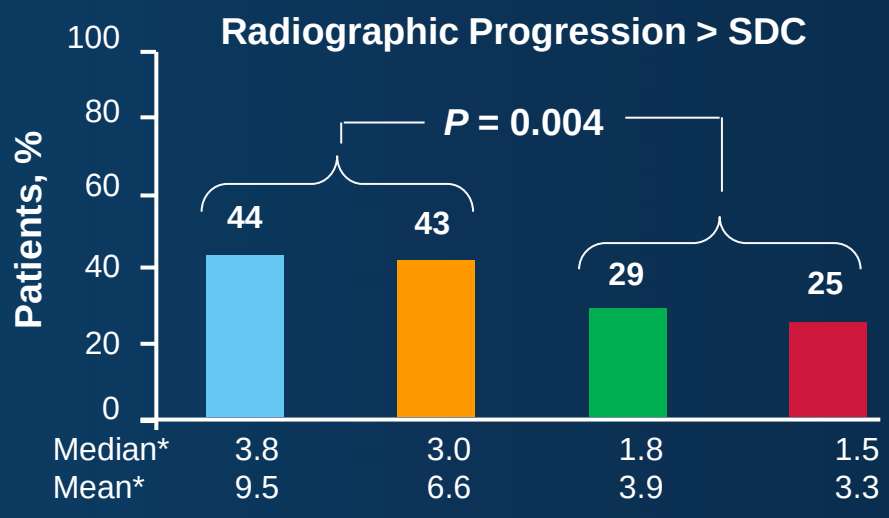
Van der Kooij SM et al. *Ann Rheum Dis*. 2009;68:1153-8.

Results From the BeSt Study at 3 Years





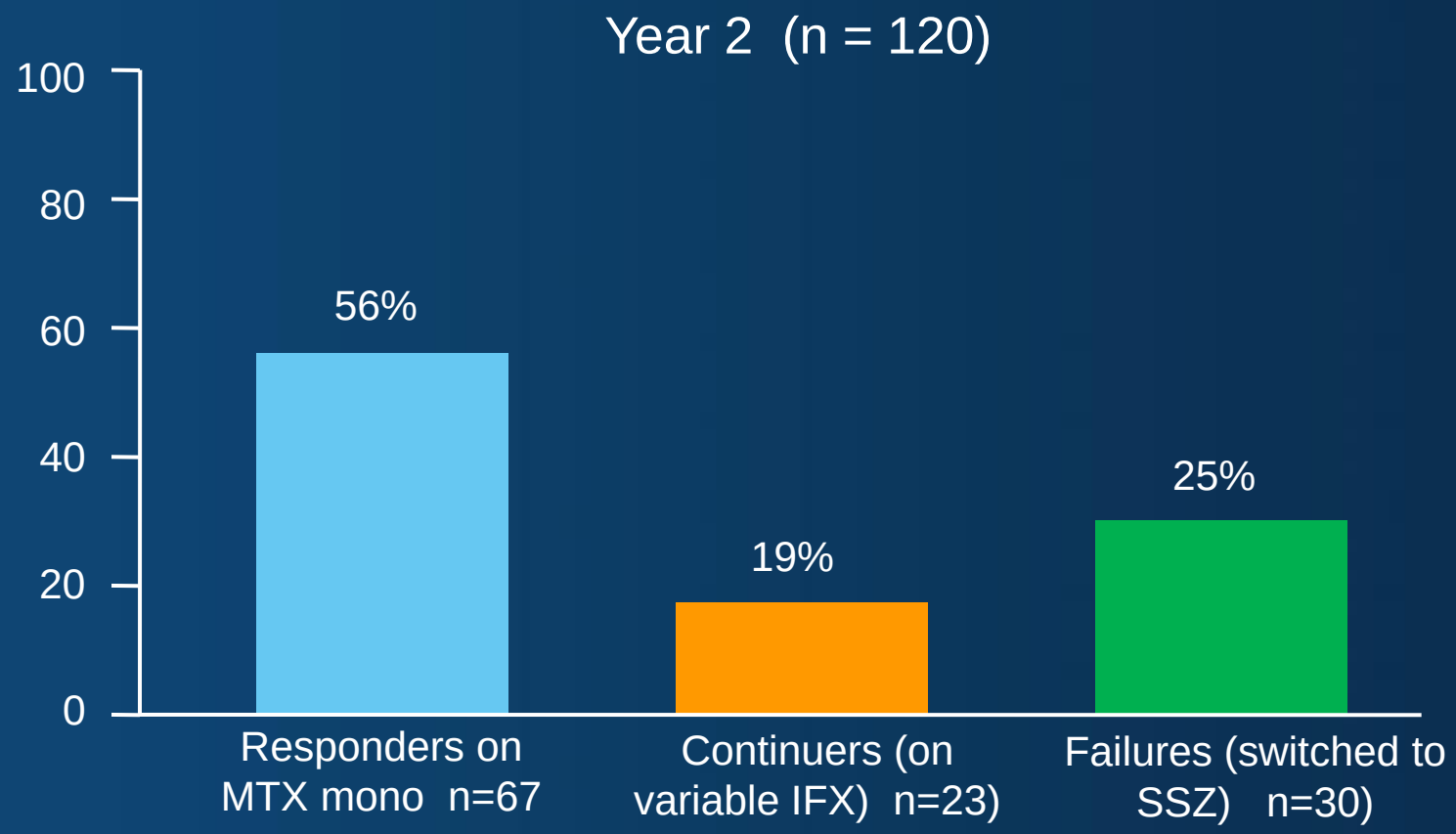




*Increases from baseline in Total Sharp Scores. SDC = smallest detectable change.

Van der Kooij SM et al. *Ann Rheum Dis*. 2009;68:1153-8.

BeSt Study: Persistent Clinical Response Following Initial Infliximab Tx – Year 2



van der Bijl AE et al. *Arthritis Rheum*. 2007;56:2129-34.

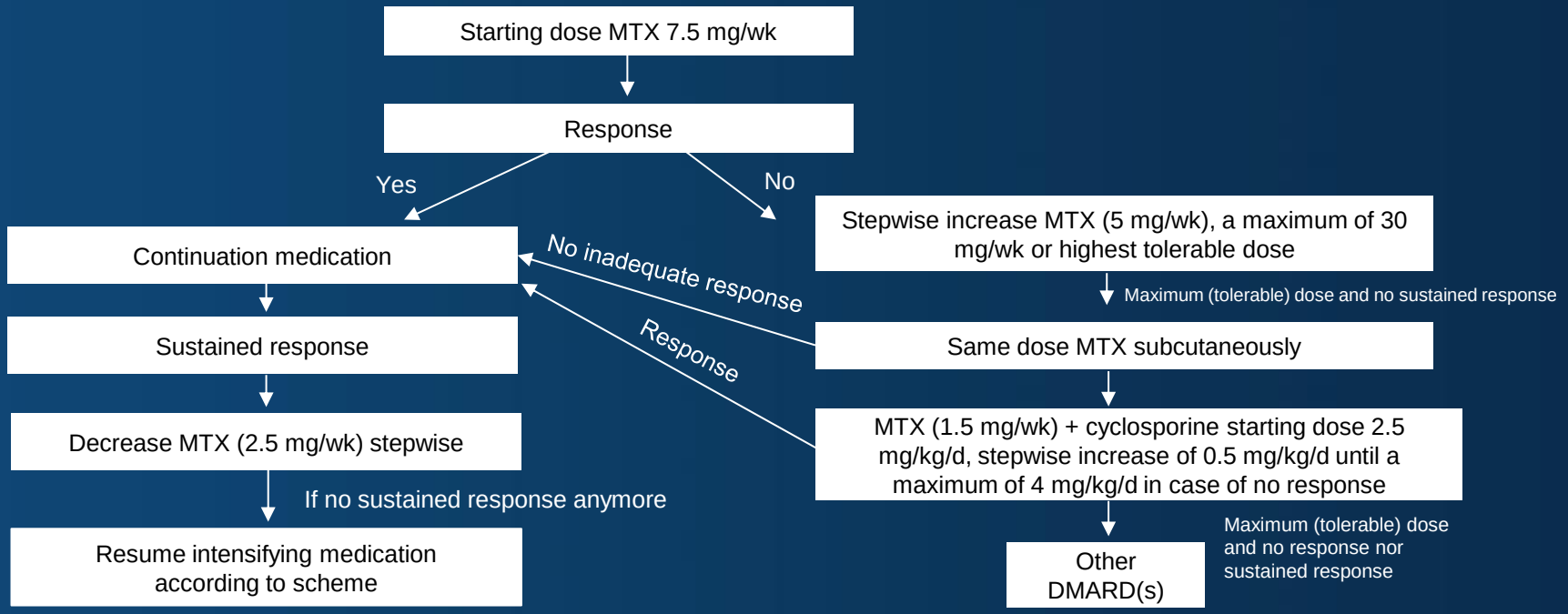
CAMERA Study

- Intensive treatment with methotrexate (MTX) according to a strict protocol and a computerized decision program is more beneficial compared to conventional treatment with MTX in early rheumatoid arthritis

- 2-year multicenter open label trial. Patients in both groups received MTX, the aim of treatment being remission

Verstappen SM et al. *Ann Rheum Dis*. 2007;66:1443-1449.

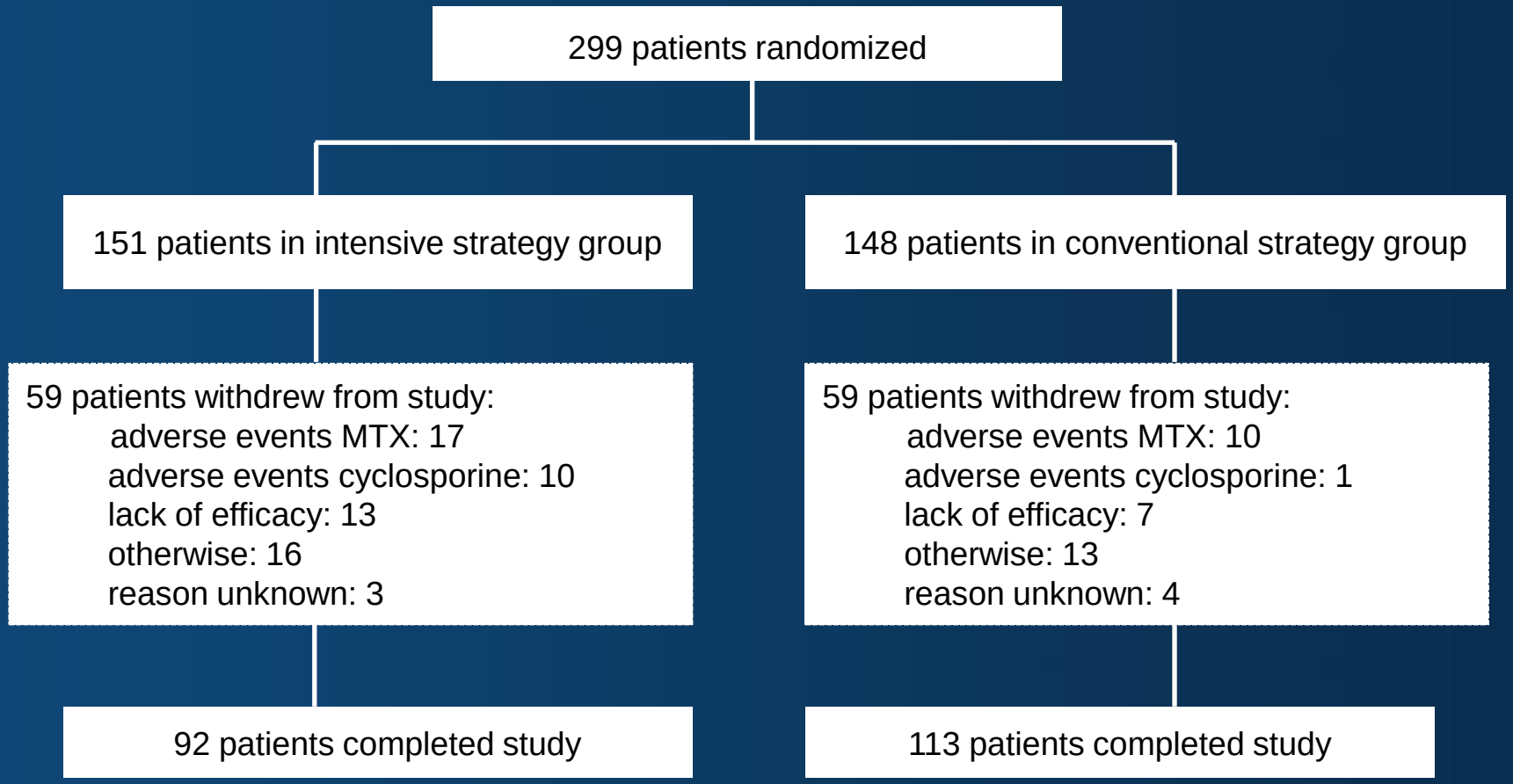
Protocol and Response Criteria for Intensive and Conventional Strategy Group Separately



	Response Compared to previous visit:	Inadequate response	Sustained response
Intensive strategy group	>20% improvement of a number of swollen joints and >20% improvement in 2 out of 3 criteria: ESR, number of tender joints, and VAS general well-being.	<50% improvement from baseline for number of swollen joints and >50% improvement from baseline for 2 out of 3 variables: ESR, number of tender joints, and VAS general well-being.	No swollen joints and 2 out of 3 criteria: number of painful joints =3, ESR ≥ 20 mm/h[1], VAS general well being ≤20 mm.
Conventional strategy group	- Decrease of number of swollen joints - If number of swollen joints uncharged, decision of response depended on assessor's judgement, looking at number of tender joints, ESR, and VAS general well-being.	Number of swollen joints >6, number of painful joints ≥3, ESR ≥28 mm/h[1], and morning stiffness >4.5 min.	

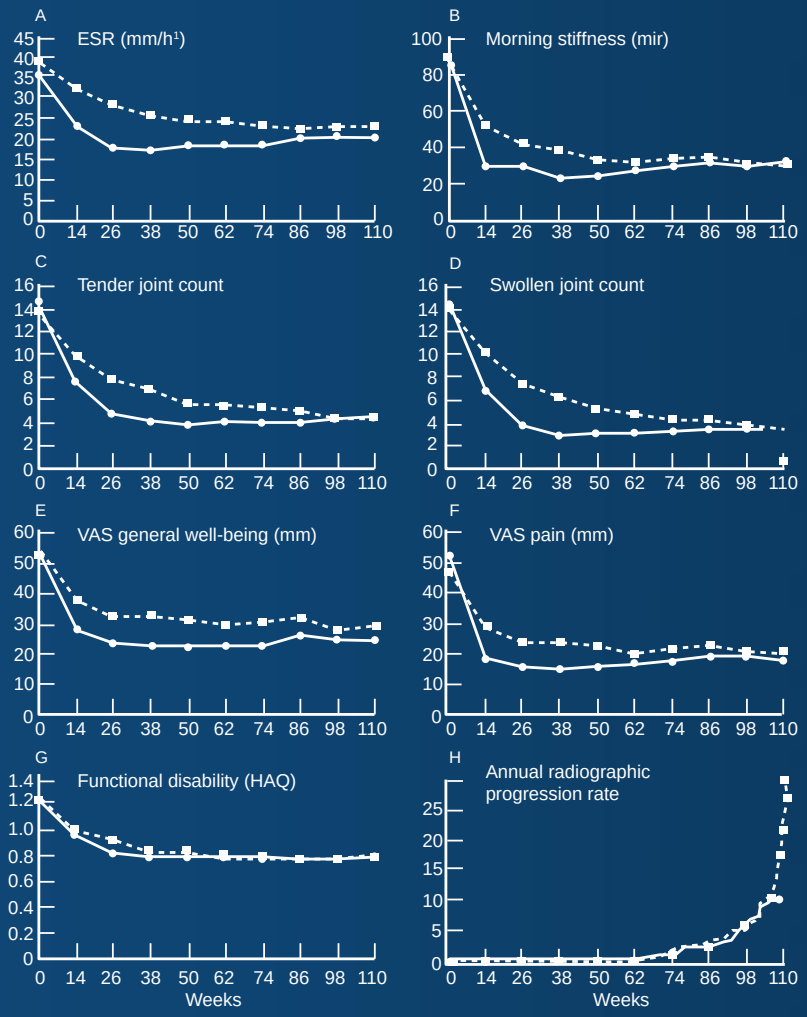
Verstappen SM et al. *Ann Rheum Dis*. 2007;66:1443-1449.

Study Population of Intensive and Conventional Strategy Group



Verstappen SM et al. *Ann Rheum Dis*. 2007;66:1443-1449.

Mean Scores Over Time for All Clinical Variables:



- **Conclusion:** Substantially enhance the clinical efficacy early in the course of the disease by intensifying treatment with MTX, aiming for remission, tailored to the individual patient.

— Solid line: Intensive strategy group
- - - Dotted line: Conventional strategy group

Verstappen SM et al. *Ann Rheum Dis*. 2007;66:1443-1449.

Real World Experience?

Clinical Trials vs. Practice

Do patients in clinical trials reflect what is seen in the clinic?

- Objective: To compare the efficacy of anti-TNF treatments for RA patients in randomized controlled trials (RCTs) and in daily clinical practice
- Methods:
  - RCT's etanercept, infliximab and adalimumab
  - DREAM (Dutch Rheumatoid Arthritis Monitoring) - patients starting for the first time on one of the TNF-blocking agents - comparator representing clinical practice (appropriately stratified)
- Results:
  - Only 34–79% of DREAM patients fulfilled the selection criteria used in RCT's
  - In 10 of 11 comparisons, the ACR20 response percentages were lower in daily clinical practice
- Conclusion:
  - The efficacy of TNF-blocking agents in RCTs exceeded the efficacy of these drugs in clinical practice
  - In clinical practice more patients with lower disease activity were treated with TNF-blocking agents

Kievit W et al. *Ann Rheum Dis* 2007;66:1473-1478.

DREAM Remission Induction Cohort Study

- From 2006, consecutive patients newly diagnosed RA Symptom duration of 1 year or less
- DAS 28 $\geq$ 2.6
- No previous treatment with DMARDs or prednisolone
- The rheumatology clinics of 5 hospitals in The Netherlands
- Prospective Non- randomized non - blinded “cohort type” observational study

Vermeer M et al. *Arthritis Rheum*. 2011; 63: 2865–2872.

Treatment Protocol

Time	DAS28	Medication
Week 0	≥ 2.6	MTX 15 mg/week
Week 8	≥ 2.6	MTX 25 mg/week
Week 12	≥ 2.6	MTX 25 mg/week SSZ 2,000 mg/day
Week 20	≥ 2.6	MTX 25 mg/week SSZ 3,000 mg/day
Week 24	≥ 3.2†	MTX 25 mg/week ADA 40 mg every 2 weeks
Week 36	≥ 2.6 & dec 1.2‡	MTX 25 mg/week ADA 40 mg/week
Week 52	≥ 3.2†	MTX 25 mg/week Etan. 50 mg/week
1 yr 3 mo	≥ 3.2†	MTX 25 mg/week Inflix. 3 mg/kg every 8 weeks
1 yr 6 mo	≥ 2.6 & dec 1.2‡	MTX 25 mg/week inflix. 3 mg/kg every 4 weeks

- If DAS $\leq$ 2.6 for 6 mo meds tapered
- The goal of treatment was remission (Disease Activity Score in 28 joints [DAS28] 2.6). Treatment was intensified when this target was not met.

† Following the guidelines of the Dutch Society of Rheumatology and Dutch reimbursement regulations, anti–tumor necrosis factor (anti-TNF) therapy could be prescribed to patients with at least moderate disease activity (DAS28 3.2) and in whom treatment with at least 2 disease-modifying antirheumatic drugs had failed (including methotrexate [MTX] 25 mg/week).

‡ Anti-TNF therapy could be continued only if the DAS28 had decreased by 1.2 after 3 months.

Primary Outcomes

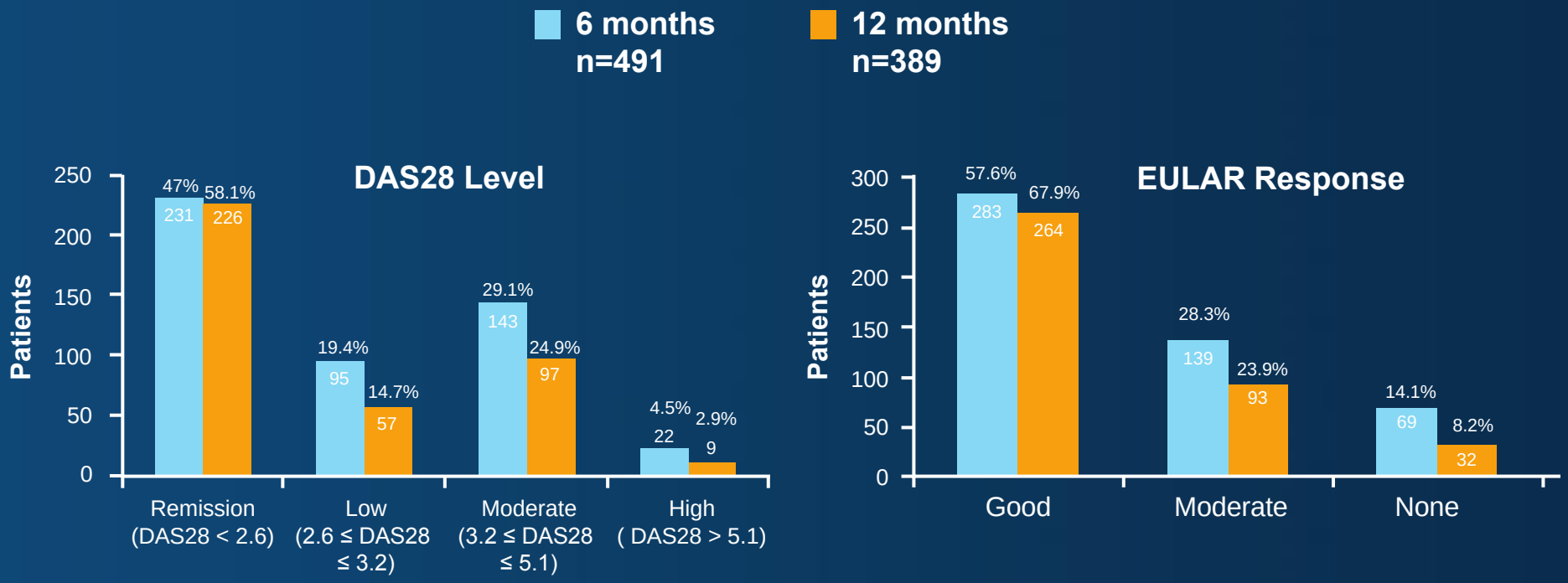
Table 3. Clinical Outcomes in the Patients after 6 Months and 12 Months of Follow-up*

	6 months (n=491)	12 months (n=389)
DAS28		
Remission (DAS28 < 2.6)	231 (47.0)	226 (58.1)
Low (2.6 ≤ DAS28 ≤ 3.2)	95 (19.4)	57 (14.7)
Moderate (3.2 < DAS28 ≤ 5.1)	143 (29.1)	97 (24.9)
High (DAS28 > 5.1)	22 (4.5)	9 (2.3)
EULAR response		
Good	283 (57.6)	264 (67.9)
Moderate	139 (28.3)	93 (23.9)
None	69 (14.1)	32 (8.2)
ACR remission	123/384 (32.0)	149/321 (46.4)

*Values are the number (%). American College of Rheumatology (ACR) remission could not be evaluated in all patients due to missing values for morning stiffness. DAS28 = Disease Activity Score in 28 joints; EULAR = European League Against Rheumatism.

The successful implementation of this treat-to-target strategy aiming at remission demonstrated that achieving remission in daily clinical practice is a realistic goal

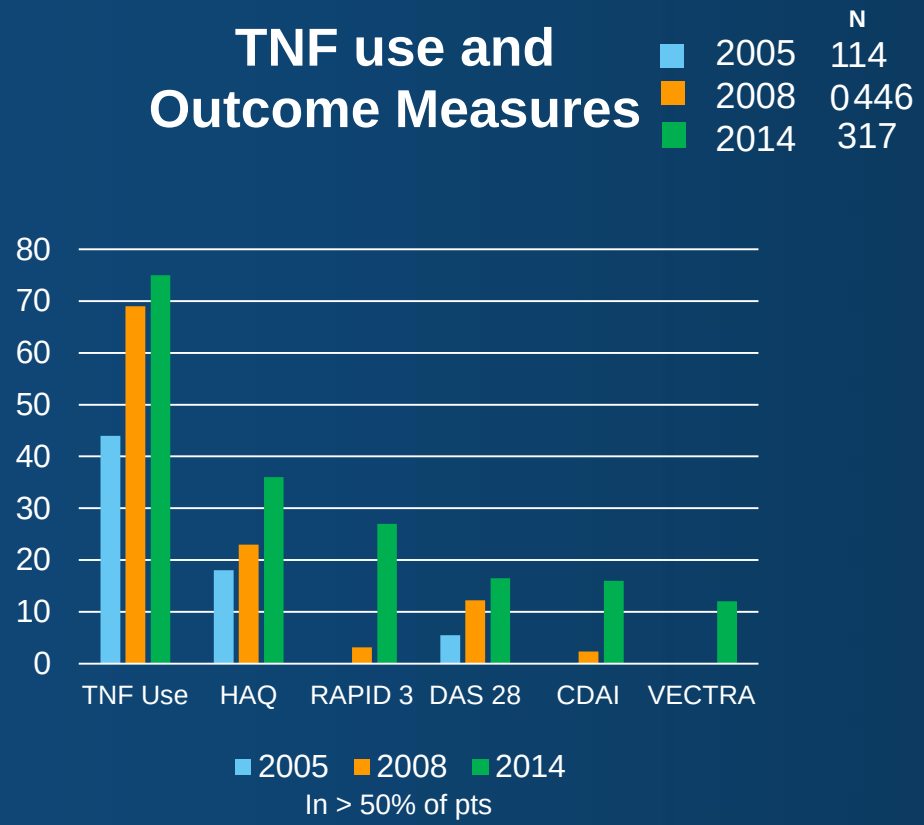
Vermeer M et al. *Arthritis Rheum*. 2011; 63: 2865–2872.



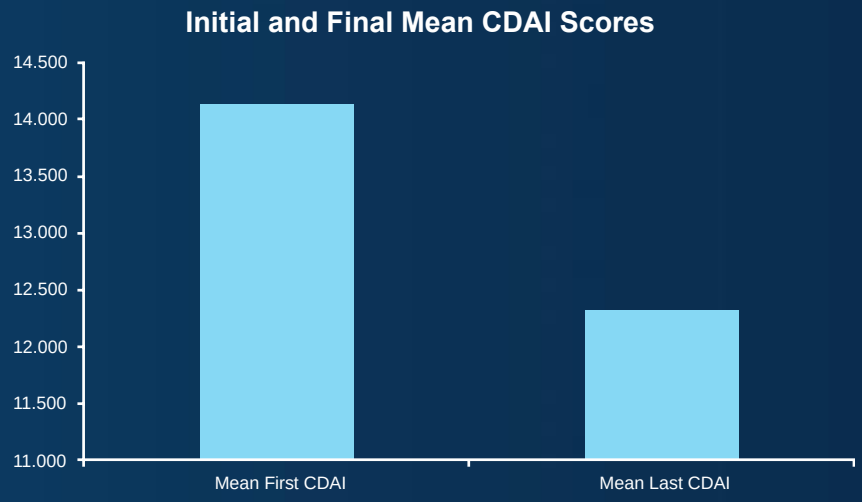
Vermeer M et al. *Arthritis Rheum*. 2011; 63: 2865–2872.

Are We Measuring and Treating to Target ?

TNF use and Outcome Measures



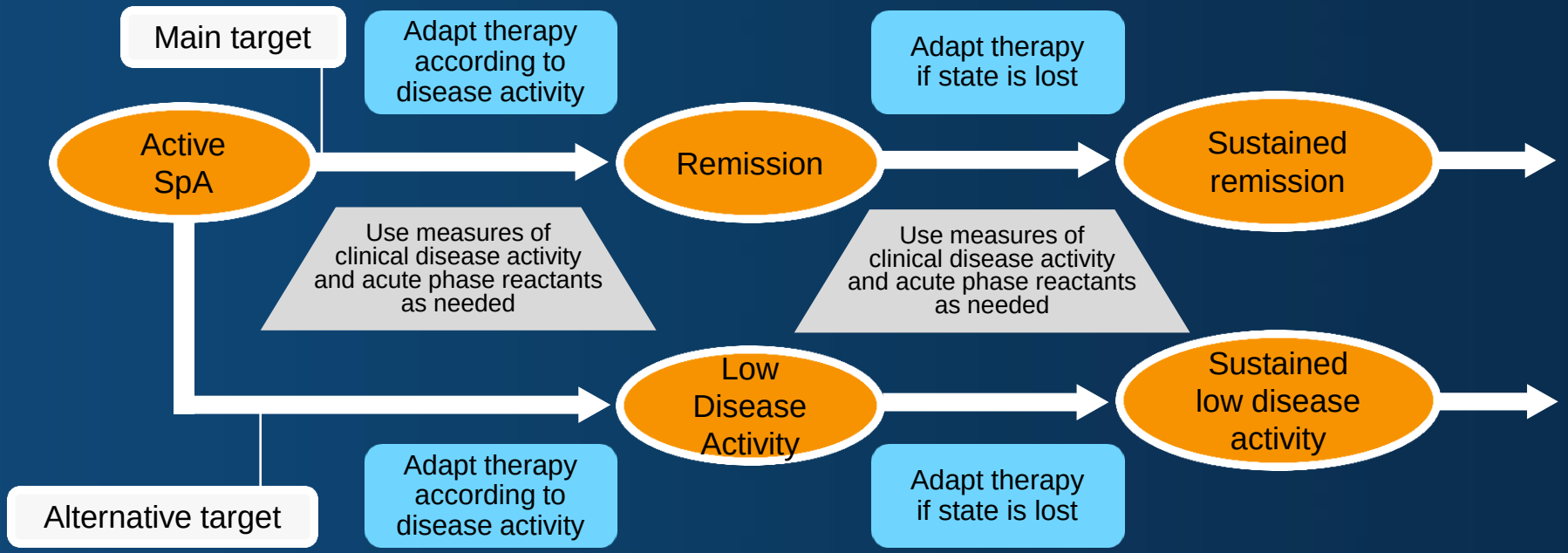
Are "Measurers" Achieving Appropriate Goals ?



Cush J, Curtis J ACR 2014 Abstract 45027 Treat-to-Target (T2T) and Measuring Outcomes in RA Care: A 2014 Longitudinal Survey of US RheumatologistsACR 2013 *Abstract #2300*
Rheumatologists Who Are Consistently Using An Objective Outcome Instrument Do Not "Treat To Target" In a Real World Setting
Schwartzman, Sergio MD Craig, Gary MD: Kenney, Howard MD: Knapp, Keith PHD

Algorithm for Treating SpA to Target

SpA and RA differ pathophysiologically, clinically, and therapeutically.



SpA = Spondyloarthritis

Smolen JS, et al. *Ann Rheum Dis*. 2010;69(4):631-637.

Outcome Measures in PsA and Peripheral SpA[1]

	DAS28	PsAJAI	DAPSA	CPDAI	PASDAS	AMDF
Arthritis (joint counts)	28	66/68	66/68	66/68	66/68	66/68
Skin disease	N	N	N	Y	N	N
Enthesitis	N	N	N	Y	Y	N
Dactylitis	N	N	N	Y	Y	N
Spinal disease	N	N	N	Y	N	N
Health-related quality of life	N	N	N	Y	Y	Y
Physical function	N	Y	N	Y	N	Y
Patient's arthritis disease activity assessment	N	N	N	N	N	Y
Patient's skin disease activity assessment	N	N	N	N	N	Y
Patient's global disease activity assessment	Y	Y	Y	N	Y	Y
Patient's pain assessment	N	Y	Y	N	N	N
Physician's global disease activity assessment	N	Y	N	N	Y	N
Acute-phase response	Y	Y	Y	N	Y	N

DAS28=Disease Activity Score 28 joints. PsAJAI=Psoriatic Arthritis Joint Activity Index. DAPSA=Disease Activity in PSoriatic Arthritis. CPDAI=Composite Psoriatic Disease Activity Index. PASDAS=Psoriatic Arthritis Disease Activity Scale. AMDF=Arithmetic Mean of Desirability Functions.

1. Coates LC, et al. *J Rheumatol*. 2014;41(4):782-791.

Minimal Disease Activity (MDA) Criteria in Psoriatic Arthritis[1]

- Tender joint count ≤1
- Swollen joint count ≤1
- PASI ≤1 or BSA ≤3
- Patient pain VAS ≤15
- Patient global activity VAS ≤20
- HAQ ≤0.5
- Tender enthesial points ≤1

- 5 of the 7 Criteria Must Be Met for MDA

PASI – Psoriasis Area Severity index; BSA – body surface area; VAS=Visual Analog Scale.

Mease PJ, et al. *J Rheumatol*. 2013;40(5):647-652.

Outcome Measures in Ankylosing Spondylitis

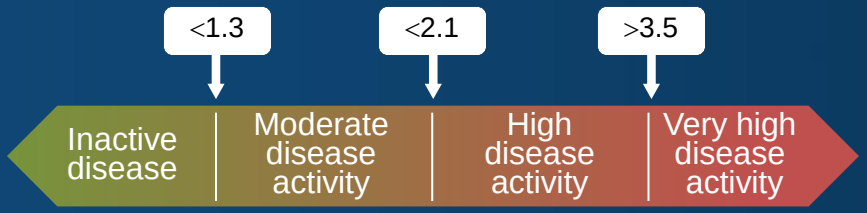
Measure	Target	Administration
ASDAS	Disease activity	Self report and lab
BASDAI	Disease activity	Self-report
ASQoL	Quality of life	Self-report
BAS-G	Well-being	Self-report
BASMI	Mobility	Healthcare provider
BASFI	Functional	Self-report
DFI	Functional	Self-report
HAQ-S	Functional	Self-report

ASDAS=Ankylosing Spondylitis Disease Activity Score. BASDAI=Bath Ankylosing Spondylitis Disease Activity Index. ASQoL=Ankylosing Spondylitis Quality of Life Scale. BAS-G=Bath Ankylosing Spondylitis Global Score. BASMI=Bath Ankylosing Spondylitis Metrology Index. BASFI=Bath Ankylosing Spondylitis Functional Index. DFI=Dougados Functional Index. HAQ-S=Health Assessment Questionnaire for the Spondylarthropathies. 1. Zochling J. *Arthritis Care Res (Hoboken)*. 2011;63(suppl 11):S47-S58.

Disease Activity in AS

- ASDAS-CRP 0.12 x back pain + 0.06 x duration of morning stiffness + 0.11 x patient global + 0.07 x peripheral pain/swelling + 0.58 x Ln (CRP + 1)
- ASDAS-ESR 0.08 x back pain + 0.07 x duration of morning stiffness + 0.11 x patient global + 0.09 x peripheral pain/swelling + 0.29 x √ESR

Cutoffs for Disease Activity States



Cutoffs for Improvement Scores (Response Levels)

BASDAI

How would you describe the overall level of:
Fatigue/tiredness you have experienced?
Ankylosing spondylitis neck, back, or **hip** pain you have had?
Pain/swelling in joints other than neck, back, or hips you have had?
Discomfort you have had from any areas tender to touch or pressure?
Discomfort you have had from the time you wake up?
How long does your morning stiffness last from the time you wake up?

CRP=C-reactive protein. Ln=natural log. ESR=erythrocyte sedimentation rate.

1. Machado P, et al. *Ann Rheum Dis*. 2011;70(1):47-53.

TICOPA: Tight Control of PsA[1]

UK multicenter, open-label, randomized controlled trial of 206 early PsA patients

- Standard of care with Q12-week review—treating clinician
- Intensive management Q4-week review—protocol
- 48 weeks
- Primary—ACR20
- Secondary—ACR50, ACR70, PASI75

Coates LC et al. *BMC Musculoskeletal Disorders* 2013, 14:101.
1. Coates LC, et al. *BMC Musculoskelet Disord*. 2013;14:101.

Rationale for the TICOPA Study

- **RA:** treat to target improves clinical and radiographic outcomes vs routine approaches[1,2]
- **Availability of newer therapies**
  - → Minimal level of disease activity a realistic treatment target in PsA[4]
- **Targets** for LDA in PsA are now available
  - Development of composite measures of disease activity, eg, MDA, encompass all clinically important aspects of PsA[5]


Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force

1. Grigor C, et al. *Lancet*. 2004;364:263-269. 2. Schoels M, et al. *Ann Rheum Dis*. 2010;69:638-643.
3. Smolen JS, et al. *Ann Rheum Dis*. 2014;73(1):6-16. 4. Gossec L, et al. *Ann Rheum Dis*. 2012;71:4-12.
5. Coates LC, et al. *J Rheumatol*. 2014;41(4):782-791.

Rationale for the TICOPA Study (cont.)

All treat to target recommendations for PsA and SpA are based on expert opinion[1]

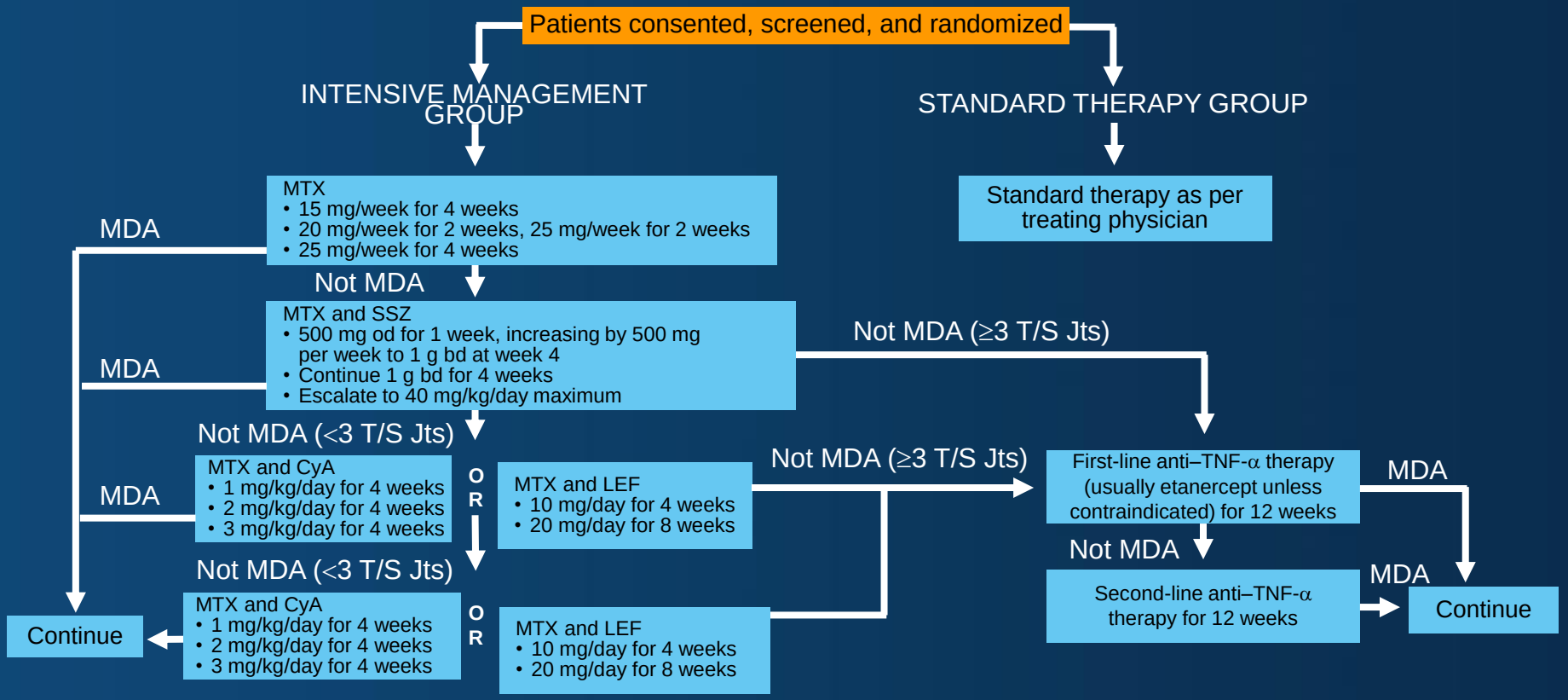
Evidence from RCT for the benefits of treat to target in PsA and SpA is lacking[1]

- **Tight control of early PsA (TICOPA) study[2]**
- First RCT study in PsA (and SpA) to use a treat-to-target approach
- **Aim:** Investigate if tight control using MDA as a target improves outcomes vs standard care in PsA

RCT=randomized controlled trial.

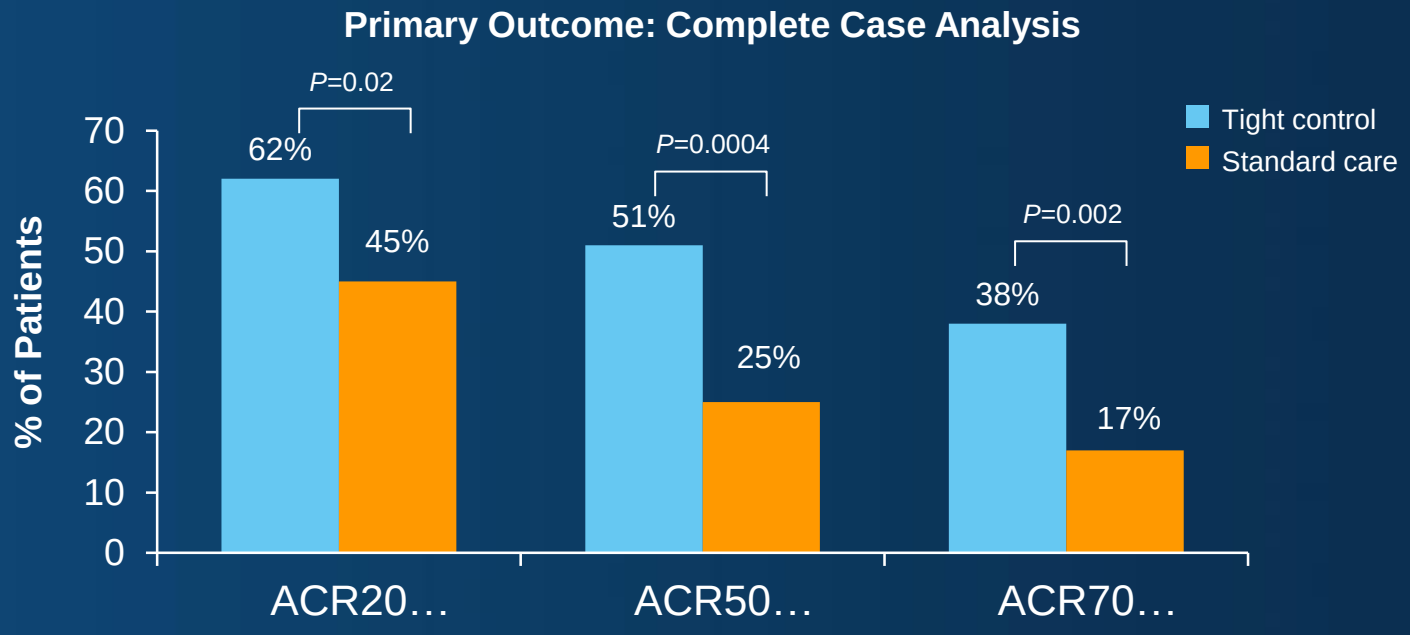
1. Smolen JS, et al. *Ann Rheum Dis*. 2014;73(1):6-16. 2. Coates LC, et al. *BMC Musculoskelet Disord*. 2013;14:101.

TICOPA Study Flow Diagram[1]



MTX=methotrexate. SSZ=sulfasalazine. od=once daily. bd=twice daily. T/S Jts=tender/sore joints. CyA=cyclosporine A. LEF=leflunomide. TNF-□=tumor necrosis factor alpha. 1. Coates LC, et al. *BMC Musculoskelet Disord.* 2013;14:101.

Tight Control Was Associated With Significantly Greater Improvements in Signs and Symptoms of Disease at Week 48

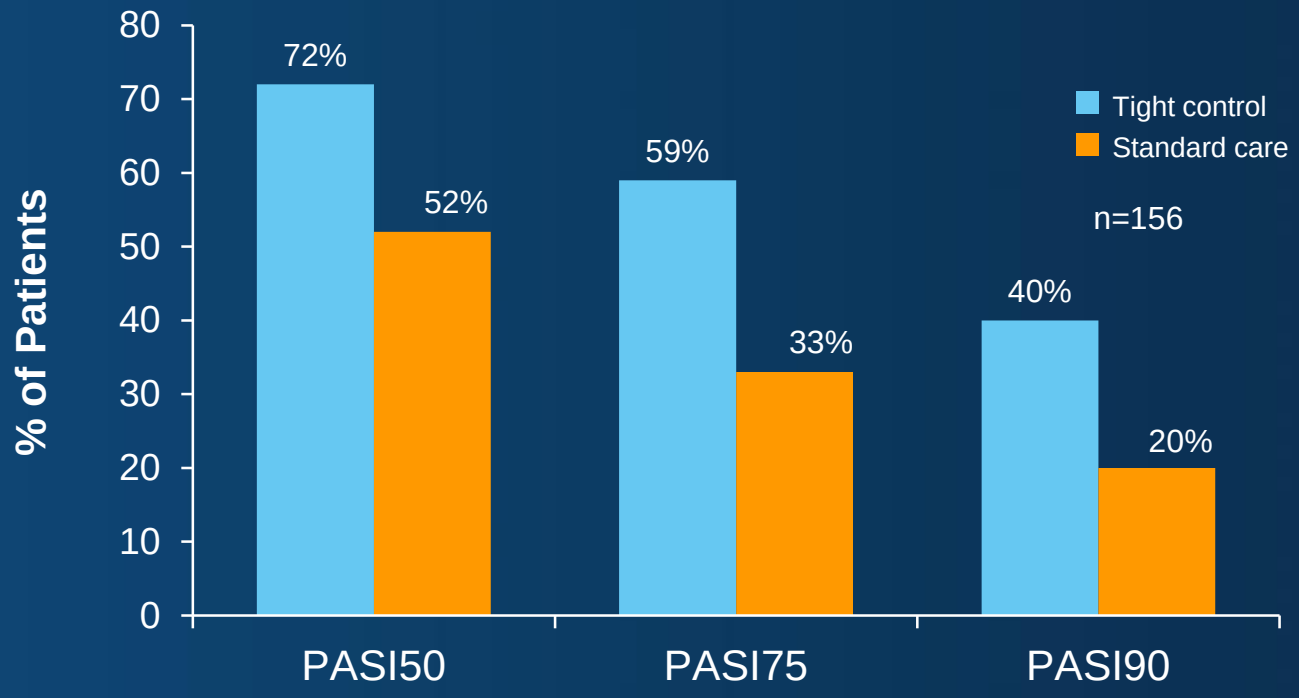


ITT With Multiple Imputations

Outcome Measure	Odds Ratio	Lower 95% CI	Upper 95% CI	*P*-Value
ACR20	1.91	1.03	3.55	0.0392
ACR50	2.36	1.25	4.47	0.0081
ACR70	2.64	1.32	5.26	0.0058

Coates LC, et al. ACR 2013. Abstract 814.

Reduction in Psoriasis Severity Was Achieved in a Higher Proportion of Patients in the Tight Control Arm



Outcome Measure	Odds Ratio	Lower 95% CI	Upper 95% CI	*P*-Value
PASI75	2.92	1.51	5.65	0.0015

1. Coates LC, et al. ACR 2013. Abstract 814.

TICOPA Conclusions

- TICOPA is the first ever open-label RCT in patients with early PsA using a treat to target/tight control approach
- **Treat-to-target approach using MDA as a treatment target in early PsA improved clinical outcomes (both joint and skin) at 48 weeks**
  - Higher use of biologics vs standard care
- MDA may represent a realistic treatment target in patients with early PsA
- Low level of radiographic change and low progression of erosions seen once patients with early PsA are on active therapy

RA and SpA Are Completely Different Clinical Entities

PATHOPHYSIOLOGY	CLINICAL articular and extra-articular manifestations	IMAGING role of X-ray, MRI and other modalities	LABORATORY CRP, ESR, new biomarkers	MEASURES BASDAI and ASDAS not validated—radiographic or histopathology

Summary Overview

- 2010 RA classification criteria and definition of remission
  - Allows earlier disease recognition for clinical study and research
  - Implications for clinical practice
- Clinical trials have demonstrated the benefit of targeted therapies
- RA disease measurement: Allows quantitative baseline measure
- Key is to use a treatment strategy to continuously strive to push disease toward improvement
  - Advance therapy in stepwise fashion while continuously measuring disease to achieve goal – or as close as is reasonably feasible

TTT – Questions Remain

- Basic Science Questions
  - Is there a “window” where TTT will be successful ?
  - Biomarkers that predict success of TTT ?
- Treatment/Clinical Questions
  - What treatment strategy ?
  - What target ?
  - Long term function, morbidity and mortality ?
  - Are there greater side effects from TTT ?
  - Is Spondyloarthritis ready for TTT
- Health Service Questions
  - Deployment strategy for TTT ?
  - Economic cost of TTT ?
  - Patient perspective of TTT ?

Solomon, D Arth & Rheum 66:4, 775-782 2014