

Peut-on prédire la réponse clinique et la progression radiographique dans la polyarthrite rhumatoïde

*Boulos Haraoui, MD FRCPC
Université de Montréal
Institut de rhumatologie de Montréal*



Outline

- **Classic predictors of outcomes**
- **Timing of response as a predictor of outcomes**
- **Predictors of response/sustained remission**
- **Concept of rapid radiographic progression**

Classic Predictors Of Prognosis

Baseline Predictors Of Poor Prognosis @ A Group Level

	Less Likely To Achieve Remission	Rapid Radiographic Progressors
Female Gender	√	√
Smoker	√	-
Early Age of Onset	√	√
High DAS	√	√
High CRP/ESR	√	√
High HAQ	√	√
Poor Response to Rx (6 mo.)	√	√
Positive RF/anti-CCP	√	√
Erosion @ BSL	√	√

CONCEPT

**Timing Of Response Is Predictive
Of Long Term Outcome**

**Is Response To Treatment @ 12 Wks a
Better Predictor of Outcomes Than BSL
Measures Of Activity ?**

ACR Core Set Measures & DAS28 @ 12 Weeks Is A Better Determinant Of Radiographic Outcome

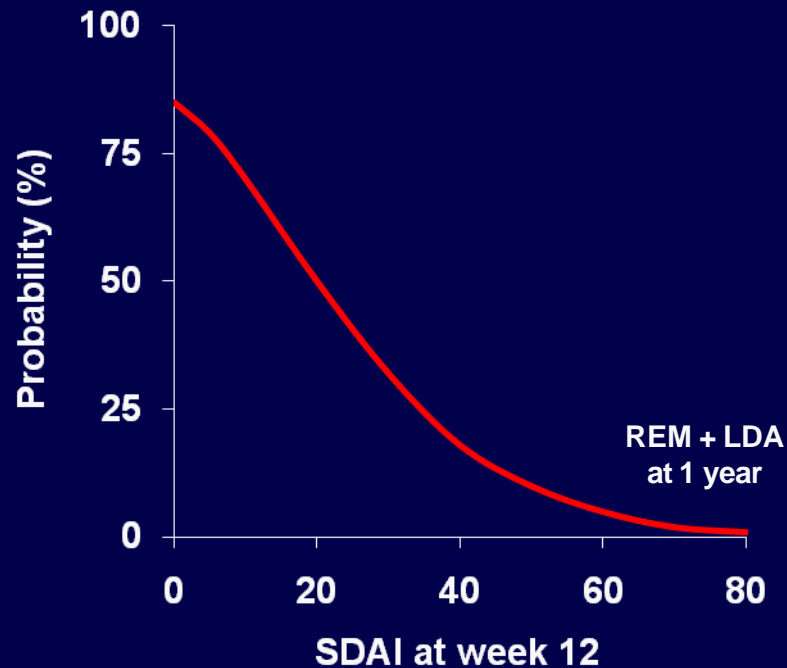
	Initial	12 Weeks
CRP	0.292*	0.477***
ESR	0.235	0.491***
MHAQ	0.138	0.183
Patients' pain estimation [†]	0.163	0.521***
Patients' global assessment ^{††}	0.152	0.500***
Swollen joint count	0.279*	0.434**
Tender joint count	0.085	0.257
Physicians' global assessment ^{†††}	0.253	0.449***
DAS28-(CRP)	0.384**	0.592***

* p < 0.05 **p < 0.001 ***p < 0.001

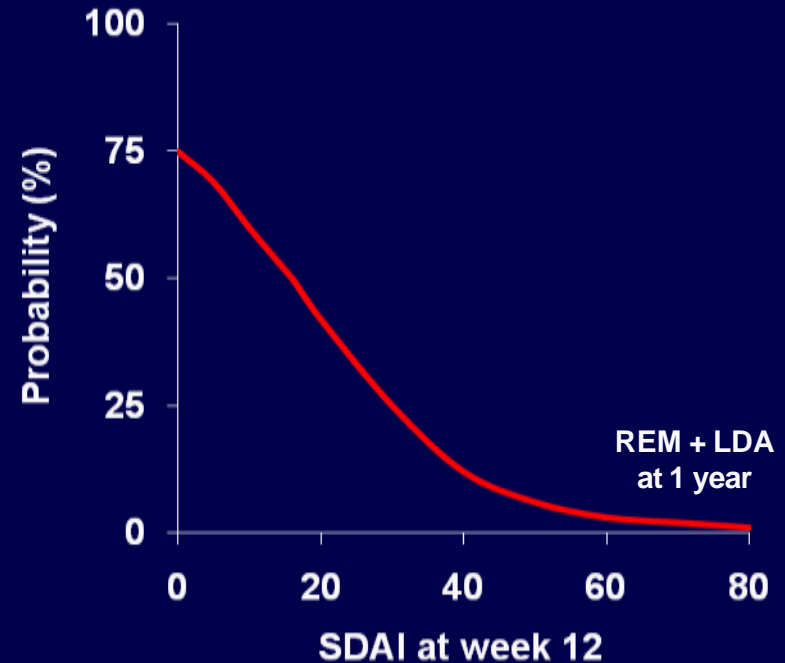
**Disease State Achieved @ 12 Weeks As
A Predictor**

Rapid Control of Signs & Symptoms is Predictive of a Good Long-Term Response

Early RA (N=1342)



Established RA (N=712)

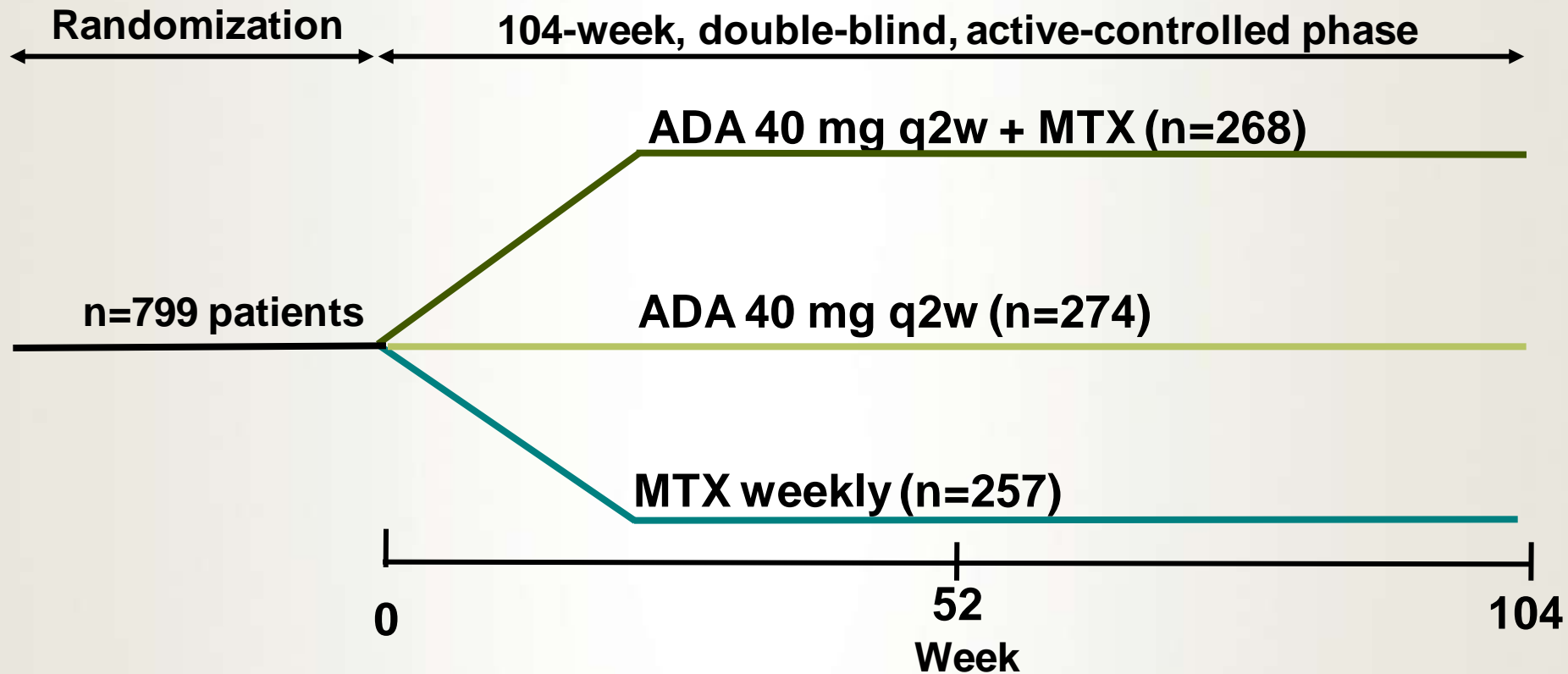


For a majority of patients, the **disease state** achieved within the first 12 weeks (3 months) is highly predictive of the degree of clinical outcome at 1 year

Rem= Remission
LDA= Low Disease Activity

Response To Treatment @ 12 vs 24 Weeks As A Predictor

Methods: PREMIER Trial Design



PREMIER = Prospective Multi-centre Randomised, Double-blind, Active Comparator-controlled, Parallel-groups Study Comparing the Fully Human Monoclonal Anti-TNF α Antibody ADALIMUMAB Given Every Second Week With Methotrexate Given Weekly and the Combination of ADALIMUMAB and Methotrexate Administered Over 2 Years in Patients With Early Rheumatoid Arthritis; ADA = adalimumab; MTX = methotrexate
Haraoui B *et al.* ACR 2010. Abstract 1101.

Timing of Good Responses: Effects On Long Term Outcome in RA

Table 2. Percentages of Subjects in Clinical Remission (DAS28[CRP] <2.6) at 52 Weeks, Categorized on the Basis of Early (12 Weeks) or Delayed (24 Weeks) Clinical Responses (ACR Response or Improvement in DAS28[CRP])

Clinical Response	MTX % (n/N)		ADA+MTX % (n/N)	
	Early	Delayed	Early	Delayed
ACR Response				
ACR20	35 (40/115)	11 (6/53)	50 (85/171)*	35 (10/29)*
ACR50	55 (28/51)	21 (13/63)	62 (69/112)	34 (16/47)
ACR70	89 (16/18)	47 (20/43)	85 (51/60)	41 (20/49)
Improvement in DAS28(CRP)				
Δ DAS28 >0.6	27 (34/166)	0 (0/15)	43 (88/207)**	20 (2/10)
Δ DAS28 >1.2	32 (42/130)	10 (4/41)	46 (85/187)*	25 (5/20)
Δ DAS28 >1.8	44 (40/91)	9 (4/44)	51 (79/155)	19 (7/37)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ between treatment groups using Pearson's chi square test or Fisher's exact test.

Very low <15%	Low 15 - <30%	Intermediate 30 - <50%	High ≥50
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Timing of Good Responses: Effect On Long Term Outcome in RA

Table 3. Percentages of Subjects With Rapid Radiographic Progression (Δ mTSS >3.0 Units/Year) at 52 Weeks, Categorized on the Basis of Early (12 Weeks) or Delayed (24 Weeks) Clinical Responses (ACR Response or Improvement in DAS28[CRP])

Clinical Response	MTX % (n/N)		ADA+MTX % (n/N)	
	Early	Delayed	Early	Delayed
ACR Response				
ACR20	32 (34/108)	62 (31/50)	9 (15/162)***	11 (3/28)***
ACR50	23 (11/47)	47 (28/60)	5 (5/109)***	19 (8/42)**
ACR70	18 (3/17)	40 (16/40)	5 (3/59)	13 (6/46)**
Improvement in DAS28(CRP)				
Δ DAS28 >0.6	43 (67/156)	64 (9/14)	11 (22/195)***	10 (1/10)*
Δ DAS28 >1.2	41 (50/123)	53 (19/36)	11 (20/176)***	5 (1/20)***
Δ DAS28 >1.8	37 (32/86)	49 (20/41)	12 (18/150)***	6 (2/34)***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ between treatment groups using Pearson's chi square test or Fisher's exact test.

Very low <20%	Low 20 – <30%	Intermediate 30 – <40%	High ≥40%
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But.....

**Patients In Clinical Trials Do Not
Reflect Patients In Clinical Practice !!**

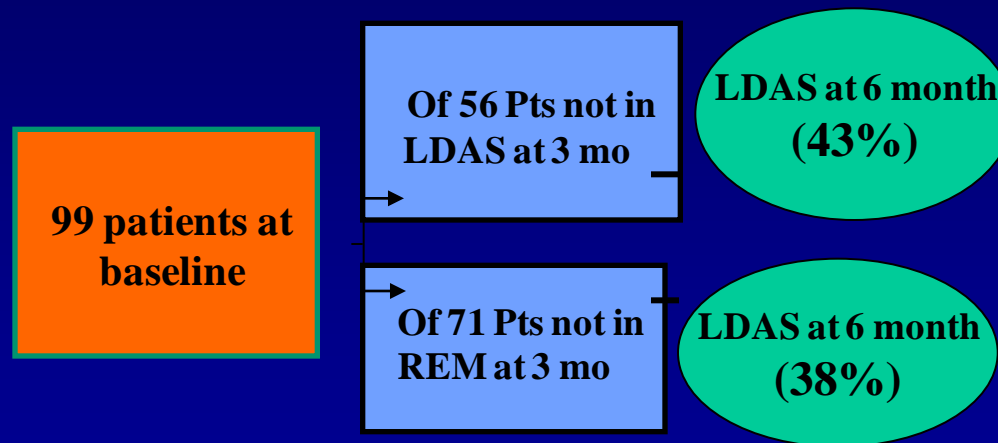
Baseline Disease Activity

	HUMIRA + MTX n=268	HUMIRA n=274	MTX n=257
SJC (0–66), mean	23	24	24
TJC (0–68), mean	33	34	34
HAQ mean	1.5	1.6	1.5
DAS28 mean	6.3	6.4	6.3
CRP (mg/dL)	4.7	5.0	4.6

Demographics and Baseline Characteristics In Patients In The Canadian Early RA Database (CATCH Cohort)

Demographics	All Eligible Patients (n=99)
Age [†]	50 (15)
Female (%)	78 (79)
Disease duration (mo) [†]	6.1 (3.0)
RF positive (%)	64 (65)
anti-CCP positive (%)	51 (65)
Disease Activity Measures	
Tender joint count (68) [†]	17 (11)
Swollen joint count (66) [†]	13 (9)
DAS 28 [†]	5.5 (1.3)
HAQ [†]	1.0 (0.7)
ESR (mm/h) [†]	28 (23)
CRP (mg/l) [†]	17 (23)

Influence of Disease Activity on Target Outcomes @ 3 vs 6 Month (N=99) (CATCH Cohort)



What about established disease ?

**Response To Treatment @ 1 to 12
Weeks As A Predictor**

Probability to Achieve Low Disease Activity at 52 Weeks in Rheumatoid Arthritis Patients Treated With Certolizumab Pegol Depends on Time to and Level of Initial Response

van der Heijde D, Schiff M, Keystone EC, et al.

Table. Probability of CZP + MTX-treated patients achieving LDA at Week 52^a

DAS28 improvement	Week						
	1	2	4	6	8	10	12
<0.3	20 (N=220)	12 (N=112)	3 (N=63)	0 (N=41)	0 (N=27)	0 (N=19)	0 (N=14)
<0.6	21 (N=352)	15 (N=209)	7 (N=126)	3 (N=79)	3 (N=63)	0 (N=45)	0 (N=34)
<0.9	23 (N=457)	17 (N=317)	9 (N=202)	4 (N=144)	3 (N=106)	0 (N=76)	0 (N=67)
<1.2	25 (N=546)	19 (N=418)	13 (N=288)	8 (N=214)	4.5 (N=157)	3 (N=129)	1 (N=103)
<1.5	26 (N=605)	22 (N=492)	17 (N=369)	12 (N=281)	7 (N=221)	6 (N=182)	2 (N=145)
<1.8	28 (N=656)	24 (N=573)	17 (N=448)	12 (N=357)	10 (N=294)	7 (N=245)	5 (N=206)
Probability:	>10%			5–10%		<5%	

^aPercentages out of those who failed to achieve DAS improvements up to the nth week of follow-up for the first 12 weeks. N numbers are denominators for % calculations and are the number of patients not achieving the DAS28 change threshold at the week presented. Population with severe (mean baseline DAS28 of 6.9 units) long-standing disease at baseline.

**Is the concept valid if we are
applying a Tight Control /
Treat to Target concept?**

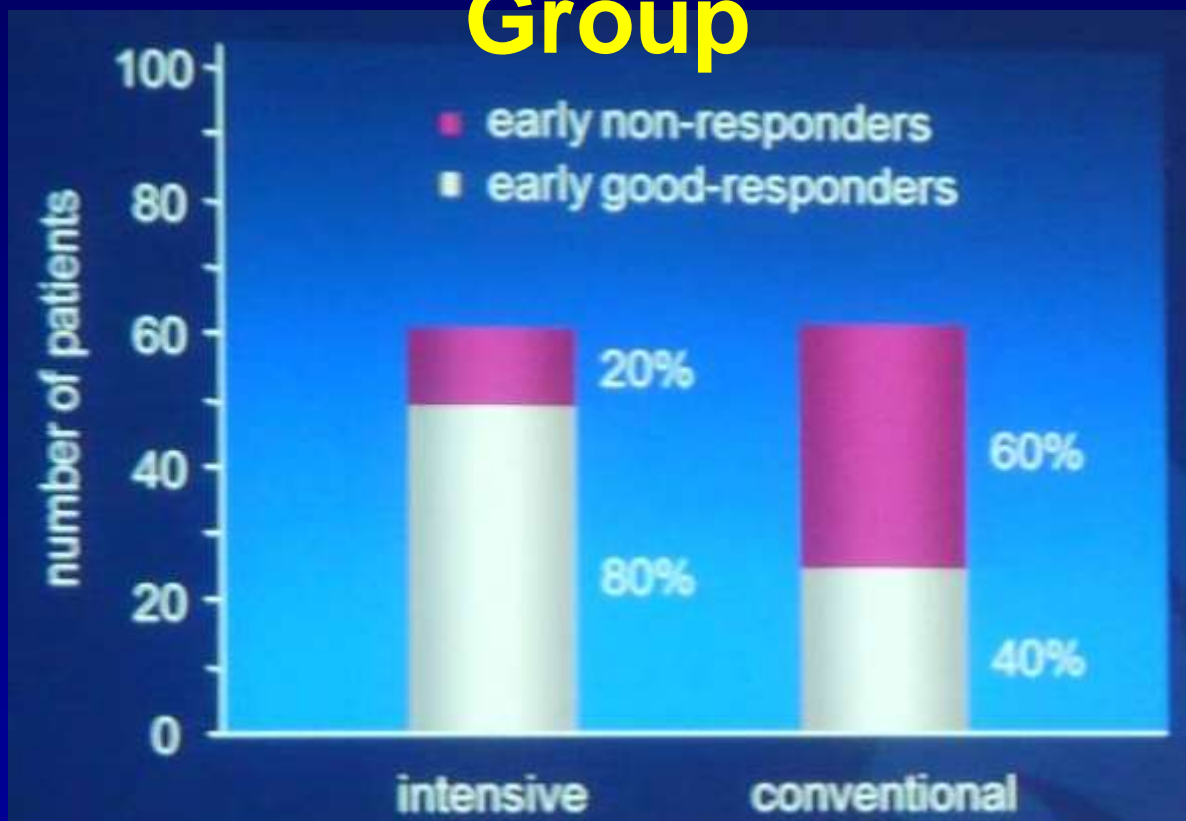
IMPORTANCE OF EARLY GOOD RESPONSE

A Better Long-Term Clinical Course and Less Radiographic Joint Damage Can Be Predicted by an Early Good Response to Therapy in RA Patients

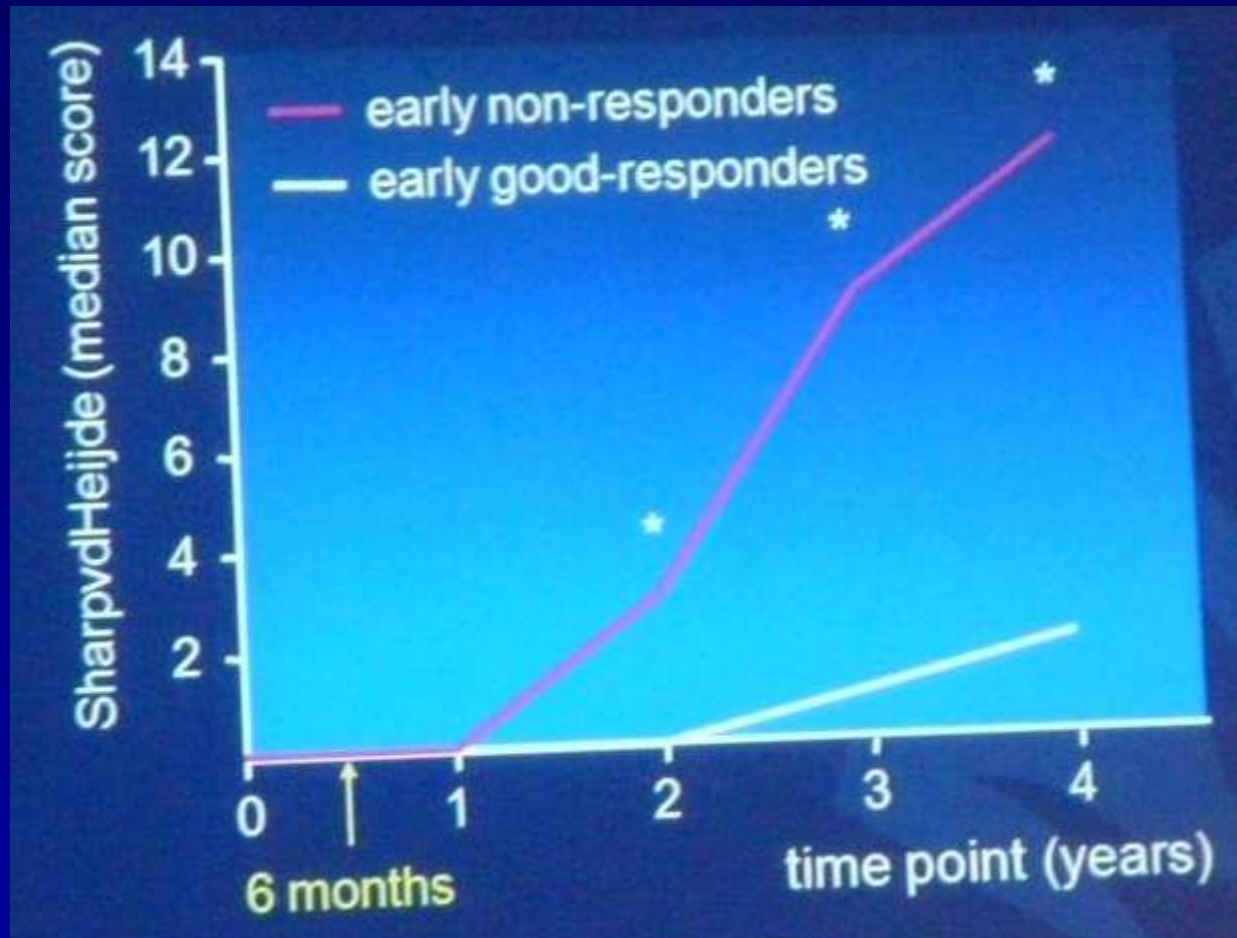
CAMERA Study Population

- 299 patients in total
- Intensive treatment strategy MTX (n=151)
 - ◆ Monthly
 - ◆ Computer decision model
- Conventional treatment strategy MTX (n=148)
 - ◆ 3-monthly
 - ◆ Usual care based on SJC

6 Months Good Responders vs. Non-Responders by Treatment Group



Results – Disease Severity



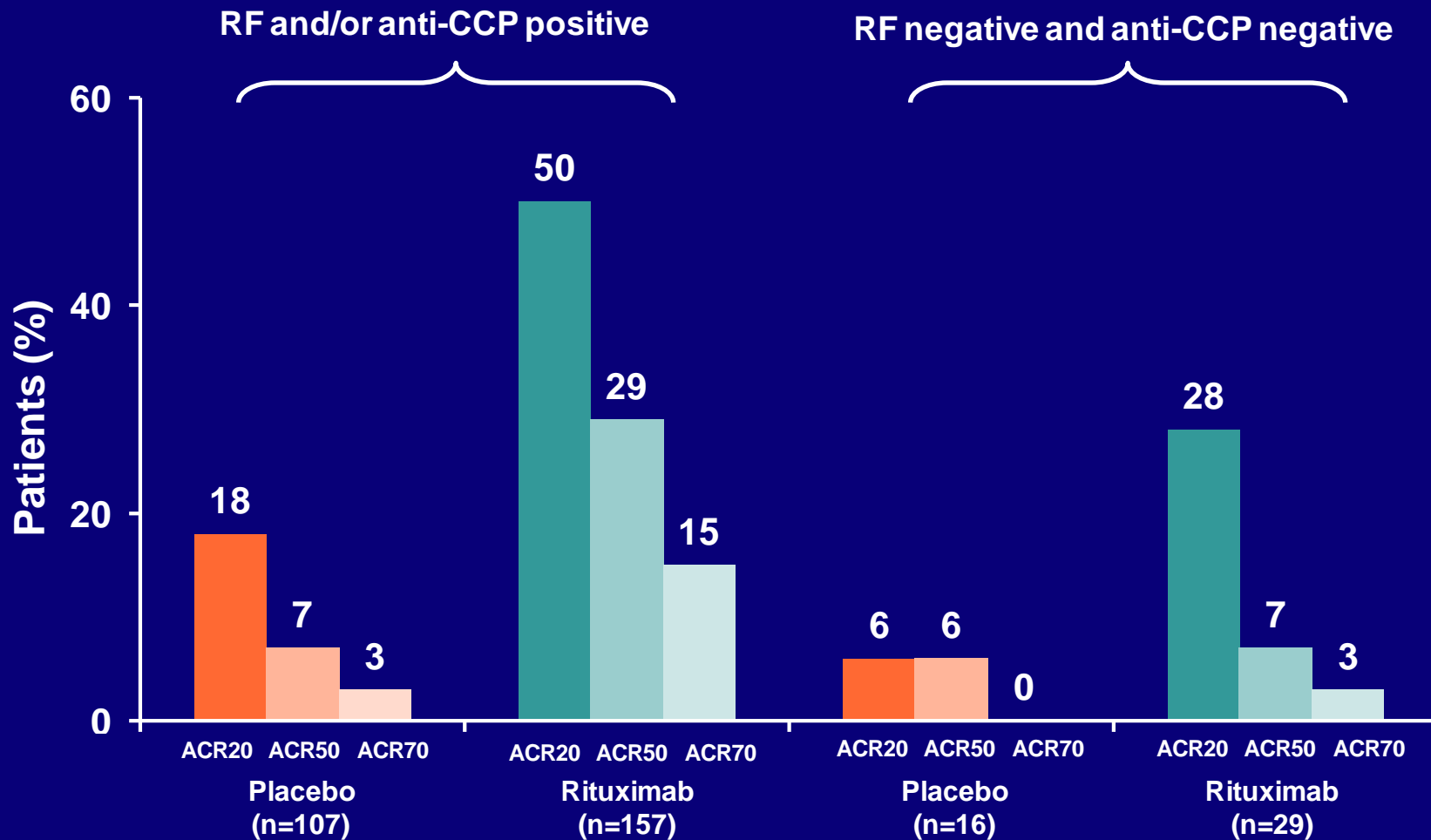
Take Home Message

- **The timing of achieving a clinical response predicts long term outcome.**
- **The more rapid the response, the better the long term outcome.**
- **Treatment should be aimed at achieving the therapeutic target as early as possible**
- **Clinical trial patients do not reflect those in clinical practice**

Other Predictors of Therapeutic Responsiveness

Biomarkers As Predictors

ACR Responses @ Week 24 According To RF & Anti-CCP Status



Autoantibodies In TNF Inhibitor Treated RA Patients

Predictor	n (%)	Mean DAS score (SD)		Association
		Baseline	Improvement	
RF -ve	59 (11)	6.72 (1)	3.03 (1.7)	p=0.02
RF +ve	462 (89)	6.59 (1)	2.43 (1.5)	
Anti-CCP -ve	96 (18)	6.61 (1)	2.90 (1.6)	p=0.02
Anti-CCP +ve	425 (82)	6.61 (1)	2.40 (1.5)	

Analyses were performed in 521 patients for whom serum samples were available. p-values stated are for linear regression, adjusted for concurrent DMARD, gender, baseline HAQ and DAS28 score.

Genetic Factors As Predictors

Genetic Factors In Anti-TNF Treatment Response

Candidate genes	Studies
TNF	15 studies: mostly -308 SNP
SE and extended MHC	6 studies
TNFR2	5 studies: exon 6 Met196Arg SNP
TNFR1	1 study: exon 1 Pro12Pro SNP
Fc γ R3a	2 studies: Val158Phe SNP
Other cytokines/receptors	1 or 2 studies each

- **Results are inconsistent and inconclusive**
 - **Small sample sizes and limited power (n=50–300)**
 - **Varied designs (e.g. TNF inhibitor, disease, outcome)**
 - **Investigate individual polymorphisms**

Conclusion

**Progress Has Been Made In Predictors
Of Outcomes, But.....**

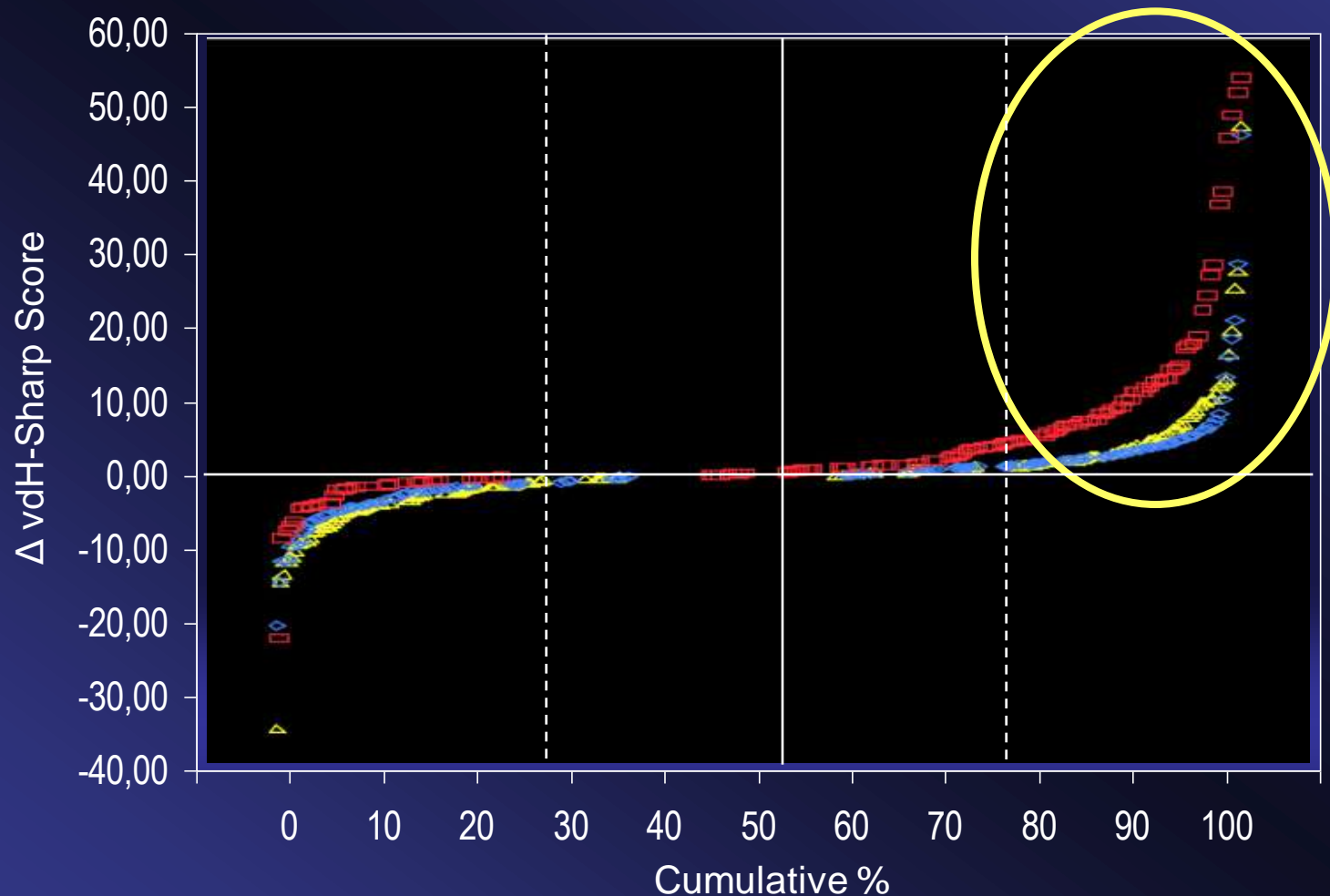
WE HAVE A LONG WAY TO GO !

**What about radiographic
progression ?**

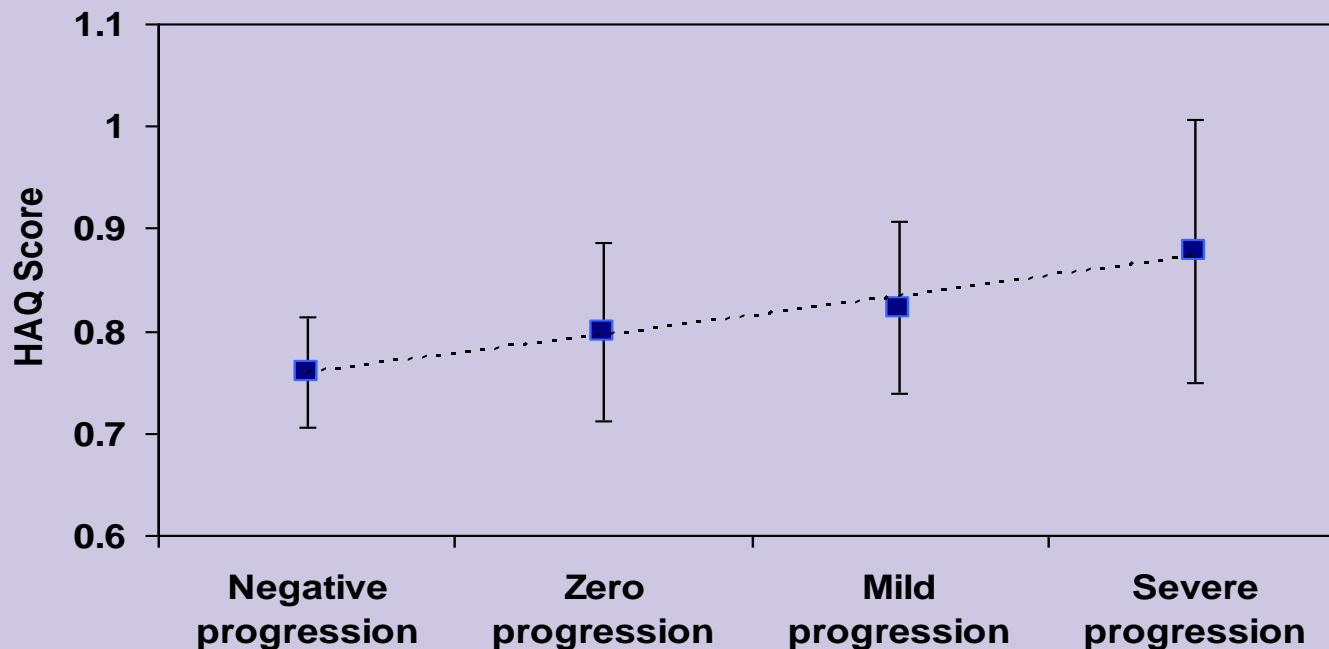
Can we predict it?

ASPIRE - Radiographic Progression

Driven by a small number of patients



Radiographic Progression Influences Disability Within Short Time Frame



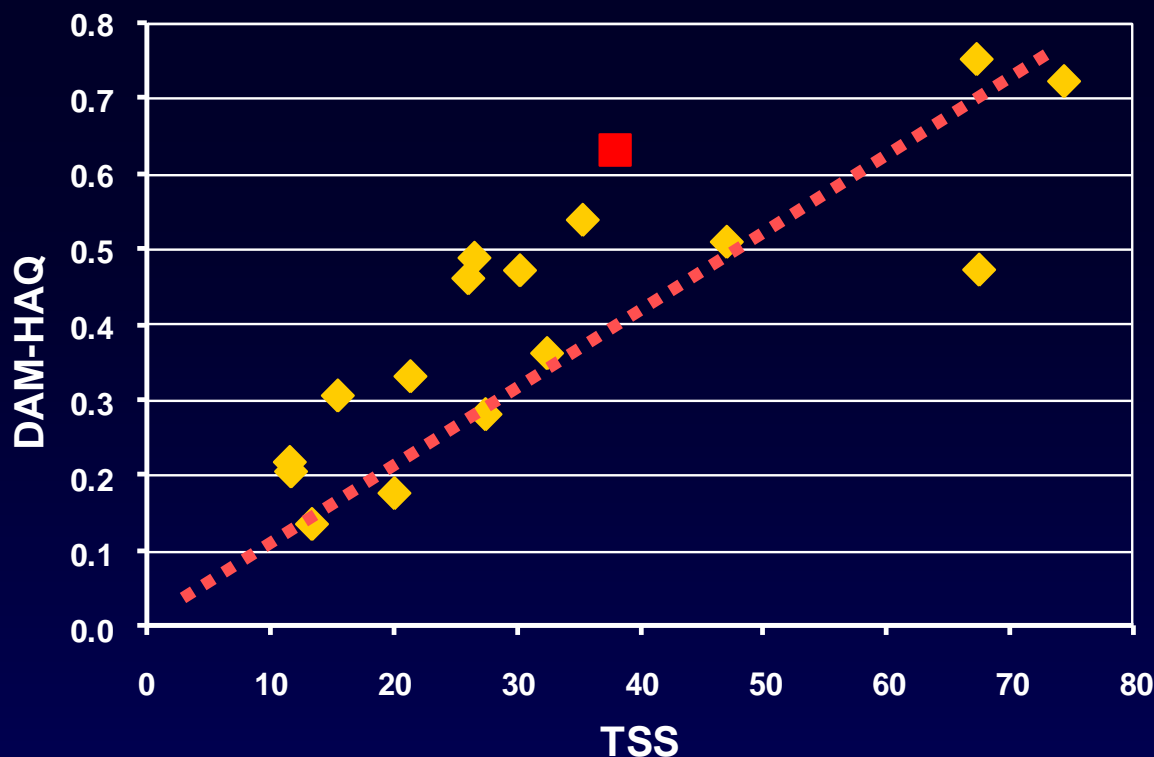
*4 categories of progression; error bars reflect standard error

Marginal means for HAQ scores adjusted for age, sex, treatment, Sharp score, and time as a function of change in Sharp score*

There is an indication at the level of the RCT that repair is associated with better physical function

What Does Progression of Joint Damage Mean for Physical Function?

Correlation of DAM-HAQ With Joint Damage

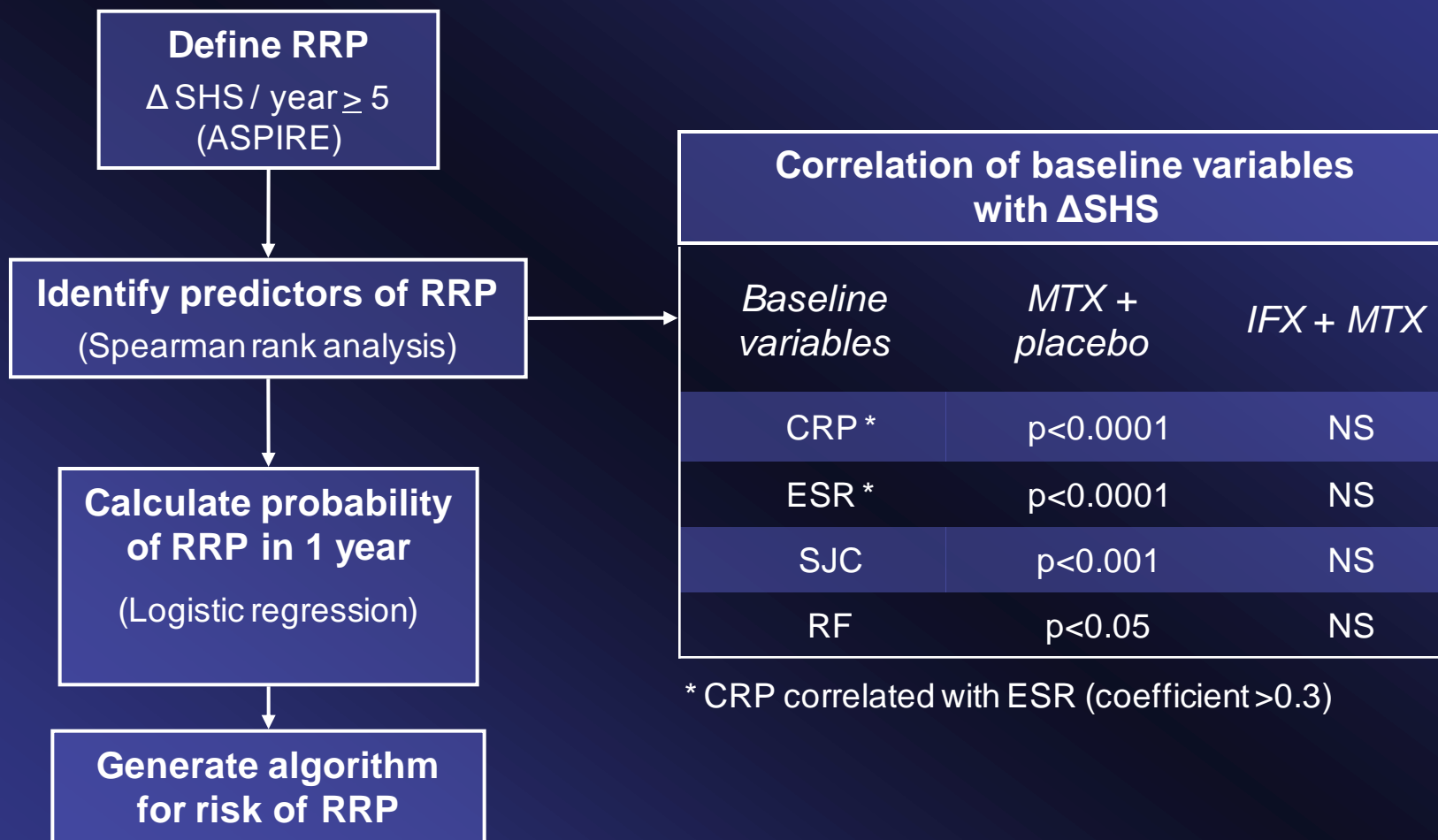


$r=0.829$

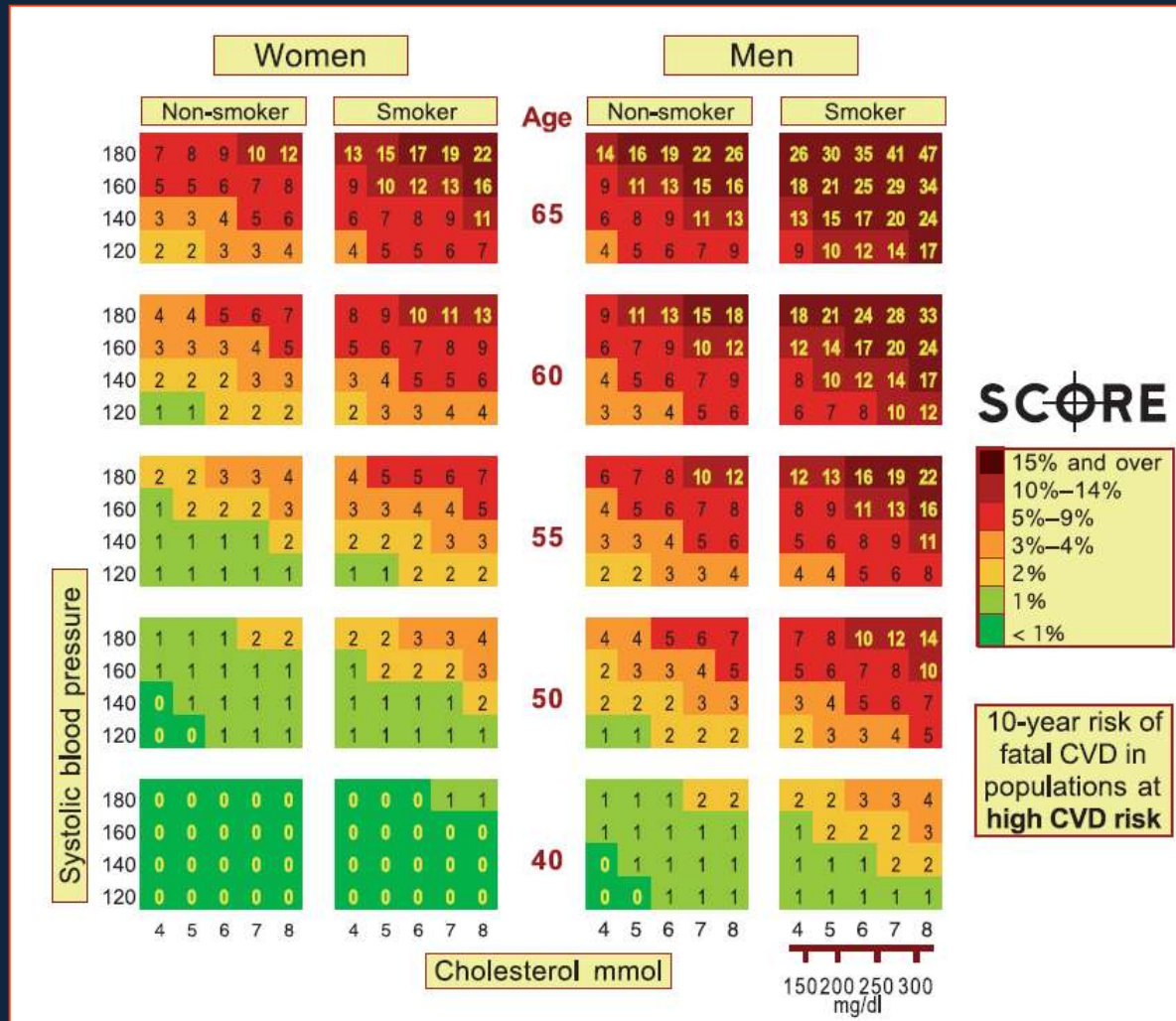
10 unit TSS
=
0.1 units HAQ

Prediction of RRP

Development of a matrix risk model



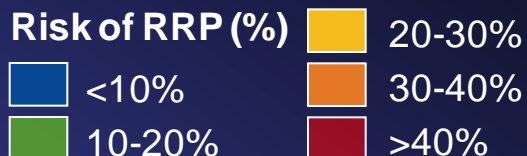
Risk Models for Cardiovascular Disease (CVD) in Europe: 10-Year Risk of Fatal CVD



Matrix Prediction Model of RRP

ASPIRE: DMARD-naïve population

		IFX + MTX			MTX mono				
		<80	80-200	>200	<80	80-200	>200		
28 Swollen Joint Count	≥3	>17	8	11	14	33	40	47	CRP (mg/dL)
		10-17	8	10	13	31	38	45	
		<10	7	9	12	29	35	42	
	0.6-3	>17	6	8	10	17	22	27	
		10-17	6	7	10	16	20	25	
		<10	5	7	9	15	19	23	
	<0.6	>17	4	6	8	8	11	14	
		10-17	4	5	7	7	10	12	
		<10	4	5	6	7	9	11	
		RF-titer (U/mL)			RF-titer (U/mL)				
		<80	80-200	>200	<80	80-200	>200		



Example: 47 year old woman

DMARD-naïve, SJC=9, CRP=1.3 mg/dL, RF=135 U/mL

		IFX + MTX			MTX mono						
		<80	80-200	>200	<80	80-200	>200				
28 Swollen Joint Count	>17	8	11	14	33	40	47	≥3	CRP (mg/dL)		
	10-17	8	10	13	31	38	45				
	<10	7	9	12	29	35	42				
	>17	6	8	10	17	22	27	0.6-3			
	10-17	6	7	10	16	20	25				
	<10	5	7	9	15	19	23				
	>17	4	6	8	8	11	14	<0.6			
	10-17	4	5	7	7	10	12				
	<10	4	5	6	7	9	11				
			RF-titer (U/mL)			RF-titer (U/mL)					

$$NNT = 8.3$$

$$1/(0.19 - 0.07)$$

Example: 47 year old woman

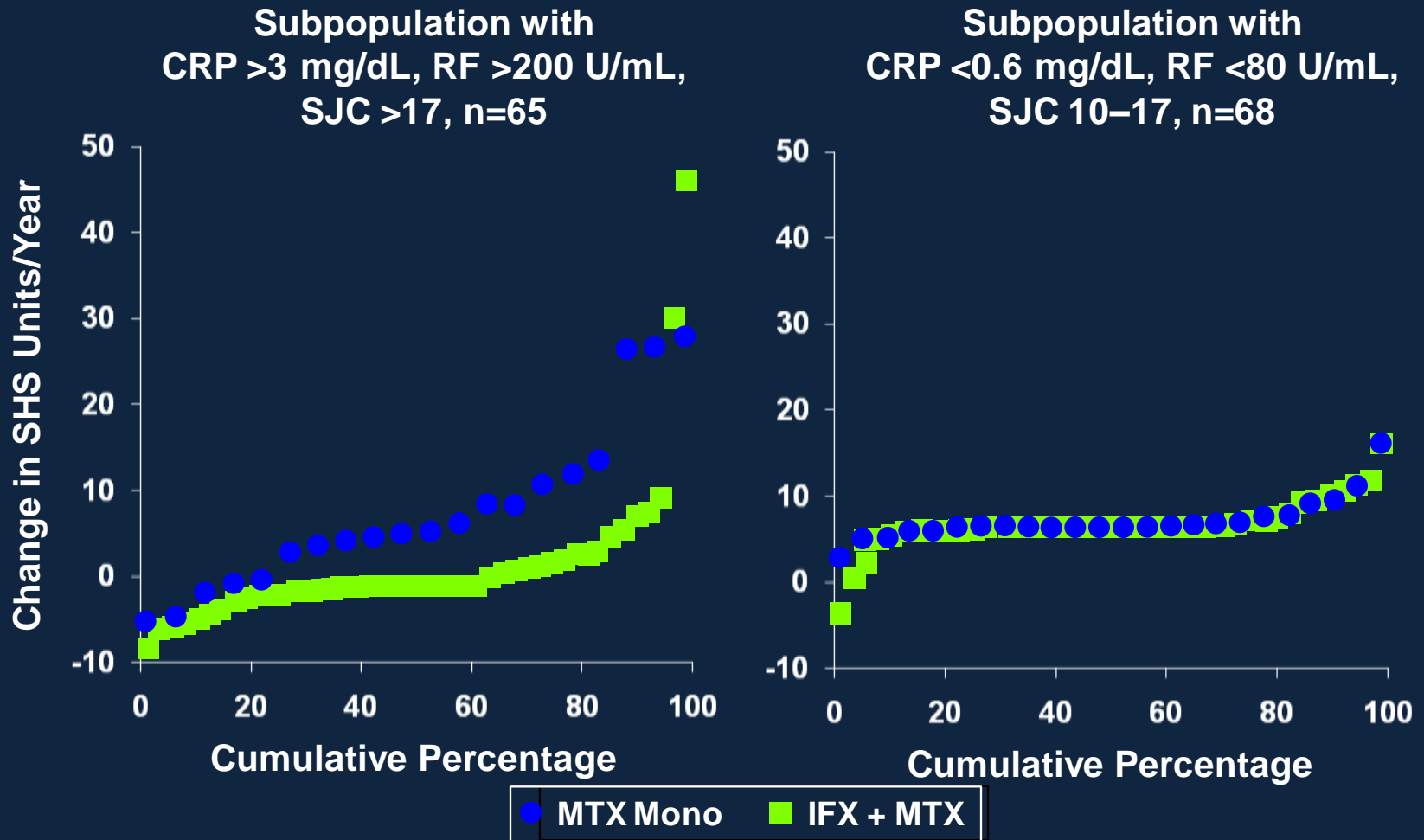
DMARD-naïve, SJC=18, CRP=3.3 mg/dL, RF=235 U/mL

		IFX + MTX			MTX mono						
28 Swollen Joint Count	>17	8	11	14	33	40	47	≥3	CRP (mg/dL)		
	10-17	8	10	13	31	38	45				
	<10	7	9	12	29	35	42				
	>17	6	8	10	17	22	27	0.6-3			
	10-17	6	7	10	16	20	25				
	<10	5	7	9	15	19	23				
	>17	4	6	8	8	11	14	<0.6			
	10-17	4	5	7	7	10	12				
	<10	4	5	6	7	9	11				
			<80	80-200	>200	<80	80-200	>200			
			RF-titer (U/mL)			RF-titer (U/mL)					

NNT = 3.0

Theory vs Reality

Radiographic progression by treatment regimen



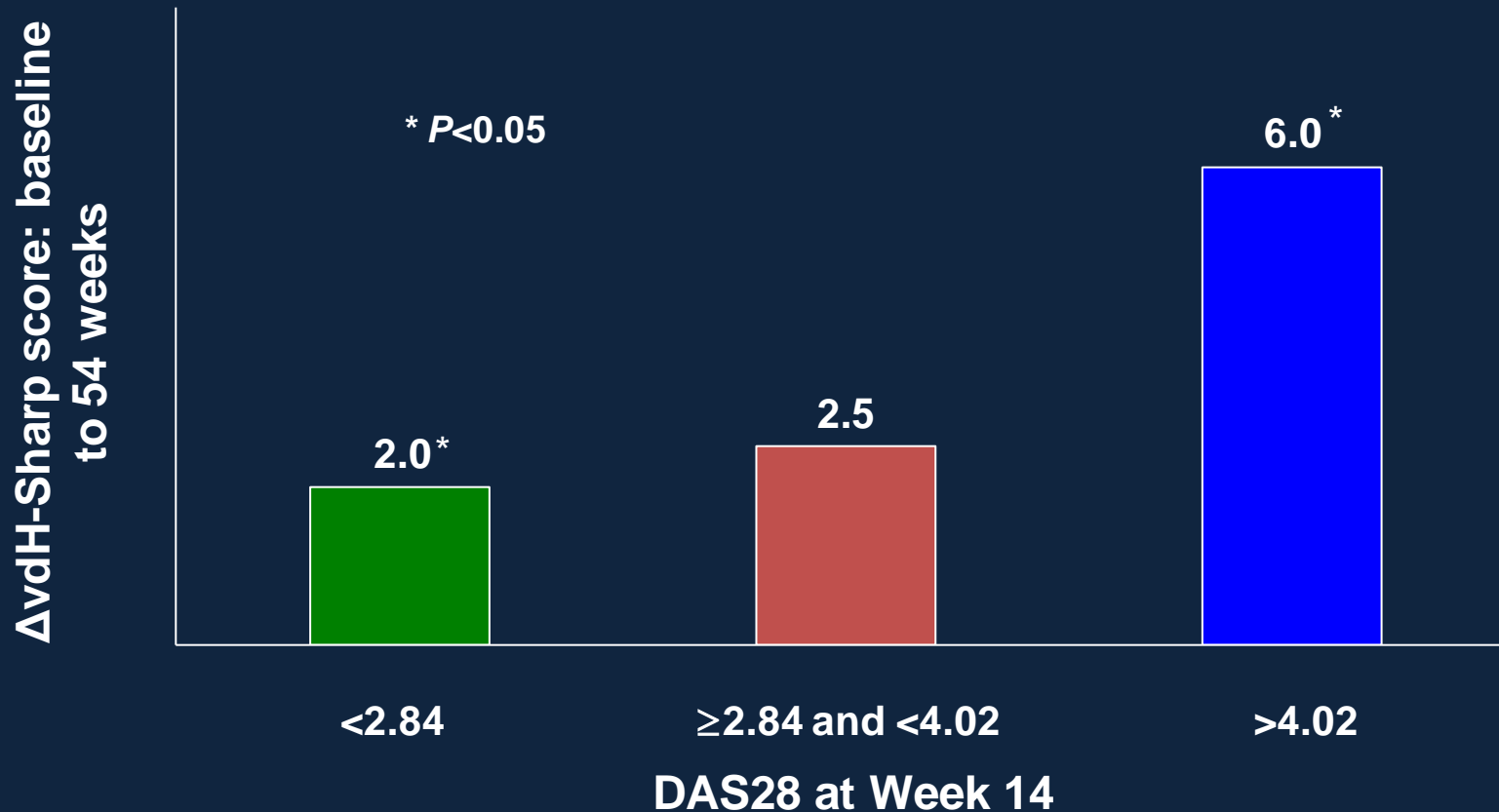
Constant Predictors

- Increasing titre of RF / Anti-CCP
- High CRP
- Other
 - SJC (ASPIRE)
 - Pt Global (PREMIER)
 - Baseline erosive score (BeSt)
 - DAS-28 score (SONORA)

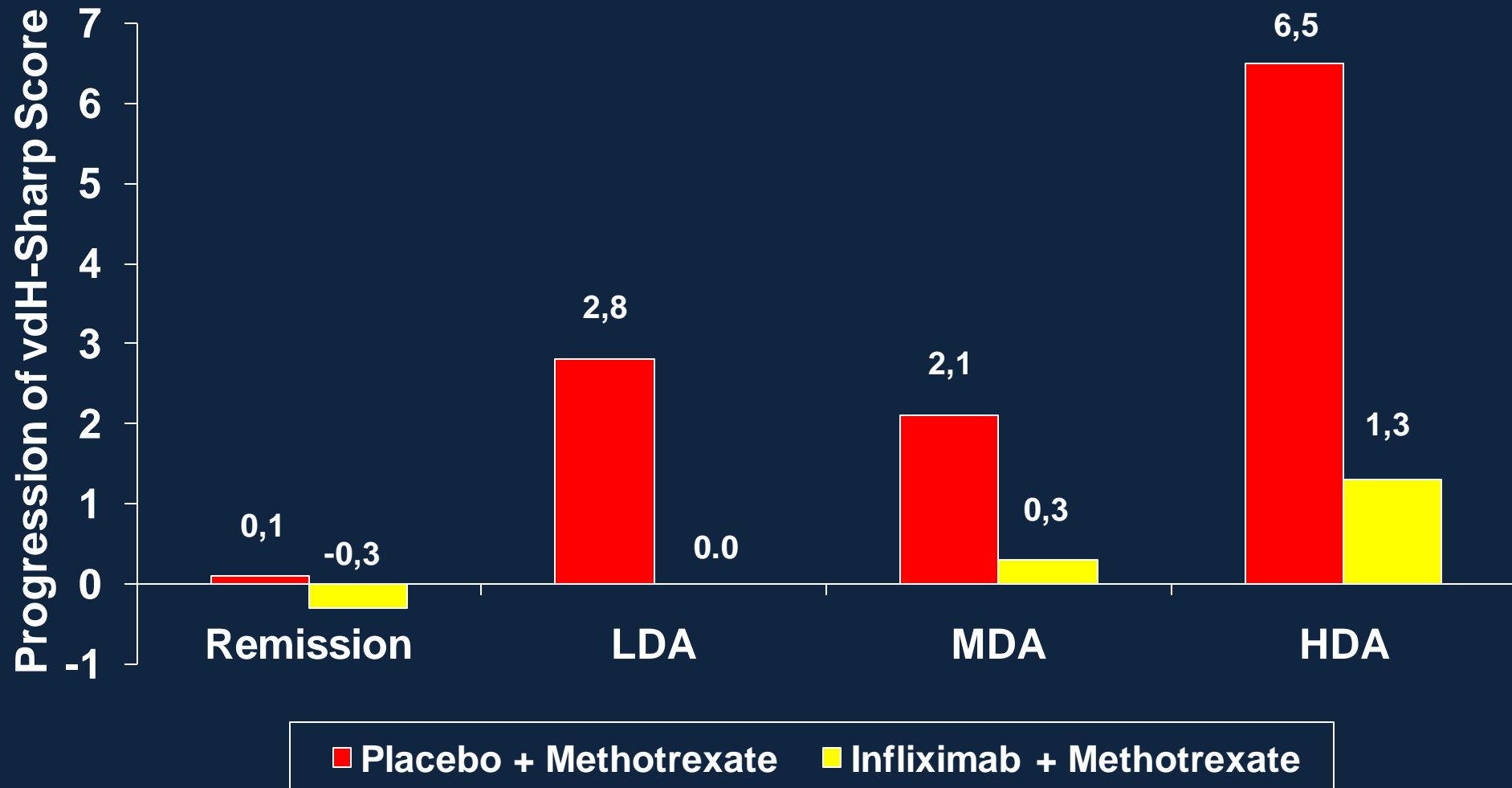
**What about reassessing patients
after 3 Months**

ASPIRE: MTX Monotherapy Group

DAS28 after 14 weeks of MTX predicts RRP

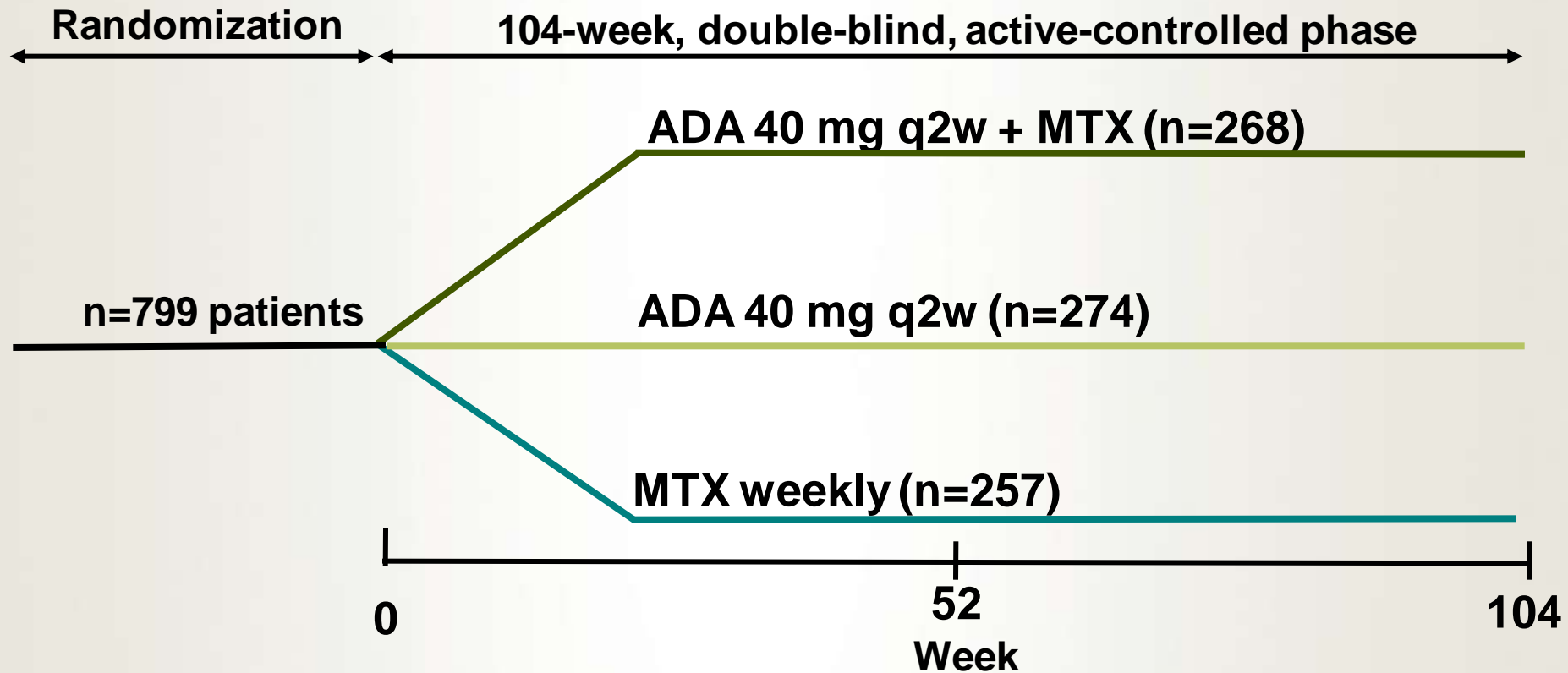


Remission Stops Progression and TNF Inhibition Interferes With Progression Even in Higher Disease Activity States (W -14)



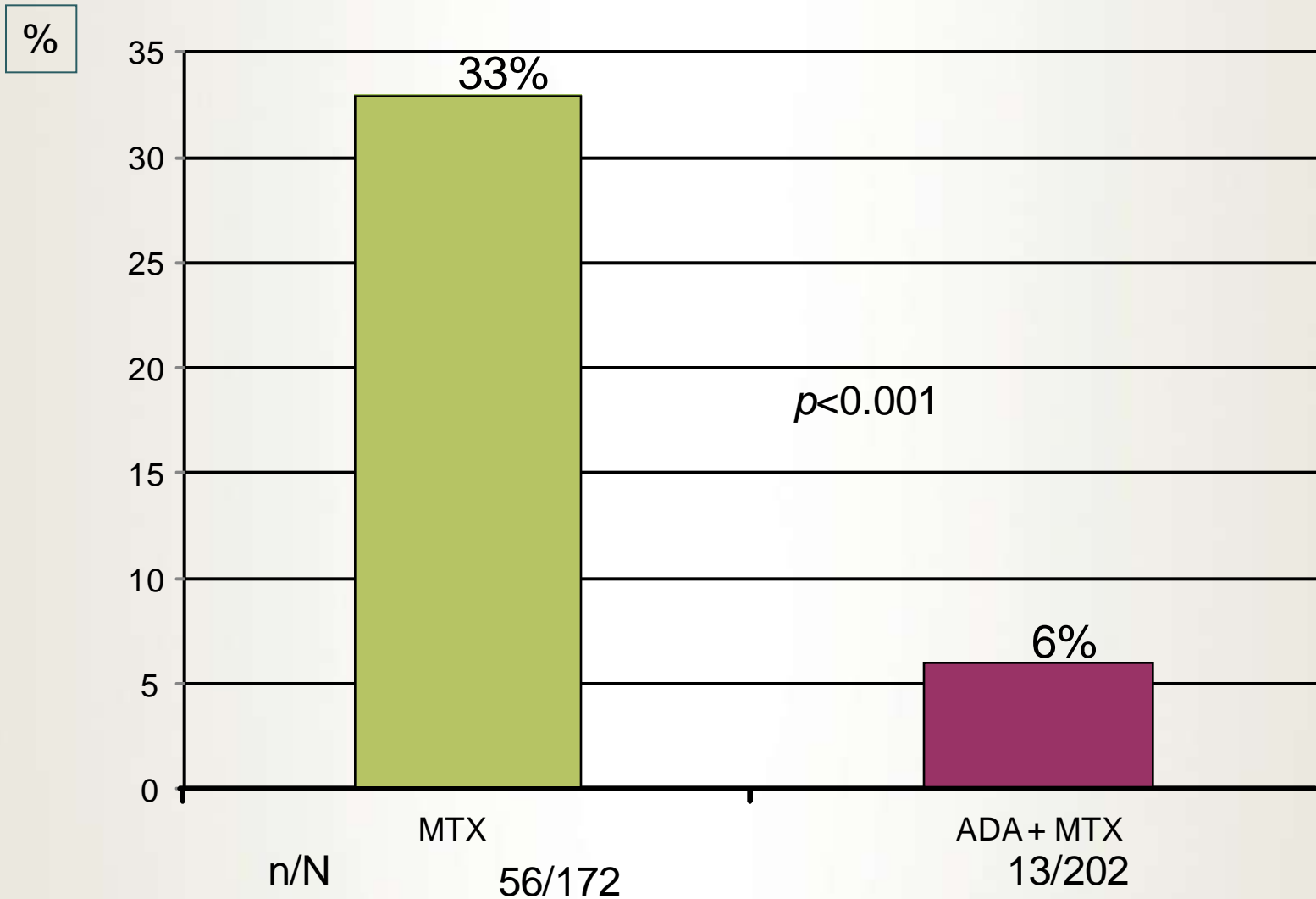
LDA, low disease activity; HDA, high disease activity; MDA, moderate disease activity.

Rapid progressors (> 3 units/year of TSS) in the PREMIER Trial

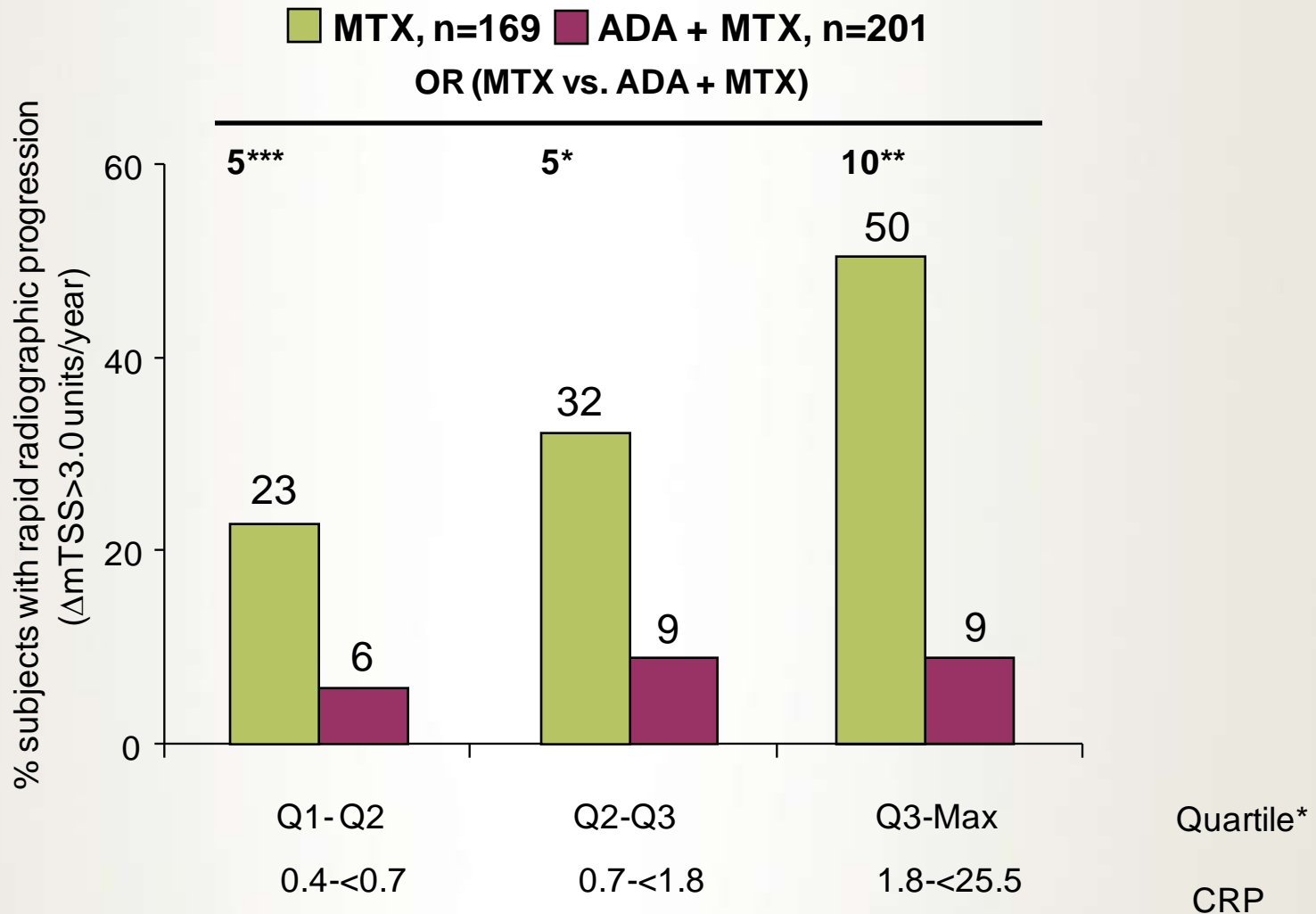


PREMIER = Prospective Multi-centre Randomised, Double-blind, Active Comparator-controlled, Parallel-groups Study Comparing the Fully Human Monoclonal Anti-TNF α Antibody ADALIMUMAB Given Every Second Week With Methotrexate Given Weekly and the Combination of ADALIMUMAB and Methotrexate Administered Over 2 Years in Patients With Early Rheumatoid Arthritis; ADA = adalimumab; MTX = methotrexate
Haraoui B *et al.* ACR 2010. Abstract 1101.

% of Rapid X-Ray Progressors (≥ 3 units of mTSS/year)



Rapid Radiographic Progression at 2 Years According to CRP Quartiles at 12 Weeks



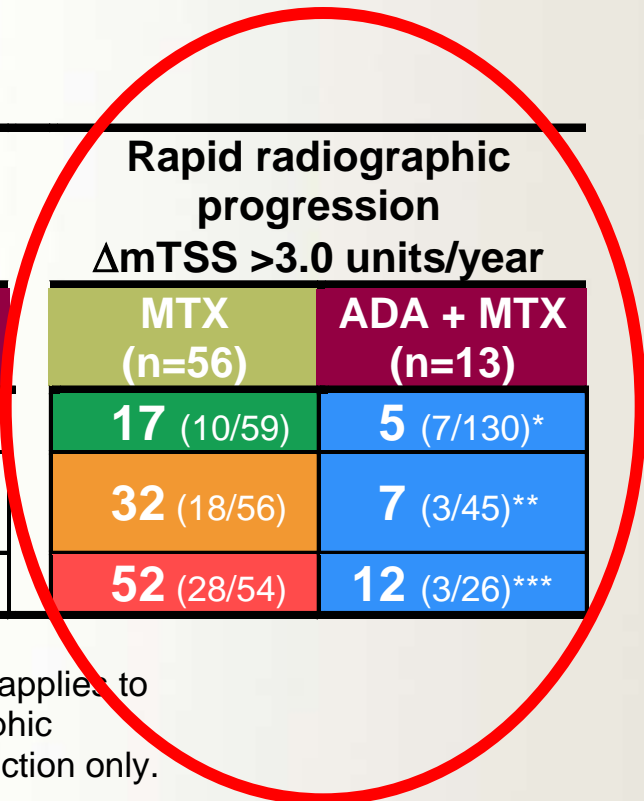
*Q1 was occupied by a single value (0.4); thus, Q1 and Q2 were combined.

CRP = C-reactive protein; mTSS = modified Total Sharp Score; MTX = methotrexate; ADA = adalimumab; OR = odds ratio; Q = quartile
 Haraoui B *et al.* ACR 2010. Abstract 1101.

Results: CRP Levels and Percentage of Subjects with Rapid Radiographic Progression



CRP level at 12 weeks	Radiographic progression Δ mTSS >0.5 units/year		Rapid radiographic progression Δ mTSS >3.0 units/year	
	MTX (n=109)	ADA + MTX (n=67)	MTX (n=56)	ADA + MTX (n=13)
<ULN, % (n/N)	42 (25/59)	29 (37/130)	17 (10/59)	5 (7/130)*
ULN to <3xULN, % (n/N)	75 (42/56)	42 (19/45)**	32 (18/56)	7 (3/45)**
\geq 3xULN, % (n/N)	78 (42/54)	42 (11/26)**	52 (28/54)	12 (3/26)***



Very low <15%	Low 15-30%	Intermediate 30-<50%	High \geq 50%
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Colour coding applies to rapid radiographic progression section only.

***, **, and * statistically significant at the $p=0.001$, $p=0.01$, and $p=0.05$ levels, respectively, for differences between treatment arms using Fisher's exact test.

CRP = C-reactive protein; mTSS = modified Total Sharp Score; MTX = methotrexate;

ADA = adalimumab; ULN = upper limit of normal

Haraoui B *et al.* ACR 2010. Abstract 1101.

Conclusions

- A combination of baseline characteristics can identify
 - Patients with RA who will rapidly progress on methotrexate monotherapy
- Use of the matrix model can help to identify patients at high risk who need intensive therapy
- Clinical response and biologic markers at 3 months can also help in the decision making

Questions?

