



# Gender differences in effectiveness of treatment in rheumatic diseases

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# What is arthritis?

- Joint inflammation

Acute Gonarthrosis (Right Knee) in a Patient with Peripheral Spondyloarthritis



ASAS

- ≠ osteoarthritis: degeneration of cartilage
  - Caused by aging
  - Due to trauma

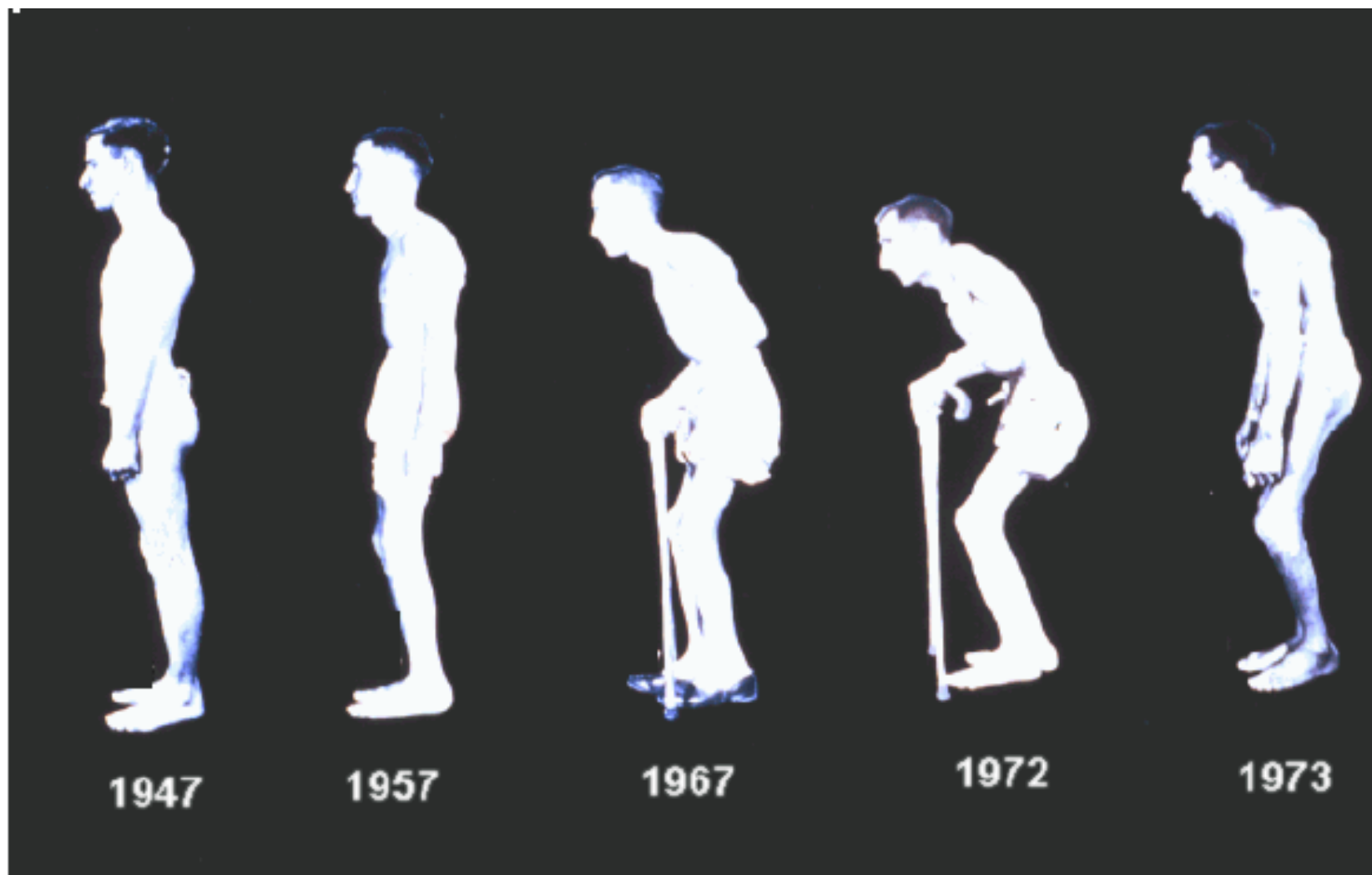
# Rheumatic diseases



- **Rheumatoïd arthritis (RA): F>M**
  - Hands, feet, all joints
- **Psoriatic Arthritis (PsA): F=M**
  - Knees, hands, feet
  - Spine
- **Axial Spondyloarthritis (AS, “ziekte van Bechterew”):**  
M>F
  - Spine/pelvis



# Axial Spondylarthritis (SpA): it's a man's world?



# ASAS Classification Criteria for Axial Spondyloarthritis (SpA)

In patients with  $\geq 3$  months back pain and age at onset  $< 45$  years

**Sacroiliitis on imaging\***  
**plus**  
 **$\geq 1$  SpA feature**

**OR**

**HLA-B27**  
**plus**  
 **$\geq 2$  other SpA features**

**\*Sacroiliitis on imaging**

- active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- definite radiographic sacroiliitis according to the modified New York criteria

**SpA features:**

- inflammatory back pain
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's/colitis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

n=649 patients with back pain;

Overall

Sensitivity: 82.9%, Specificity: 84.4%

Imaging arm alone

Sensitivity: 66.2%, Specificity: 97.3%

Clinical arm alone

Sensitivity: 56.6%, Specificity: 83.3%



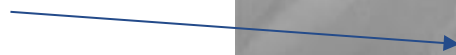
# Ankylosing Spondylitis (AS)

- Inflammatory back pain
- Family history SpA +
- sacroiliitis pelvis (X-ray, MRI, CT-scan)
- 0,9% western population
- males >females (3:1)
- Starts at young age 20-40 years, not acute
- HLA-B27 antigen > 95% +



## Lumbar spine in AS

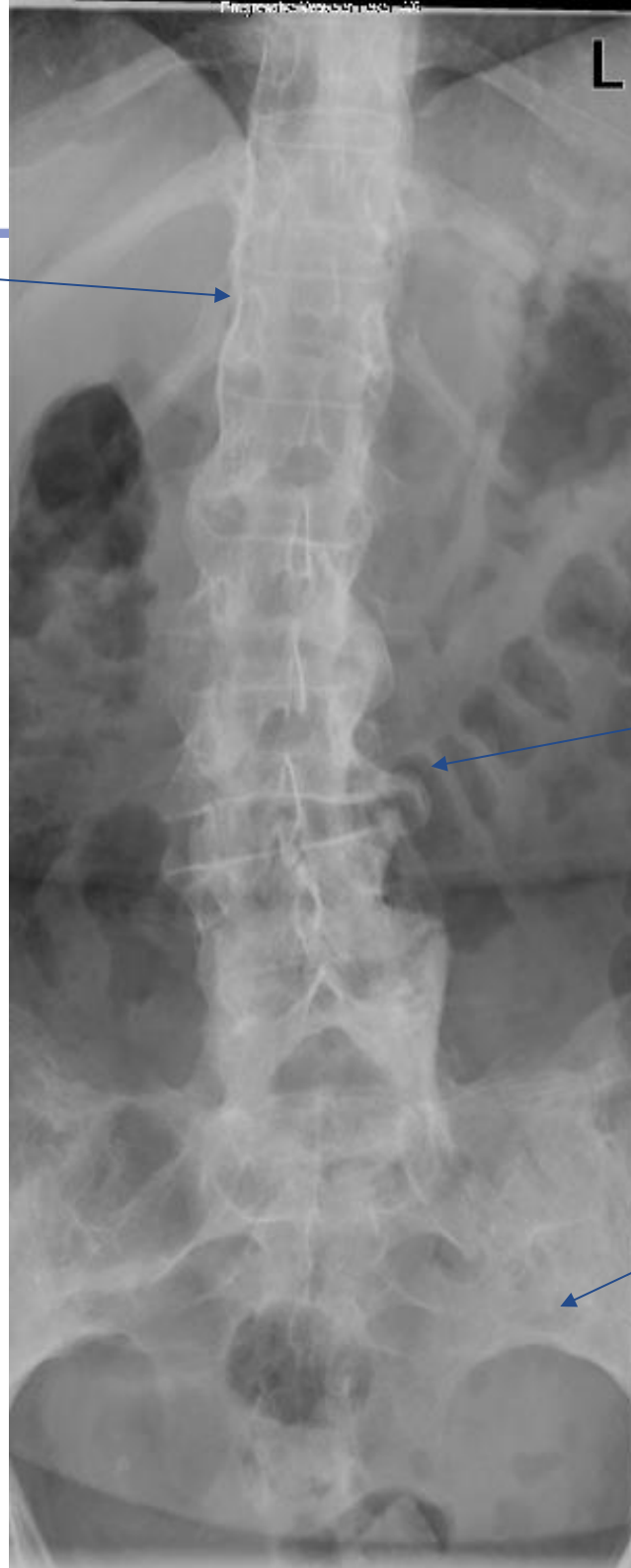
Bamboospine



syndesmofyt



sacroiliitis graad 4





# Treatment axial SpA: step 1

**NSAID's** : at least 3 months,  $\geq$  2 types of NSAID's

**Exercises/sports**

**Stop smoking:**

**Increased cardiovascular risk (1.6-1.9) in AS = Diabetes Mellitus**

Less radiographic progression



2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017 1-14; Ramiro et al.





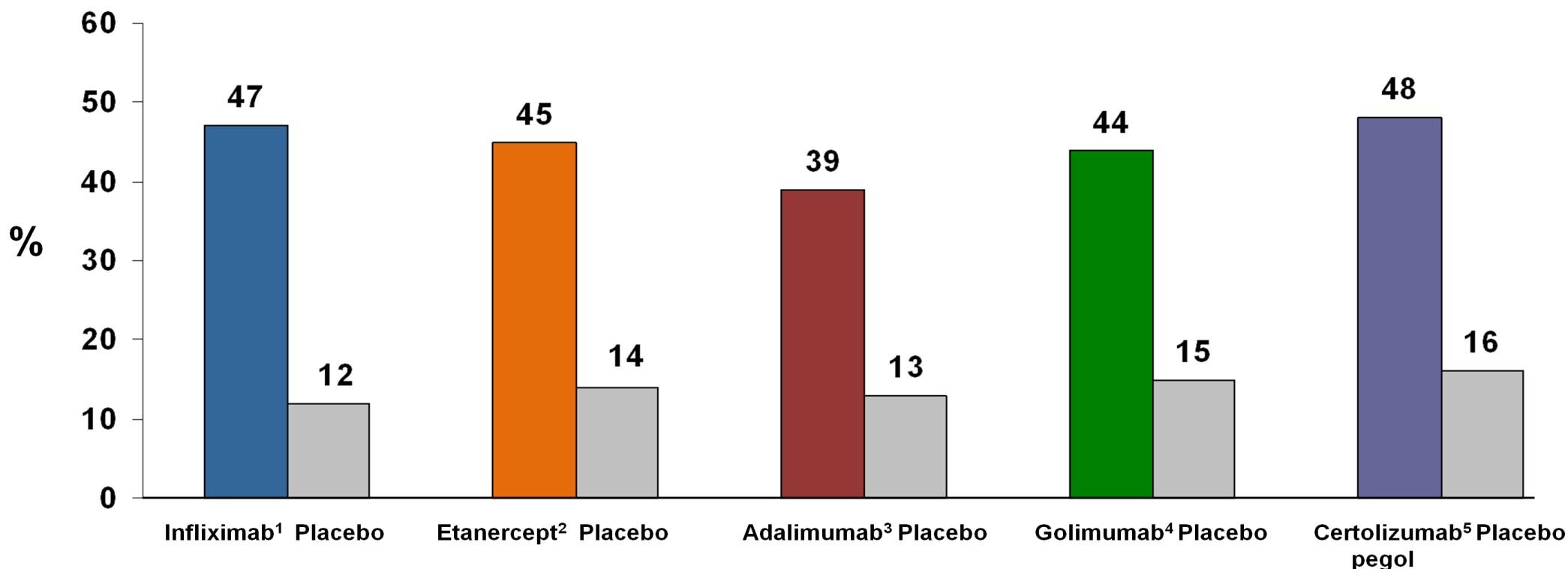
# DMARD's in Spondyloarthritis

DMARD's	Axial	Peripheral
<b>Sulfasalazine<sup>1</sup></b>	+/-	+
<b>Methotrexate<sup>2</sup></b>	-	+
<b>corticosteroids</b>		
intra-articular	-	+
high dose oral	-	+
intravenous	+/-	+
<b>Leflunomide<sup>3</sup></b>	-	+

<sup>1</sup>Braun J, Ann Rheum Dis 2006, <sup>2</sup> Haibel, H, ARD 2014, <sup>3</sup> van Denderen JC, Ann Rheum Dis. 2005:1761-4

# ASAS 40 Response after 24 Weeks of Treatment of AS Patients with TNF $\alpha$ Blocking Agents\*

\*Different studies, no head to head comparison


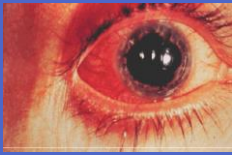





1. van der Heijde D et al. Arthritis Rheum 2005;52:582-91
2. Davis JC et al Ann Rheum Dis 2005;64:1557-62
3. van der Heijde D et al. Arthritis Rheum 2006;54:2136-46
4. Inman RD et al. Arthritis Rheum 2008;58:3402-12
5. Landewé et al. Ann Rheum Dis 2014;73:39-47



# Biologicals and extra-spinal manifestations in SpA



		Arthritis <small>Acute Gonarthritits (Right Knee) in a Patient with Peripheral Spondylarthritis</small> 	Uveitis 	Ulcer. colitis 	Crohn's dis. 	Psoriasis <small>Moderate to Severe Nail Changes in Patient with Psoriasis</small> 
Anti TNF alfa	infliximab	+	+	+	+	+
	adalimumab	+	+	+	+	+
	etanercept	+	+/-	-	-	+
	golimumab	+	+	+	?	+
	certolizumab	+	+	?	+	+

+ effective -not effective ? no data



# Drug development and gender?

- Male Mice



- Often tested in male Healthy volunteers



- No correction of dosages for body weight and gender (“normal” = male 70 kg)

- No gender correction in post marketing studies



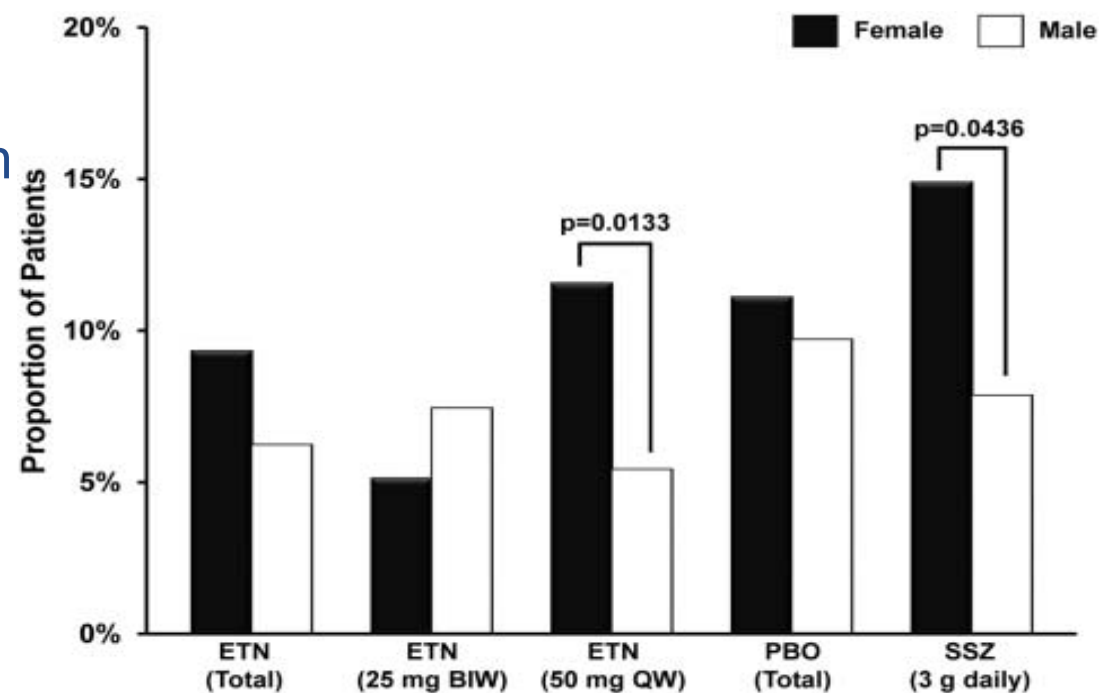
# Study discontinuations at week 12 by gender and treatment.



ETN, etanercept; PBO, placebo; SSZ, sulphasalazine

- data pooled from 4 clinical controlled trials
  - N= 1283 AS patients, treated with etanercept, sulfasalazine, or placebo
- Stratified by **gender**:discontinuation rates after 12 weeks



- **Males**: higher level of response
- **Females**: stop the drugs more often



# Gender and ASDAS (disease activity) improvement



**Table 2** Improvements in ankylosing spondylitis disease activity score (ASDAS) at week 12 of treatment

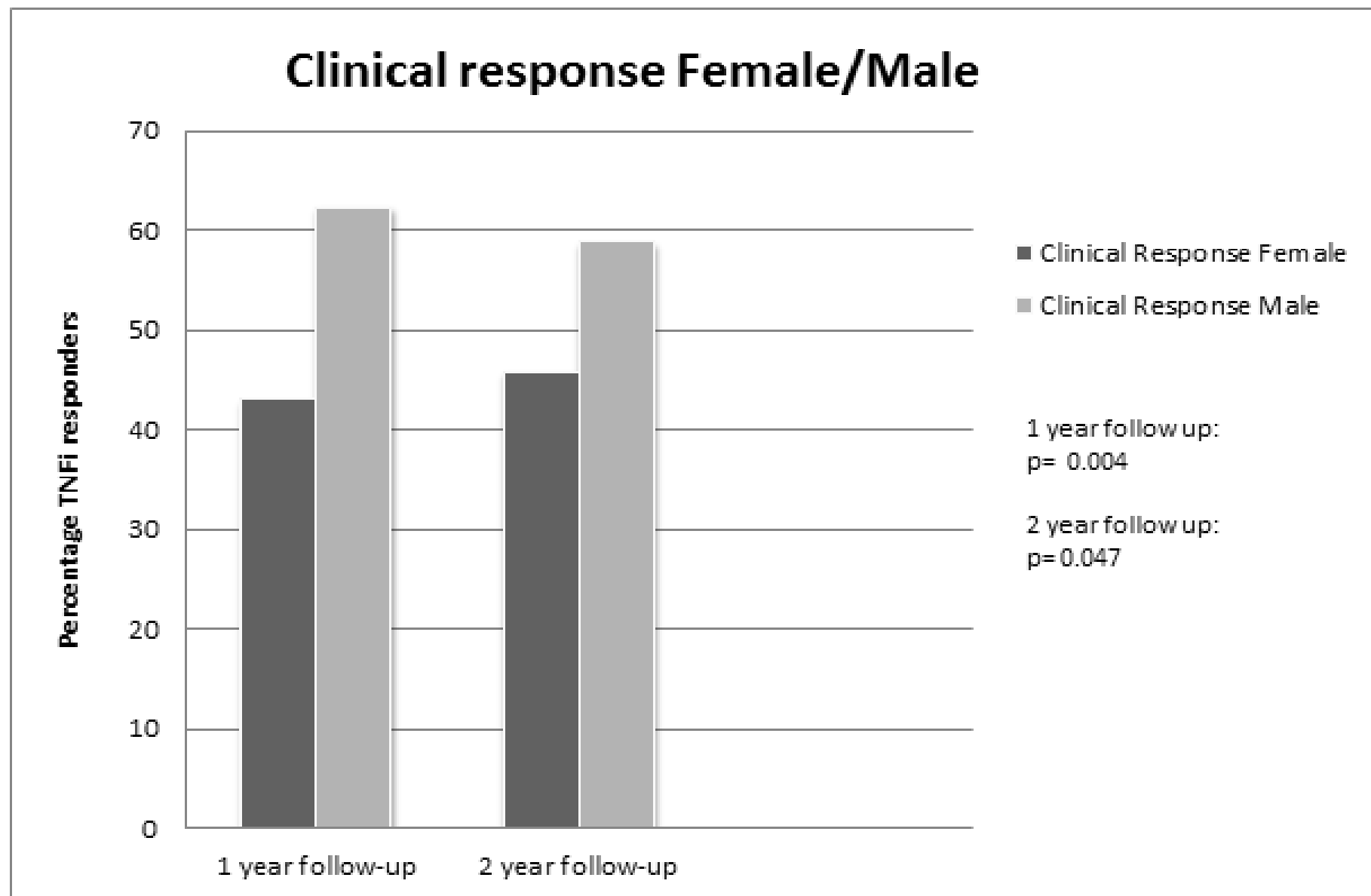
	Women (n=297)	Men (n=903)	Difference in proportions (95% CI)	Adjusted OR for women versus men (95% CI)†	p Value†
					
Patients with improvement in scores, n (%)					
ASDAS improvement $\geq 1.1$	137 (46.1)	530 (58.8)	-12.63* (-19.15 to -6.11)	0.55 (0.40 to 0.75)	0.0002
ASDAS improvement $\geq 2$	66 (22.2)	277 (30.7)	-8.49* (-14.09 to -2.88)	0.60 (0.42 to 0.87)	0.0068

\* $p < 0.05$  from Fisher's exact test.

†Logistic model of week 12 outcome, which contains baseline value, gender, study, treatment and geographic region as variables.

**Conclusion: significantly higher % of ASDAS improvement in males (59 vs 46%)**

# Women with AS have a worse response to TNF inhibitors compared with males



# Conclusions TNF blockers



- Are effective in Axial Spondyloarthritis

Women:

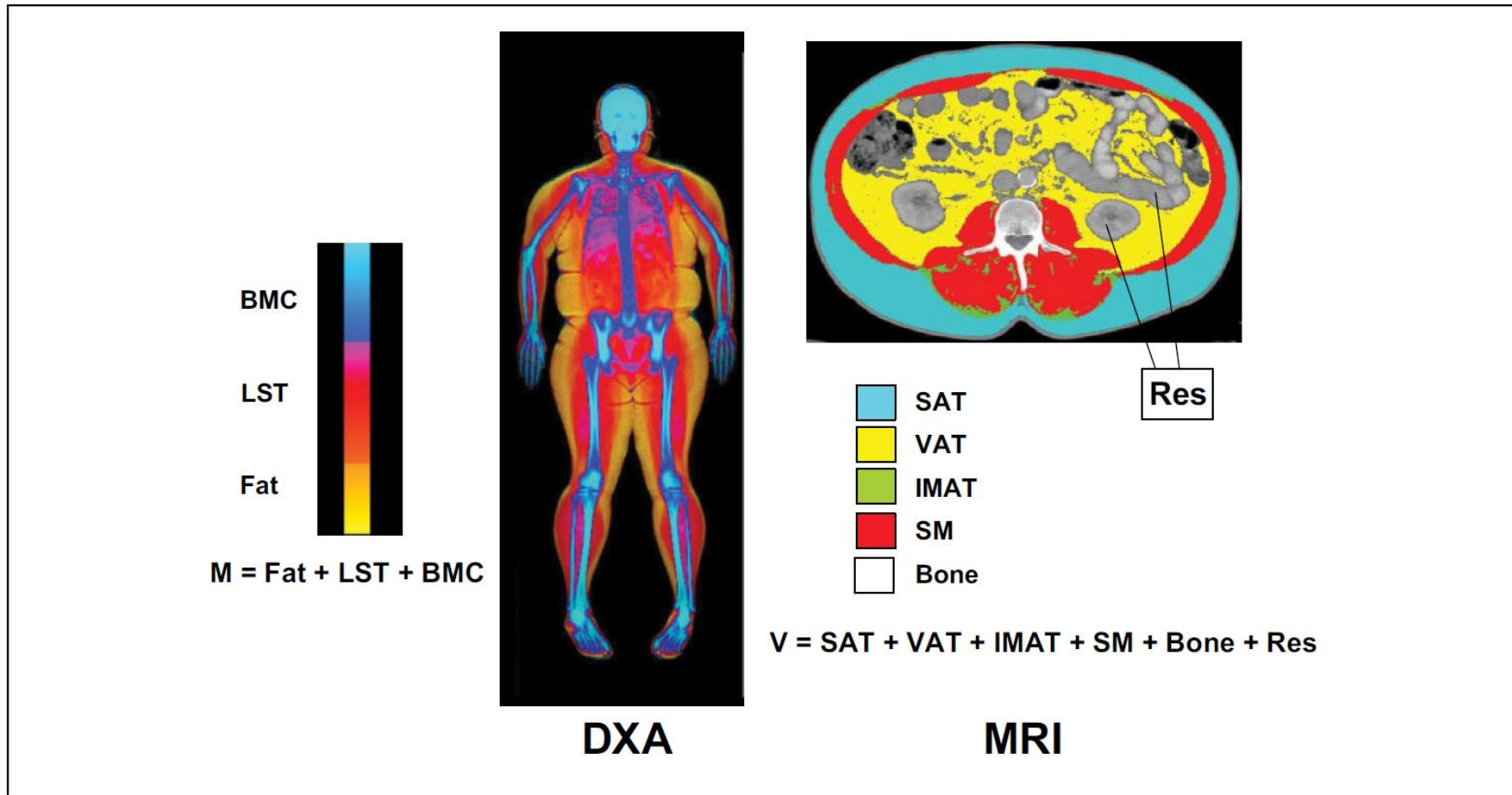
- have lower efficacy (ASDAS)
- and lower drug adherence

Compared to males

Due to differences in body composition?

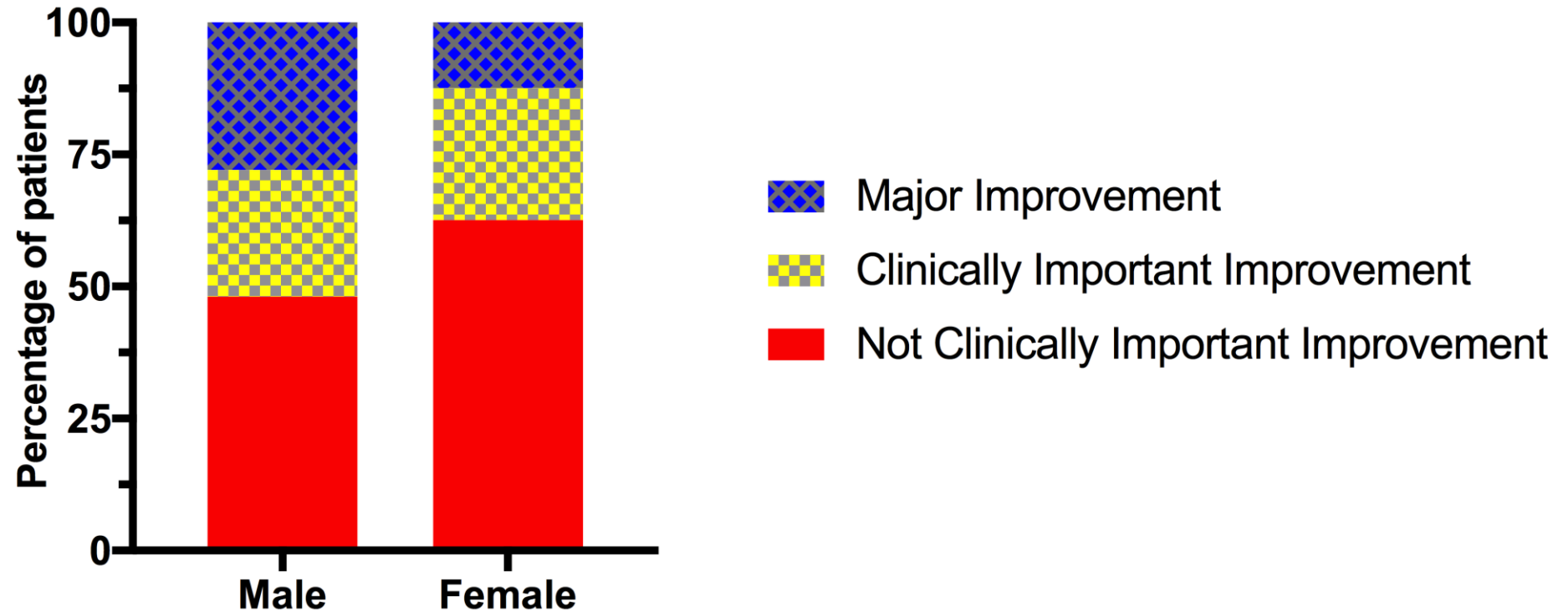


# Women: higher percentages of body fat than males



**Figure 2.** Selected body composition components measured by dual-energy x-ray absorptiometry (DXA; left) and magnetic resonance imaging (MRI; right). Body mass (M) and volume (V) represent the sum of these components for DXA and MRI, respectively. BMC, bone mineral content; IMAT, intermuscular adipose tissue; LST, lean soft tissue; Res, residual mass (organs and tissues remaining after subtracting skeletal muscle, bone, and adipose tissue volumes); SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue.

# Response to treatment with TNF blockers and body composition



52% **men** show important improvement and muscle mass ↑  
37.5% **women** „ „ and no change in muscle mass (=)

Conclusion : Higher fat percentage is associated with a lower response to TNF blockers

# Conclusions



- In axial SpA: women are:
  - Underdiagnosed
  - Show lower efficacy and lower drug adherence



Studies so far not powered to discover gender differences, only powered to measure drug response compared with placebo

Datasets stratified for gender show results that were previously overlooked

What about the gender differences in efficacy of other biologicals?

What about the gender differences in efficacy on other diseases?

- In Rheumatoid arthritis? Psoriatic arthritis?

Re-analyses of databases of pharmaceutical companies on gender are needed!