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Group for Research
and Assessment of Psoriasis and Psoriatic Arthritis

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# Our Expectation in SpA Management.

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# Disclosures

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# Axial SpA and PsA: Resetting Our Expectation in Axial SpA and PsA Management

- Axial Spondyloarthritis
  1. the updated ASAS-EULAR recommendations
  2. Radiographic versus non radiographic axial spondyloarthritis
  3. Gender differences in ax-SpA
  4. Treatment target: Treat to Target in ax-SpA
  5. Tapering: worth the effort?
  6. Difficult to treat SpA

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# ASAS-EULAR recommendations for the managment of axial spondyloarthritis (2022 update)

| | **Recommendations** | | **LoA(0-10)** | |
|---|---|---|---|---|
| | | Levels of evidence/grade of recommendation | Mean (SD) | % with score ≥8 |
| 9 | TNFi, IL-17i† or JAKi‡ should be considered in patients with persistently high disease activity despite conventional treatments current practice is to start a TNFi or IL-17i†. | 1a/A | 9.2 (1.2) | 94 |
| 10 | If there is a history of recurrent uveitis or active IBD, preference should be given to a monoclonal antibody against TNF In patients with significant psoriasis, an IL-17i† may be preferred. | 2b/B (uveitis, IBD)<br>1a/B (psoriasis) | 9.1 (1.8) | 97 |
| 11 | Absence of response to treatment should prompt re-evaluation of the diagnosis and consideration of the presence of comorbidities. | 5/D | 9.5 (0.8) | 97 |
| 12 | Following a first b/tsDMARD failure, switching to another bDMARD (TNFi or IL-17i†) or a JAKi‡ should be considered. | 2b/B (TNFi after TNFi failure)<br>1b/A (IL-17i after TNFi failure)<br>5/D (all other switches) | 9.3 (1.1) | 88 |

Sofia Ramiro et al. Ann Rheum Dis 2023;82:19-34

9,12: updated recommendations, 10&11 new recommendations

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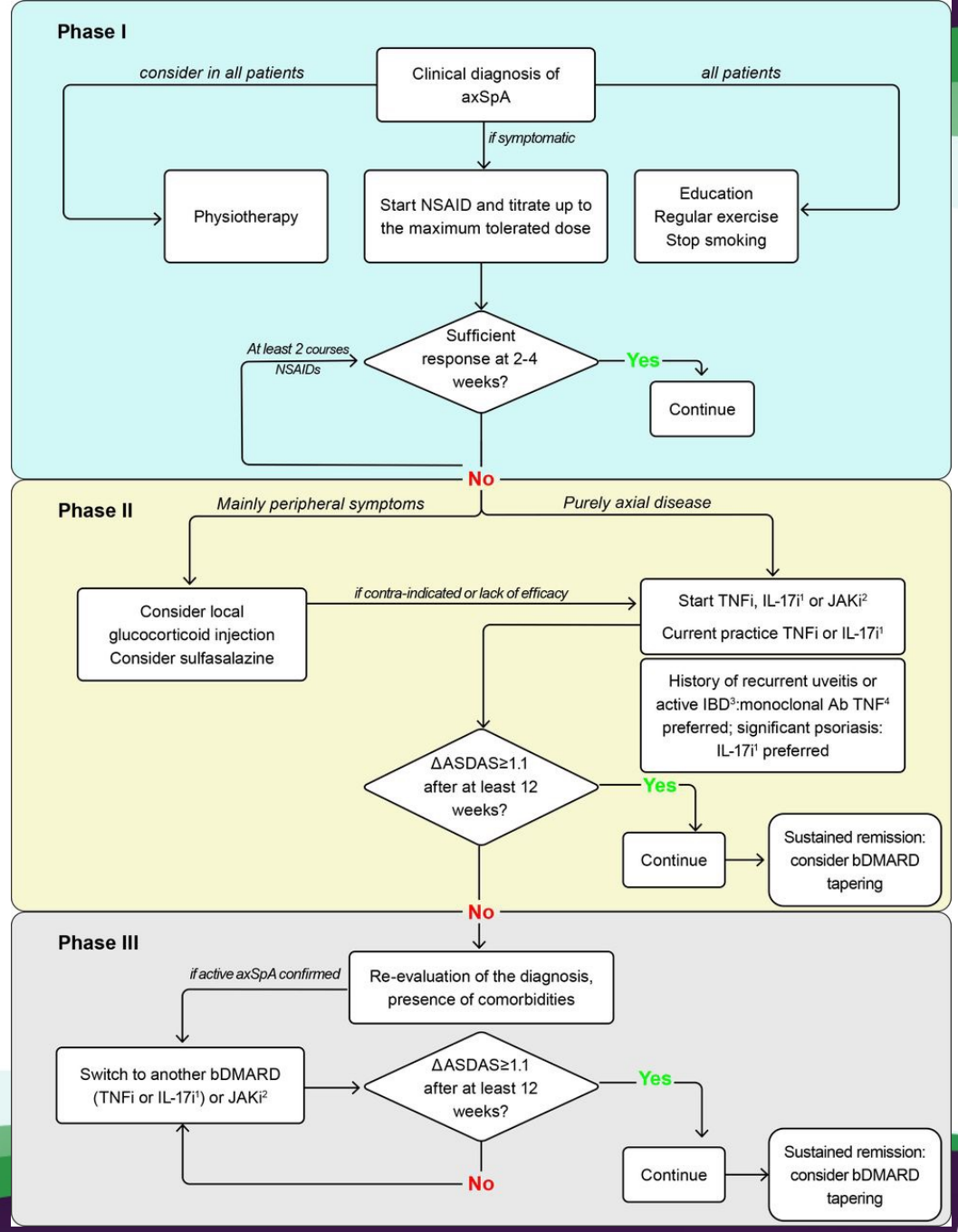
# Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis (axSpA).




Sofia Ramiro et al. Ann Rheum Dis 2023;82:19-34

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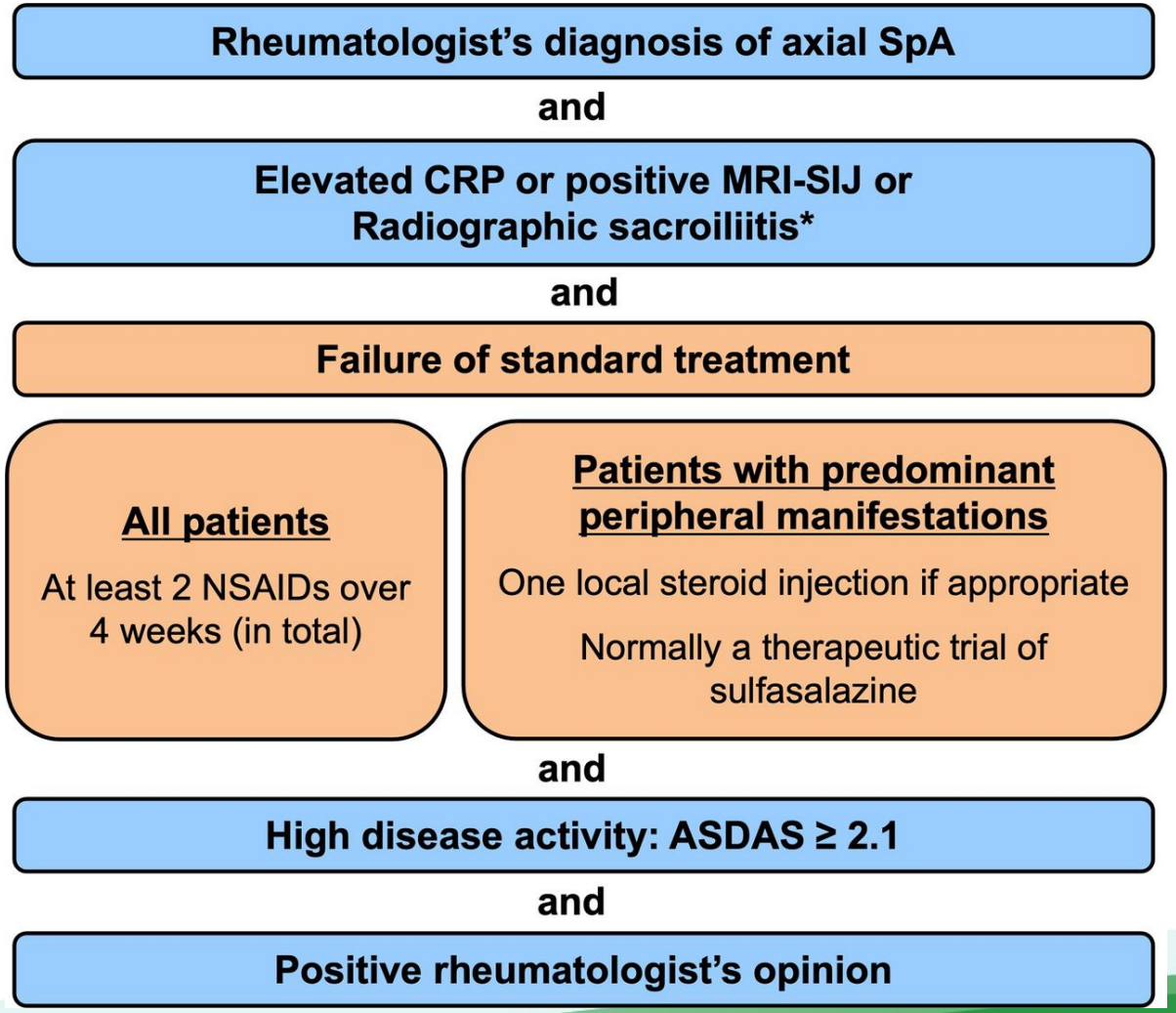


# ASAS-EULAR recommendations for the treatment of patients with axial SpA with b/tsDMARDs.

Sofia Ramiro et al. Ann Rheum Dis 2023;82:19-34

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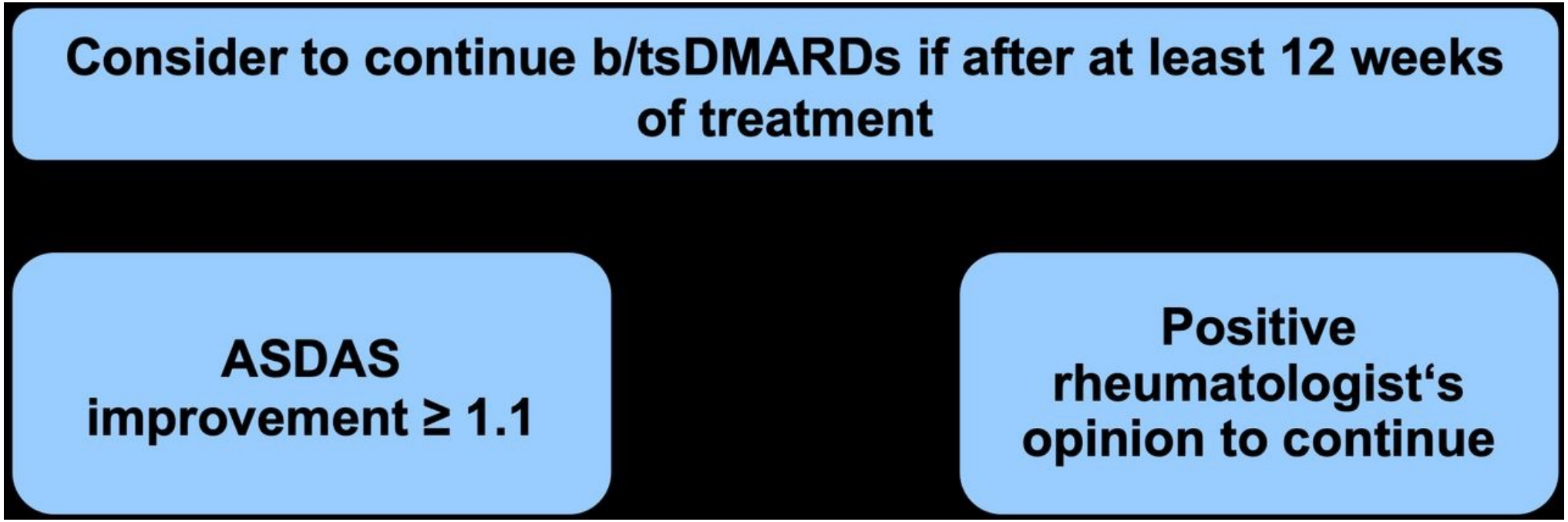
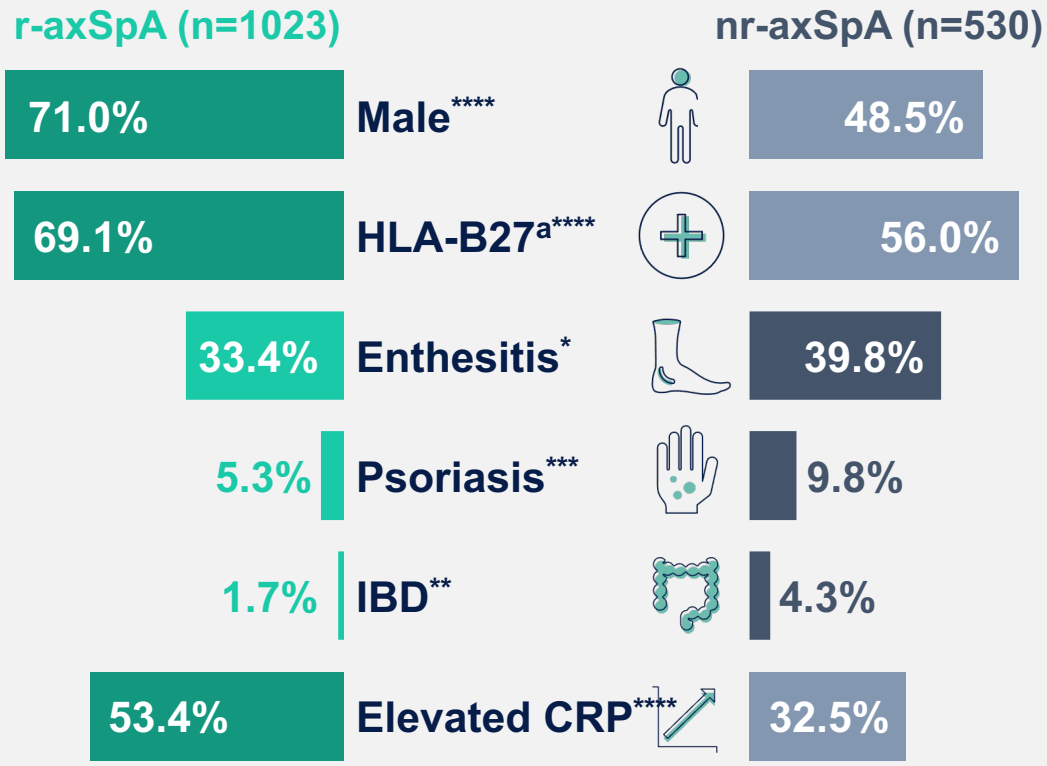
# ASAS-EULAR recommendations for the continuation of b/tsDMARDs.




Sofia Ramiro et al. Ann Rheum Dis 2023;82:19-34

# There are some differences between SpA features for patients with r-axSpA vs. nr-axSpA

## Significantly Different




## Similar between r-axSpA and nr-axSpA

- Age
- Inflammatory back pain
- Peripheral arthritis
- Dactylitis
- Uveitis
- Good response to NSAIDs
- Family history

P value for r-axSpA vs nr-axSpA: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 aBased on patients with HLA-B27 assessed
axSpA, axial spondyloarthritis; CRP, c-reactive protein; HLA-B27, human leukocyte antigen-B27; IBD, inflammatory bowel disease; nr-axSpA, non-radiographic axSpA; r-axSpA, radiographic axSpA

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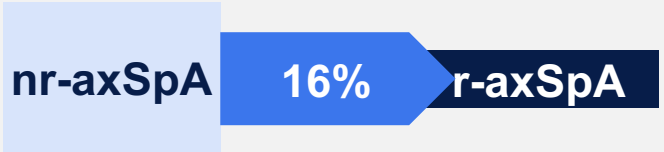
Adapted from: 1. Poddubnyy D, et al. Rheumatology (Oxford) 2021;doi: 10.1093/rheumatology/keab901.

# Predictors of radiographic progression from nr-axSpA to r-axSpA over 5 years: the PROOF study

## Patients who Progressed

- Among 246 patients with nr-axSpA who had ≥1 follow-up SIJ radiograph: **16%** (n=40) progressed from nr-axSpA to r-axSpA
- Mean time to progression: **2.4 years** (0.9-5.1 years)




## Predictors of Radiographic Progression

- Male gender
- Fulfilment of the imaging arm (i.e., the presence of sacroiliitis on MRI)
- HLA-B27 positivity
- Good response to NSAIDs

ASAS, Assessment of SpondyloArthritis international Society; HLA-B27, human leukocyte antigen B27; nr-axSpA, nonradiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis; SIJ, sacroiliac joint

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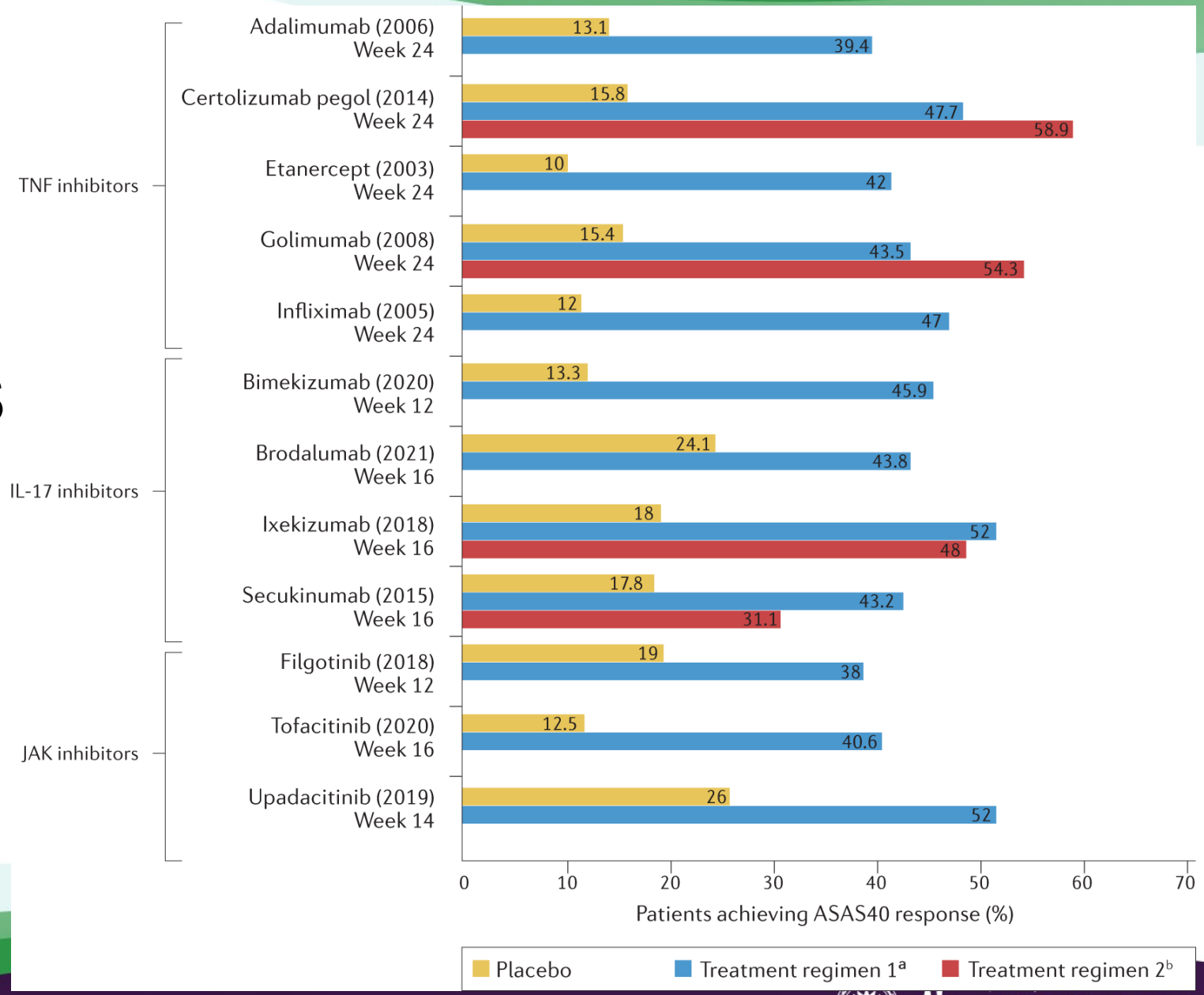
Adapted from Poddubnyy D, et al. Poster presented at EULAR 2022; 1-4Jun22, Kopenhagen (Poster 0P0149)

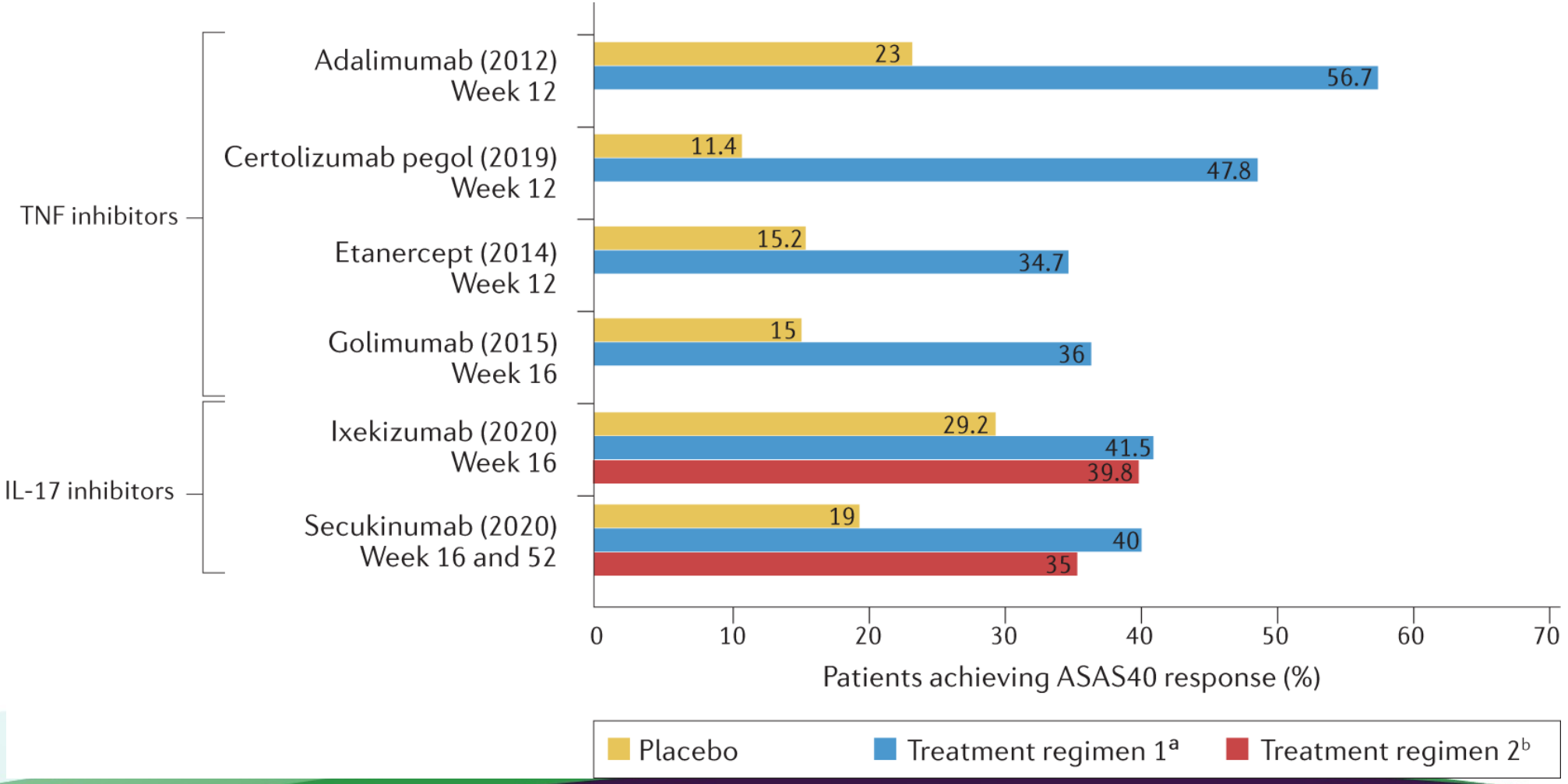
# ASAS40 responses from clinical trials in AS






Danve, A., Deodhar, A. Treatment of axial spondyloarthritis: an update. *Nat Rev Rheumatol* **18**, 205–216 (2022).

# ASAS40 responses from clinical trials in nr-axSpA




Danve, A., Deodhar, A. Treatment of axial spondyloarthritis: an update. *Nat Rev Rheumatol* **18**, 205–216 (2022).

# There are sex differences in the prevalence of axSpA subtypes

nr-axSpA has a **similar prevalence** between males and females

r-axSpA is **more prevalent** in males compared with females

**nr-axSpA (n=530)**

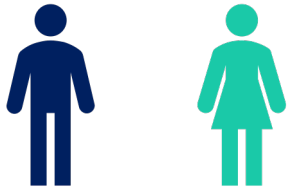
51.5%
n=273

48.5%
n=257

**r-axSpA* (n=1023)**

29.0%
n=297

71.0%
n=726



Male

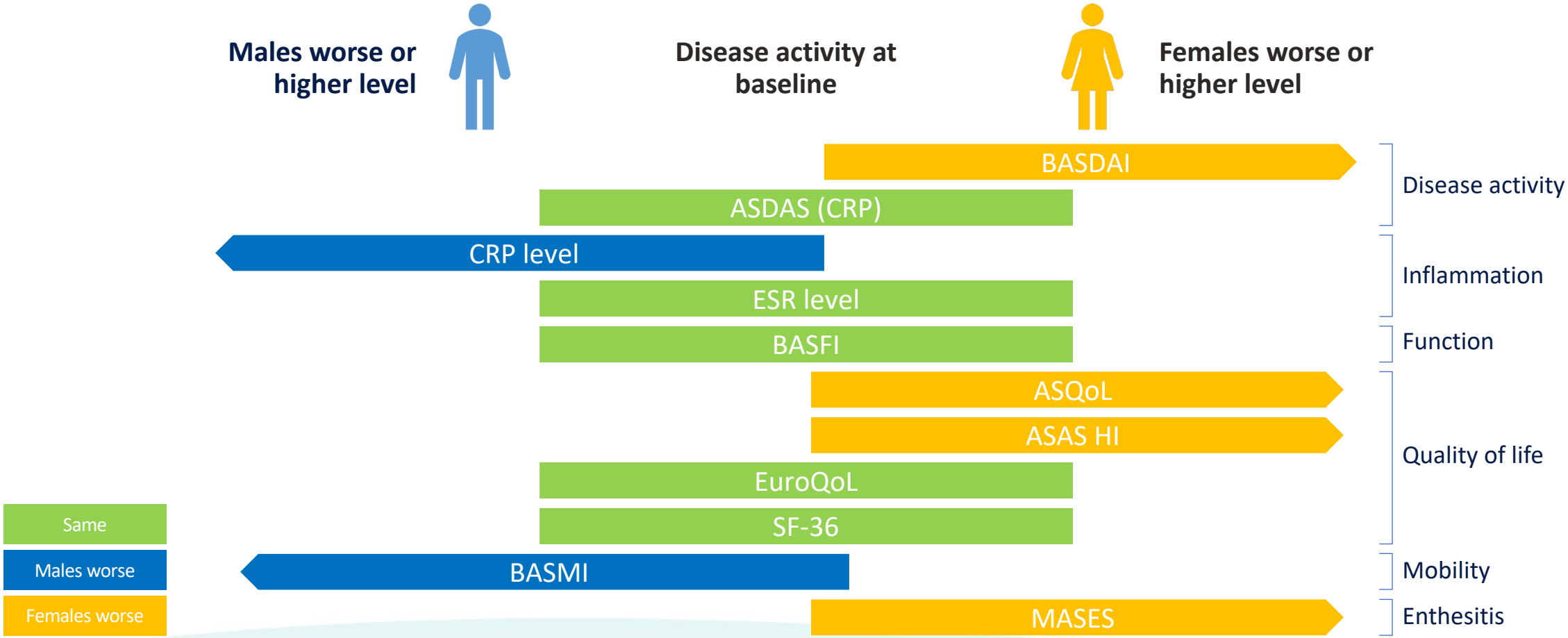


Female

*p<0.001 for r-axSpA vs nr-axSpA

axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis

# Males and females show differences in disease activity, function, and physical measures




Adapted from: Rusman T et al. Rheumatology 2020;59:iv38–iv46.

# Gender effects in TNF-inhibitor treatment response

| Study | AS or axSpA | Study design | Participants (male:female) | Treatment response (male vs female) | TNF-naive population | Follow-up period |
|---|---|---|---|---|---|---|
| Rusman et al., 2021 | AS | Prospective cohort study | 235:121 | ASDAS: 64% vs 47% (RR 1.4, 95% CI 1.1–1.9)[a] | Yes | 6 months |
| Sieper et al., 2019 | nr-axSpA | Open-label prospective study | 295:301 | ASDAS partial remission: OR 2.4, 95% CI 1.6–3.6[a] | Yes | 12 weeks |
| Hebeisen et al., 2018 | AS | Prospective cohort study | 294:146 | ASAS20: OR 0.34, 95% CI 0.16–0.71[a]; ASDAS <1.3: OR 0.10, 95% CI 0.03–0.31[a] (inverse female/male) | Yes | 1 year |
| van der Horst-Bruinsma et al., 2013 | AS | Pooled data clinical controlled trials | 957:326 | ASDAS: 89.4% vs 68.4%[a] | Yes | 12 weeks |
| Arends et al., 2011 | AS | Prospective longitudinal observational cohort | 152:68 | ASAS20 and ASAS40: greater response in men than in women[a] | Yes | ASAS20: 3 months and 6 months; ASAS40: 6 months |
| Glintborg et al., 2010 | AS | Observational cohort | 364:239 | Change in BASDAI: 27 vs 22 | Yes | 6 months |

[a] prospective studies

Adapted from Stovall, R. *Nat Rev Rheumatol* **18**, 657–669 (2022)

# Men shows greater adherence to anti TNF R/

| Study | AS or axSpA | Study design | Participants (♂/♀) | Treatment adherence[a] (♂/♀) | Study time period |
|---|---|---|---|---|---|
| Hebeisen et al., 2018 | AS | Prospective cohort study | 294/146 | **5.2** vs 2.9 years[b] | 12 years |
| Al Arashi et al., 2018 | AS | Prospective cohort | 205/75 | **91.6** vs 34.4 months[b] | Mean 6.3 years |
| Iannone et al., 2017 | SpA | Prospective observational cohort | 72/75 | **23.0** vs 19.6 months[b] | 2 years |
| Rusman et al., 2018 | AS | Prospective cohort | 74/48 | **44.9** vs 33.4 months[b] | Mean 4.8 years |
| Flouri et al., 2018 | AS | Prospective observational cohort | 446/115 | HR for R/ discontinuation in ♂/♀: **0.73** (95% CI 0.51–1.04) | 10 years |
| Arends et al., 2011 | AS | Prospective longitudinal observational cohort | 152/68 | HR for R/ discontinuation in ♂/♀: **0.41** (95% CI 0.25–0.66)[b] | 6 months |
| Kristensen et al., 2010 | AS | Prospective observational cohort | 182/61 | HR for R/ discontinuation in ♂/♀: **0.36** (95% CI 0.19–0.68)[b] | 2 years |
| Glintborg et al., 2010 | AS | Observational cohort | 364/239 | HR for R/ discontinuation in ♀/♂: **1.46** (95% CI 1.07–2.00)[b] | 5 years |
| Yahya et al., 2018 | axSpA | Retrospective review of routinely recorded clinical data | 386/115 | No gender effects observed | 1, 5 and 10 years |

Adapted from Stovall, R. *Nat Rev Rheumatol* **18**, 657–669 (2022)

# Estimated retention rate during the 1st year of secukinumab treatment according to diagnosis, gender, and BMI.

| Diagnosis | Retention % | 95%CI | Gender | Retention % | 95%CI | BMI | Retention % | 95% CI |
|---|---|---|---|---|---|---|---|---|
| AxSpA | 82% | (74%; 89%) | Female | 95% | (93%; 97%) | <30 kg/m$^2$ | 93% | (89%; 96%) |
| | | | | | | ≥30 kg/m$^2$ | 99% | (98%; 100%) |
| | | | Male | 77% | (68%; 86%) | <30 kg/m$^2$ | 80% | (72%; 89%) |
| | | | | | | ≥30 kg/m$^2$ | 64% | (50%; 78%) |
| PsA | 78% | (70%; 87%) | Female | 66% | (54%; 79%) | <30 kg/m$^2$ | 57% | (42%; 73%) |
| | | | | | | ≥30 kg/m$^2$ | 91% | (87%; 95%) |
| | | | Male | 89% | (84%; 93%) | <30 kg/m$^2$ | 91% | (88%; 96%) |
| | | | | | | ≥30 kg/m$^2$ | 81% | (73%; 89%) |

Patients (*n* = 138) diagnosed with AxSpA by ASAS (*n* = 77) or PsA by CASPAR) (*n* = 61)

Garcia-Dorta A, Front Med 2022

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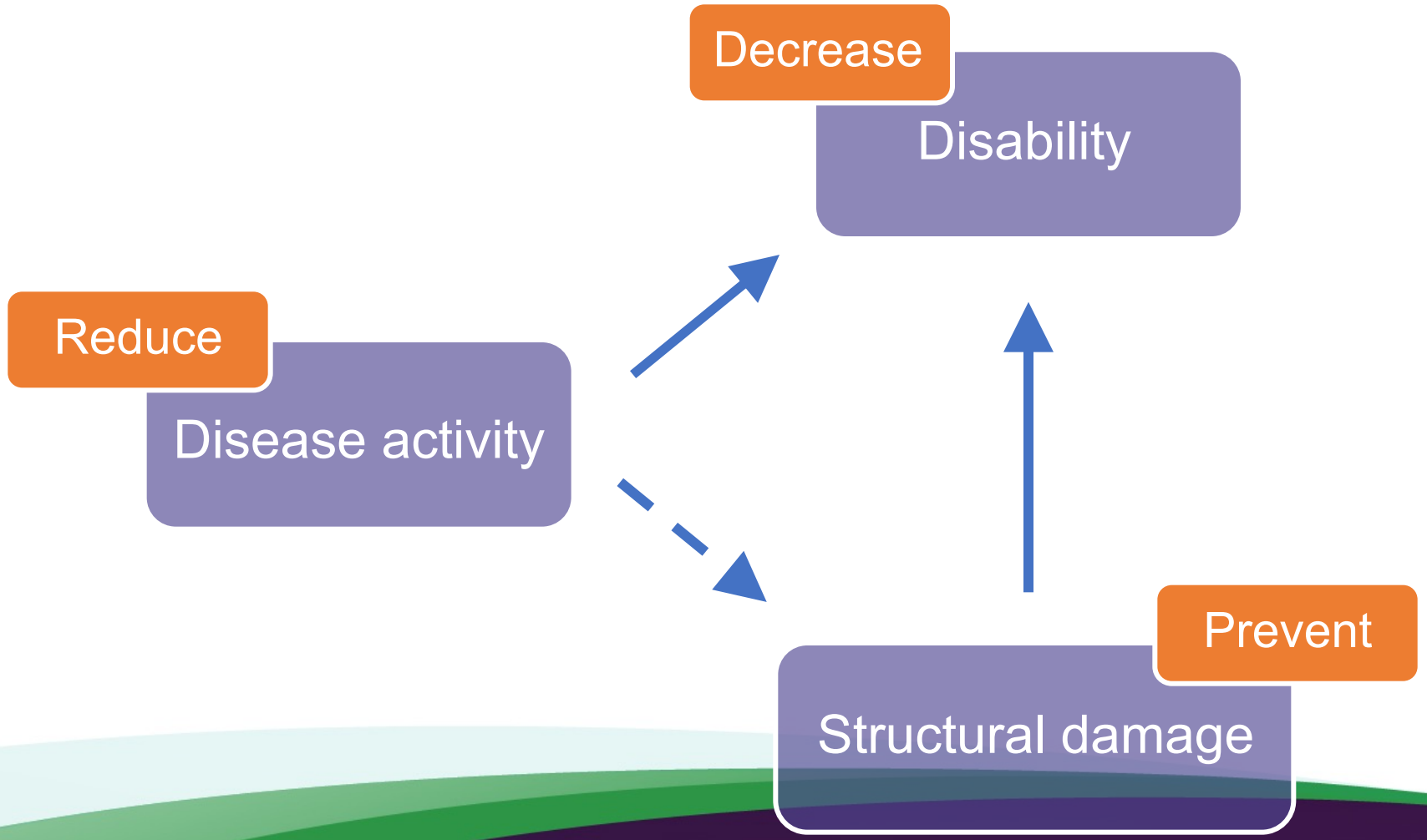
# Treatment goals in chronic arthritis



# Potential treat to target strategies in axial spondyloarthritis

| Risk | Disease | | Structural damage | | | Cardiovascular diseases | | | |
|---|---|---|---|---|---|---|---|---|---|
| Reversible Predisposing factor | Smoking | Smoking | Biological inflammation | Disease activity | Smoking | NSAID intake | Obesity | Hypertension | Diabetes |
| Outcome measure | Smoking status | Smoking Status | CRP* | ASDAS | Smoking Status | - dose and frequency | Body Mass index | Blood pressure | Hb A1C |
| Threshold (TARGET) | Cessation | Cessation | <ULN* | <1.3 or <2.1 | Cessation | Cessation? | Normal range | <130mHg systolic <80 mHg diastolic | <7% |
| Time to Reach the target | <6 months | <6 months | <6 months | <6 months | <6 months | <6 months | <12 months | <3 months | <3 months |

Dougados M, J Autoimm 2020



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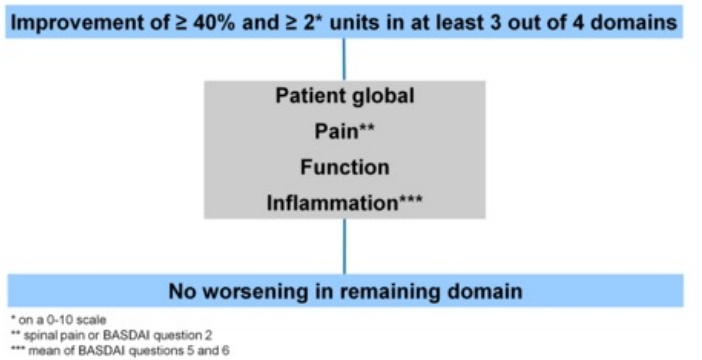
# What currently defines HCPs treatment & management of AxSpA (AS & nr-AxSpA)?

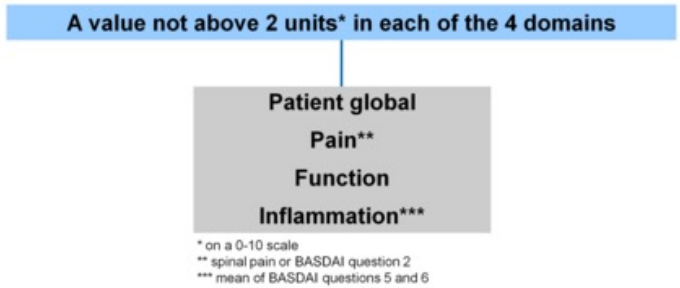
✓*Do you employ treat-to-target strategies in your practice? Which target do you aim for?*

## ASAS 40 Improvement Criteria



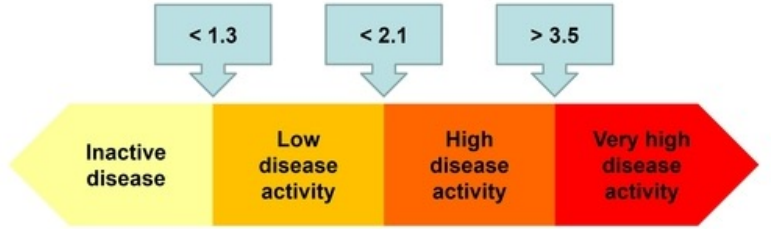

*Adapted from* Brandt J et al. Ann Rheum Dis 2004;63:1438-44 (with permission)

## ASAS Partial Remission Criteria




Anderson JJ et al. Arthritis Rheum 2001;44:1876-86

## ASDAS Cut-Offs for Disease Activity States

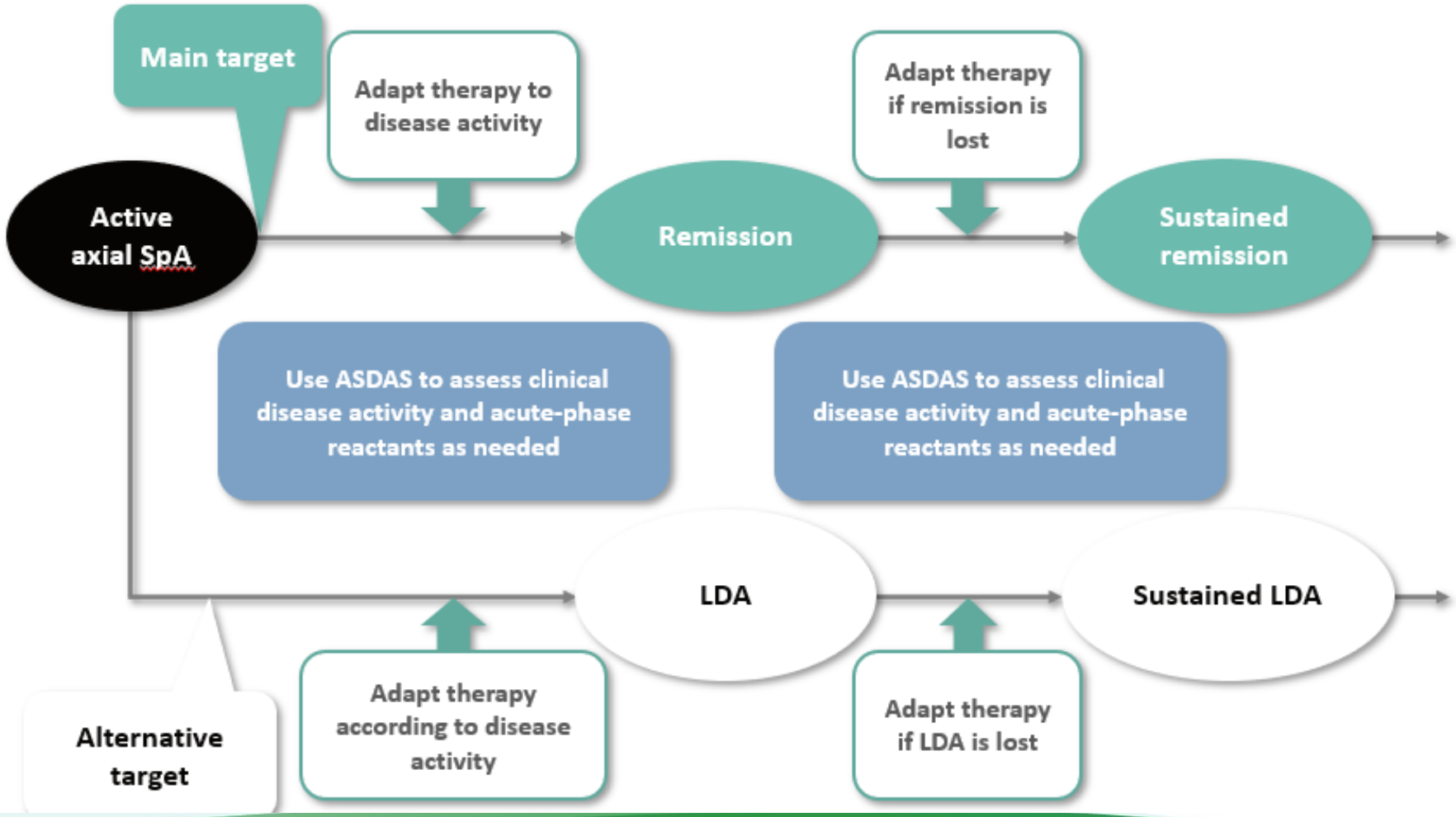



Machado P et al. Ann Rheum Dis 2011;70:47-53 (with permission)
Machado P et al. Ann Rheum Dis 2018;77:1539-40 (with permission)

- Spinal pain (back, neck, hips)
- Duration of morning stiffness
- Peripheral joint pain/swelling
- Patient global assessment of disease activity
- hs-CRP

axSpA, axial spondyloarthritis; AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis

# Treat-to-target algorithm for axial spondyloarthritis




ASDAS, Ankylosing Spondylitis Disease Activity Score; LDA, low disease activity; SpA, spondyloarthritis

Smolen JS et al. Ann Rheum Dis 2018;77:3-17

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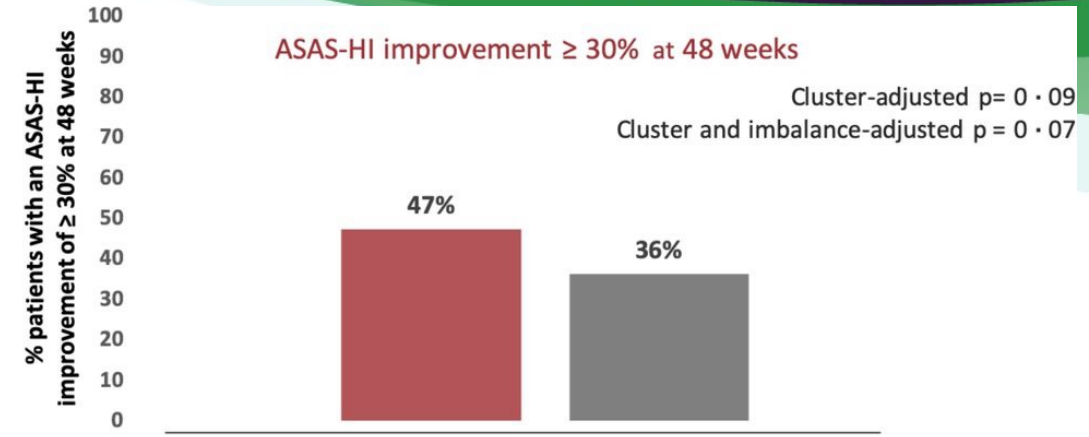
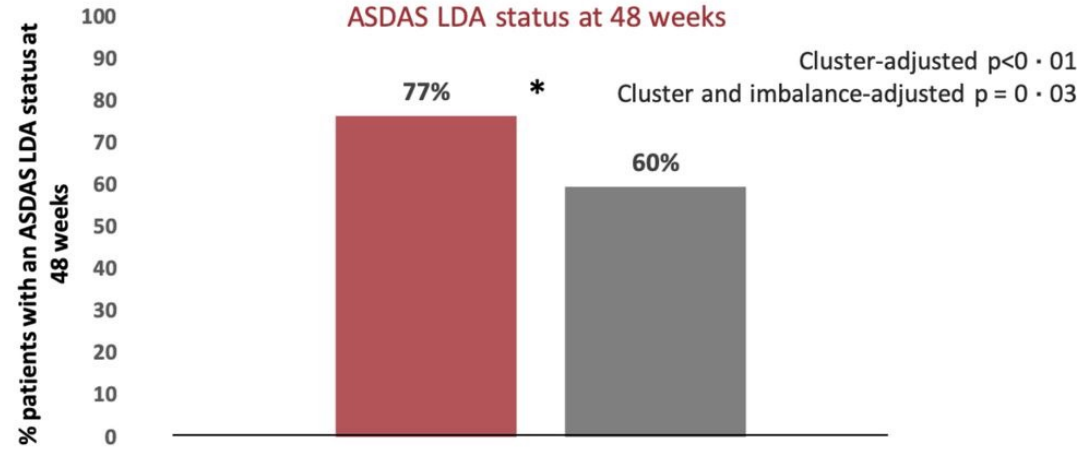
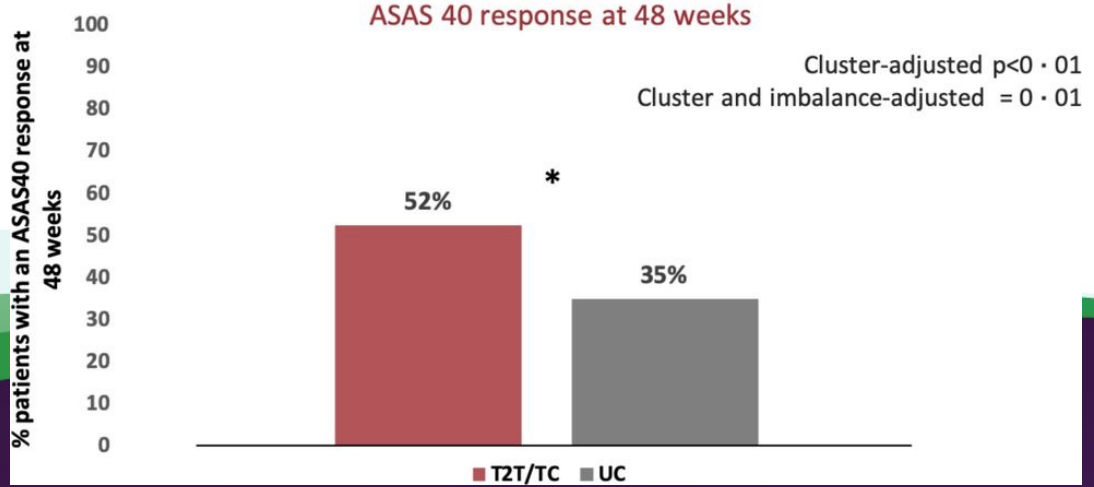
# TICOSPA:

## ASAS-HI improvement ≥30%, ASDAS LDA status and ASAS40 response estimated at 48 weeks.




Anna Molto et al. Ann Rheum Dis 2021;80:1436-1444

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- Treat-to-target in axial spondyloarthritis — what about physical function and activity

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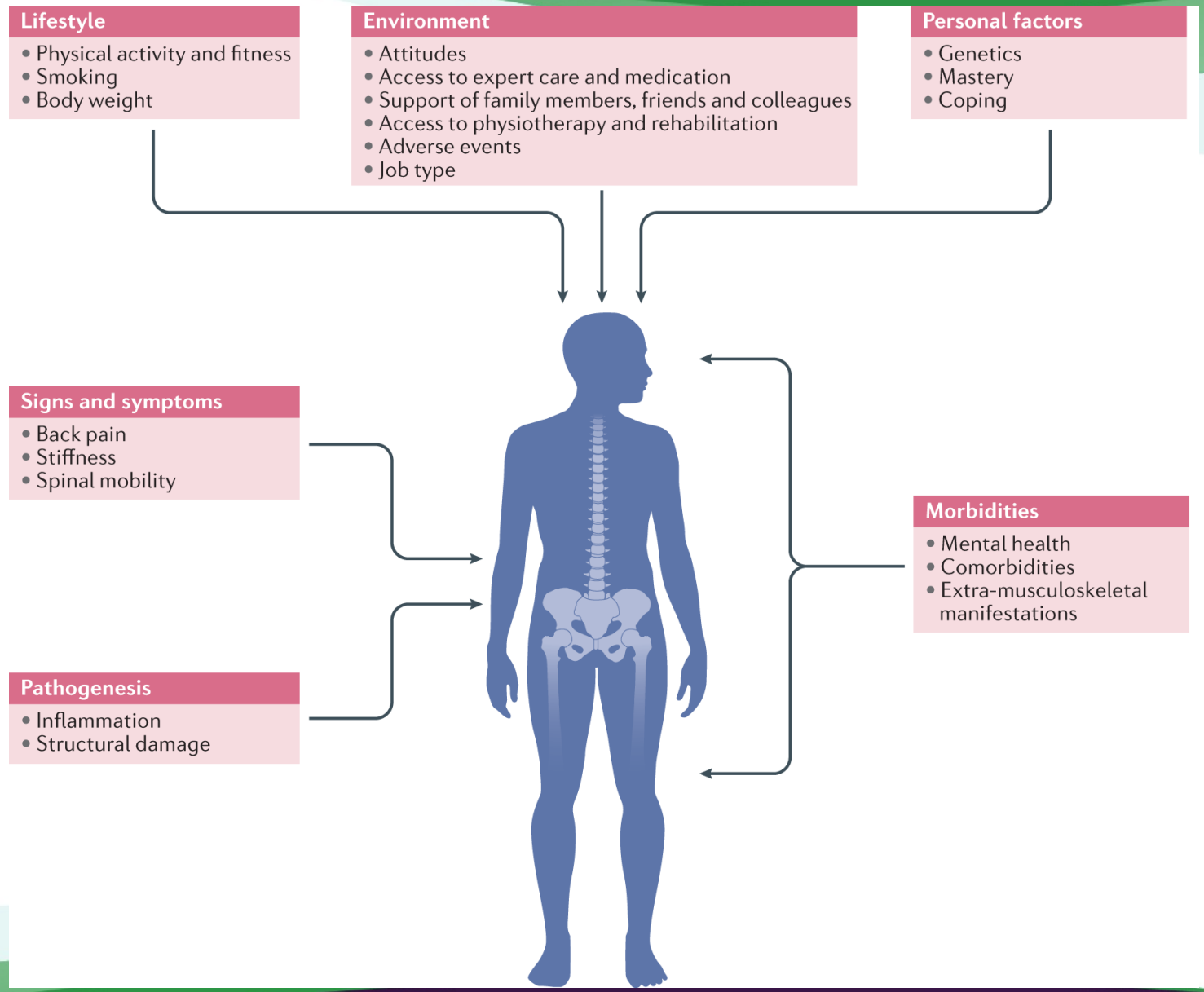
# Factors that affect physical function in axial spondyloarthritis.




Braun, J. *Nat Rev Rheumatol* **17**, 565–576 (2021)

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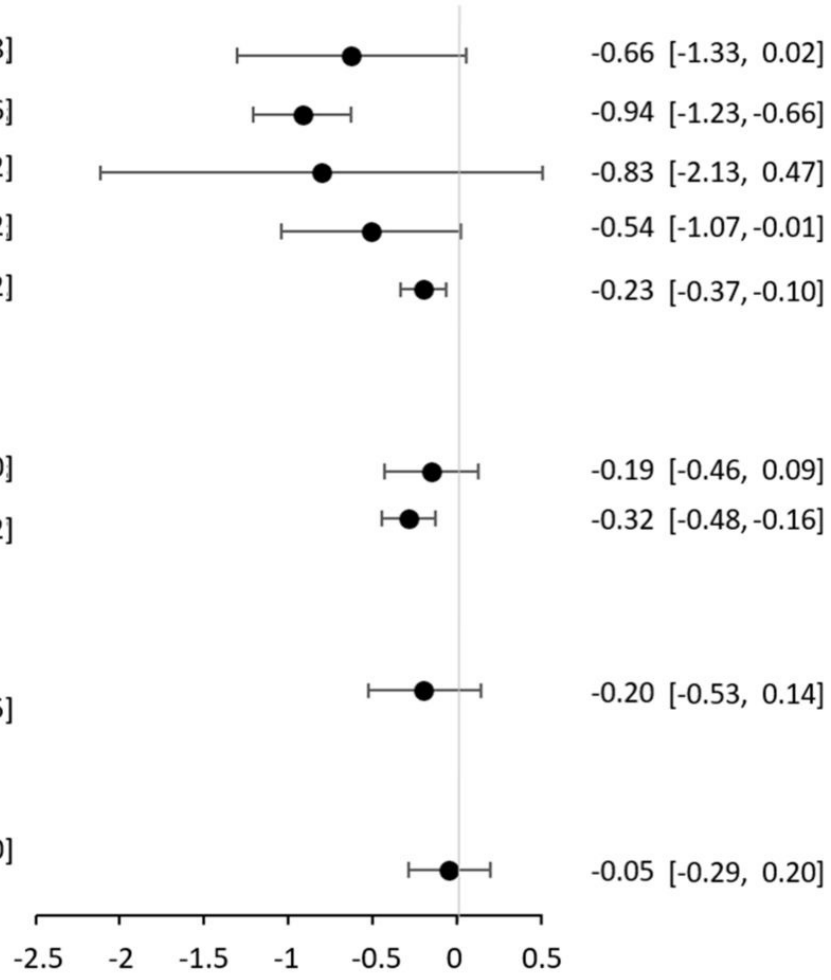
| Interventions | Included studies | SMD, 95% CI |
|---|---|---|
| **Physical activity or exercise** | | |
| Systemic Sclerosis | [48, 78] | -0.66 [-1.33, 0.02] |
| Spondyloarthritis | [39, 47, 53, 64, 69, 71, 77, 106] | -0.94 [-1.23, -0.66] |
| Sjogren's Syndrome | [50, 62] | -0.83 [-2.13, 0.47] |
| Systemic Lupus Erythematosus | [44, 56, 60, 66, 72] | -0.54 [-1.07, -0.01] |
| Rheumatoid Arthritis | [40, 42, 45, 51, 52, 54, 57, 59, 60, 63, 75, 102] | -0.23 [-0.37, -0.10] |
| **Psychoeducational interventions** | | |
| Systemic Lupus Erythematosus | [80, 86, 90] | -0.19 [-0.46, 0.09] |
| Rheumatoid Arthritis | [81, 83-85, 87-89, 91-97, 99-102] | -0.32 [-0.48, -0.16] |
| **Physical Activity or Exercise + Psychoeducational** | | |
| Rheumatoid Arthritis | [104, 105] | -0.20 [-0.53, 0.14] |
| **Follow-up model in consultations** | | |
| Rheumatoid Arthritis | [108, 110] | -0.05 [-0.29, 0.20] |




Eduardo José Ferreira Santos et al. RMD Open 2023;9:e003350

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# Difficult to treat?
# Difficult to manage?

# Difficult to treat RA patients are well defined, but can the concept apply beyond RA?

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## EULAR definition of D2T RA

- Treatment according to EULAR guidelines and failure of ≥2 b/tsDMARDs (with different mechanisms of action), after failure of csDMARD

- Suggestive evidence of disease activity/progression, defined as ≥1 of;
  - At least MDA (DAS28-ESR>3.2 or CDAI >10)
  - Signs (including biology and imaging) and/or symptoms suggesting active disease (joint or otherwise)
  - Inability to reduce systemic steroid therapy (<7.5 mg/day prednisone equivalent)
  - Rapid radiographic progression
  - Controlled disease, but with persistent RA symptoms causing reduced quality of life

- Management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient

**All 3 criteria must be present**

## Caveats for applying to axSpA

- Only 3 classes of Tx (in RA there are 5)
- Could be defined as ASDAS-CRP >1.3 or possibly BASDAI >4/10
- CRP within normal limits is frequent in axSpA
- MRI primarily used at diagnostic stage
- Can allow for consideration of extra-rheumatological manifestations (e.g., uveitis, PsO and IBD)
- Systemic corticosteroids not indicated in axSpA
- Could be adapted to "unable to reduce/discontinue NSAIDs"
- Not applicable to axSpA
- Could be applied to axSpA and might include persistent pain
- Applicable but subjective

NO

axSpA, axial spondyloarthritis; ASDAS-CRP, ankylosing spondylitis disease activity score- C-reactive protein; BASDAI, bath ankylosing spondylitis disease activity index; b/tsDMARDs, biologic/targeted synthetic DMARDs; CDAI, clinical disease activity index; CRP, C-reactive protein; csDMARD, conventional synthetic DMARD; DAS28-ESR, disease activity score assessing 28 joints using erythrocyte sedimentation rate; D2T, difficult to treat; DMARD, disease-modifying antirheumatic drug; EULAR, European Alliance of Associations for Rheumatology; IBD, inflammatory bowel disease; MDA, moderate disease activity; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; PsO, psoriasis; RA, rheumatoid arthritis.

Adapted from:
Wendling D, et al. Joint Bone Spine. 2023;90:105511.

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Abbreviations: D2T-axSpA: difficult-to-treat axial spondyloarthritis.

# Factors associated with D2T axial SpA

| Characteristic | Bivariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| **Female sex** | 1.93 (1.75 to 2.14) | <0.001 | **1.79 (1.61 to 1.99)** | **<0.001** |
| **Peripheral symptoms** | 2.02 (1.84 to 2.23) | <0.001 | **1.84 (1.67 to 2.04)** | **<0.001** |
| **Psoriasis** | 1.61 (1.46 to 1.77) | <0.001 | **1.33 (1.20 to 1.47)** | **<0.001** |
| Inflammatory bowel disease | 1.05 (0.91 to 1.22) | 0.50 | – | – |
| Severe uveitis | 1.43 (0.78 to 2.65) | 0.24 | – | – |
| Diabetes | 1.14 (0.95 to 1.38) | 0.17 | – | – |
| Dyslipidaemia | 1.13 (0.98 to 1.30) | 0.11 | – | – |
| **Hypertension** | 1.24 (1.11 to 1.38) | <0.001 | **1.20 (1.06 to 1.36)** | **<0.001** |
| Severe smoking | 1.47 (1.22 to 1.78) | <0.001 | – | – |
| Severe obesity | 1.99 (1.52 to 2.59) | <0.001 | – | – |
| **Depression** | 2.19 (1.98 to 2.43) | <0.001 | **2.09 (1.87 to 2.33)** | **<0.001** |

Adapted from Fakih O, *RMD Open* 2023

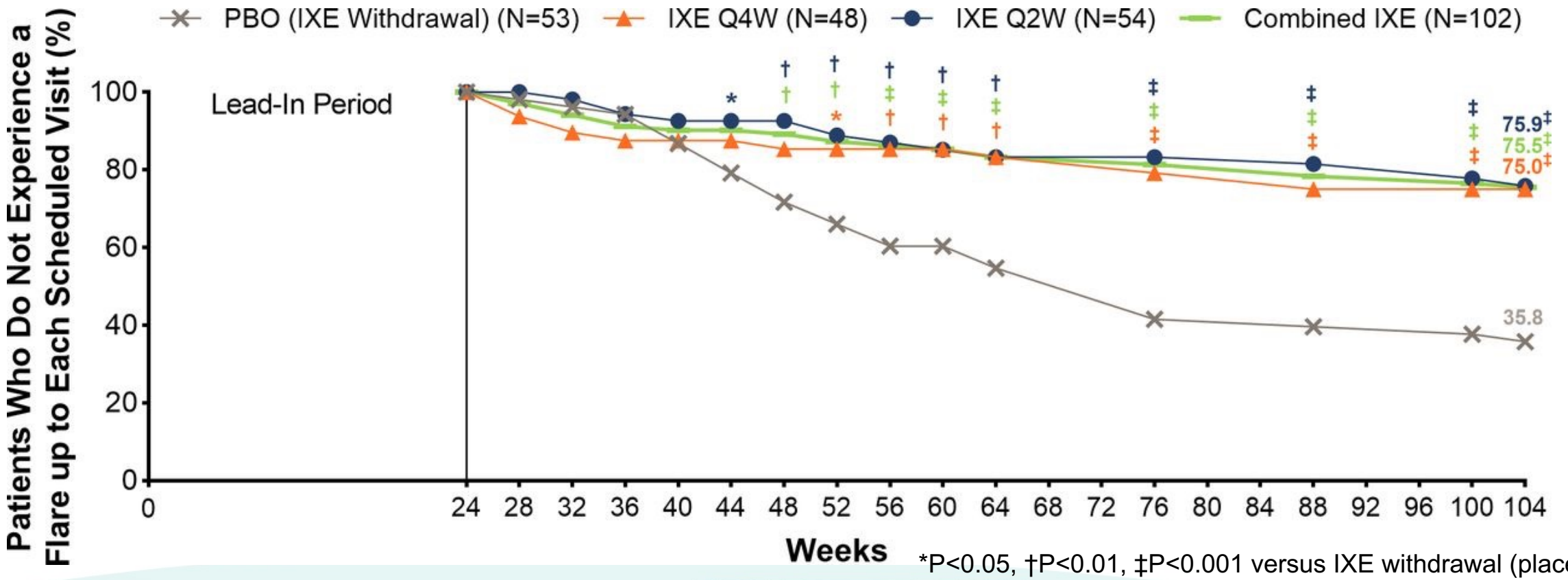
# Approach to patients with axSpA, after multiple pharmacological therapy failures

- Is the diagnosis correct?
- Is the disease still active (consider C-reactive protein level, erythrocyte sedimentation rate, sacroiliac joint or spine MRI)
- What am I treating? Inflammation or structural damage?
- Is the patient compliant with treatment?
- Is fibromyalgia, depression or sleep disturbance causing the symptoms?
- Have I set realistic expectations with the patient (and myself)?
- Should I try sacroiliac joint corticosteroid injections, nerve ablation (pain clinic), intravenous pamidronate (a bisphosphonate), maximize NSAIDs, or conventional synthetic DMARDs?

# Tapering – withdrawal in axSPA

| Study | Study design; number of patients | Strategy | Results |
|---|---|---|---|
| ABILITY-3 | Multi-centre, randomized, double-blind; 305 | Adalimumab withdrawal. Patients who achieved inactive disease (ASDAS <1.3) with open-label adalimumab treatment were randomly assigned to treatment with adalimumab or placebo for 40 weeks | 70% of patients continuing adalimumab did not experience flare, compared with **47% of those who received placebo** |
| RE-EMBARK | Multi-centre, open-label, phase IV trial; 119 (in the withdrawal phase) | Etanercept withdrawal. Patients who achieved inactive disease after treatment with etanercept (50 mg subcutaneously weekly) for 24 weeks discontinued treatment | **75% of patients experienced flare within 40 weeks;** 50% experienced flare within 16 weeks. The probability of experiencing ≥1 flare after etanercept withdrawal increased from 22% at week 4 to 67% at week 40 |
| C-OPTIMISE | Two-part multi-centre phase IIIb, open-label; 313 randomized at week 48 | CZP dose reduction or withdrawal study. Patients with ASDAS <1.3 after open-label treatment with CZP for 48 weeks[a] were randomized to CZP 200 mg subcutaneously every 2 weeks (CZPQ2W), CZP 200 mg subcutaneously every 4 weeks (CZPQ4W) or placebo for a further 48 weeks | 83.7% of patients in the CZPQ2W group and 79.0% in the CZPQ4W group remained **flare free** through weeks 48–96, compared with **20.2% of patients in the placebo group** |
| COAST-Y | Double-blind RCT long-term extension; 155 | IXE withdrawal<br>Patients completing COAST-V, COAST-W and COAST-X trials (with ASDAS <1.3 at week 24[b]) were enrolled and treated with open label ixekizumab. Patients were randomized to IXE 80 mg Q4W, 80 mg Q2W or placebo for the next 40 weeks | 83% of patients are flare free compared with **54% of those in the placebo group** |

# Proportion (%) of patients who remained flare-free through 104 weeks.




*P<0.05, †P<0.01, ‡P<0.001 versus IXE withdrawal (placebo).

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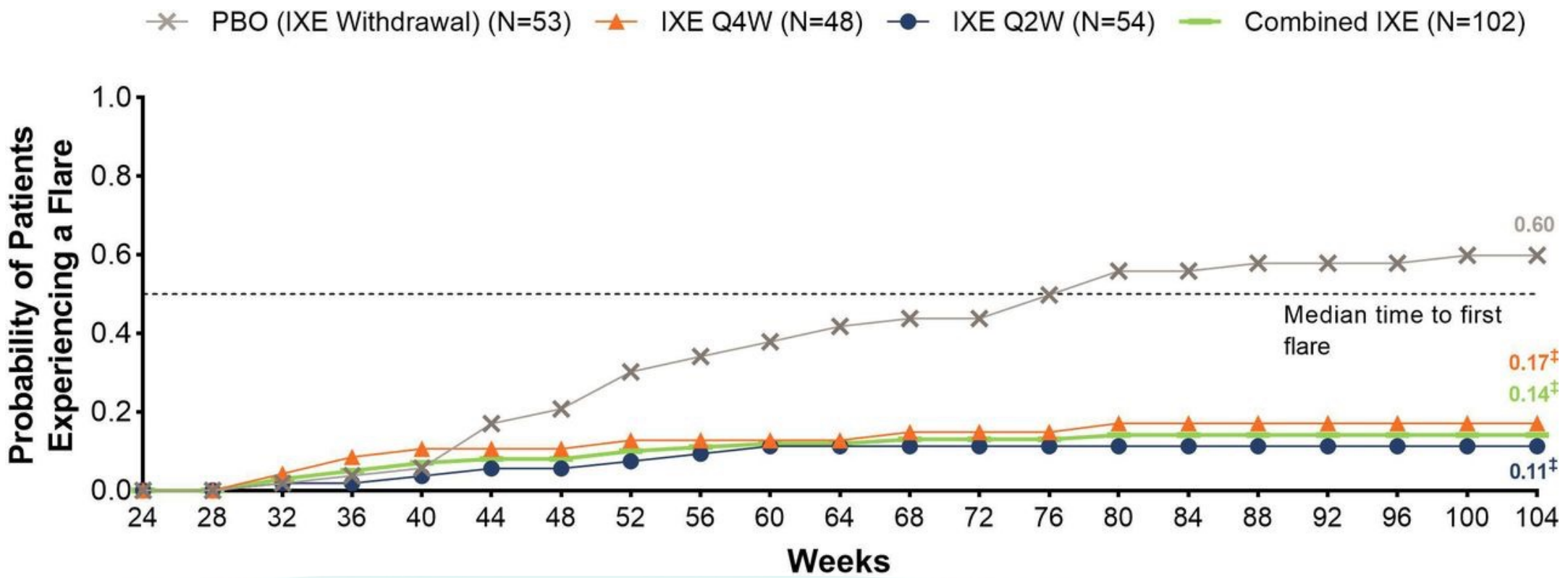
# estimate of time to first flare (weeks) through 104 weeks in placebo (IXE withdrawal) vs continuous IXE




. ‡P<0.001 versus placebo (IXE withdrawal).

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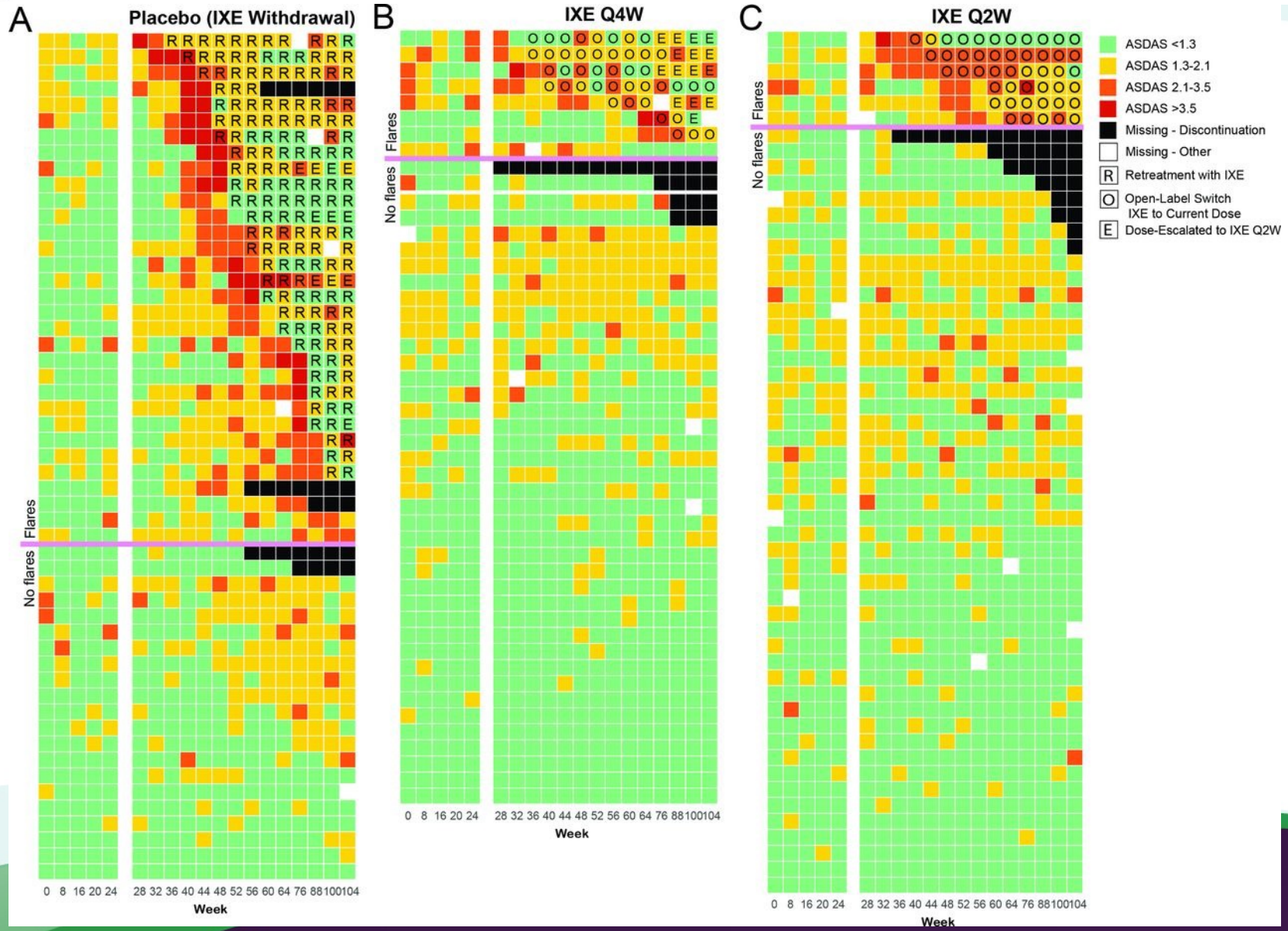
# Heatmap diagram showing ASDAS disease activity status through 104 weeks

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# Thank you for your attention !

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# I am happy to take questions

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