Τί νεότερο στην αξονική σπονδυλαρθρίτιδα

Γ.Ε Φραγκούλης
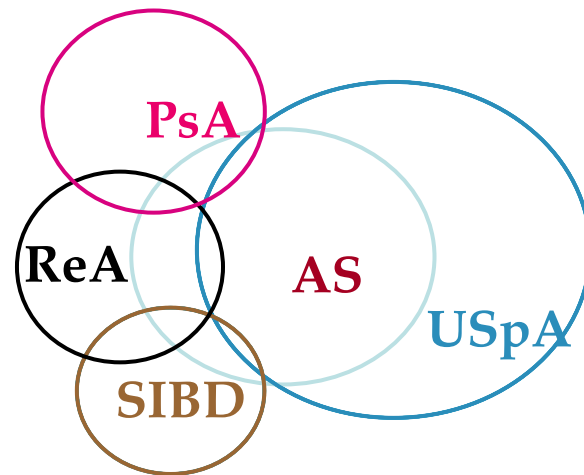
Επίκουρος Καθηγητής Ρευματολογίας, ΑΠΠΚ, Νοσοκομείο «Λαικό»

Ηράκλειο 2023

Spondyloarthritis
Psoriatic Arthritis

SpA: Overlapping entities

AS   Ankylosing spondylitis

PsA   Psoriatic arthritis

USpA   Undifferentiated SpA

ReA   Reactive arthritis

SIBD   SpA με IBD

Davis JC & Mease PJ Semin Arthr & Rheum 2008

Definitions

- About 160 ASAS members

- 88% in favour for this definition

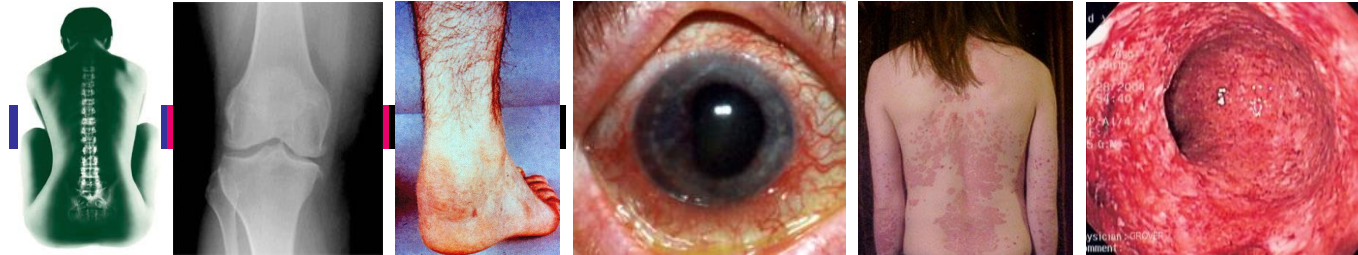Patients with a diagnosis of axSpA with duration of axial symptoms of ≤2 years*

*Axial symptoms should include spinal/buttock pain or morning stiffness and should be considered by a rheumatologist as related to axSpA.

Figure 3 ASAS definition of early axial spondyloarthritis (axSpA). ASAS, Assessment of SpondyloArthritis international Society.
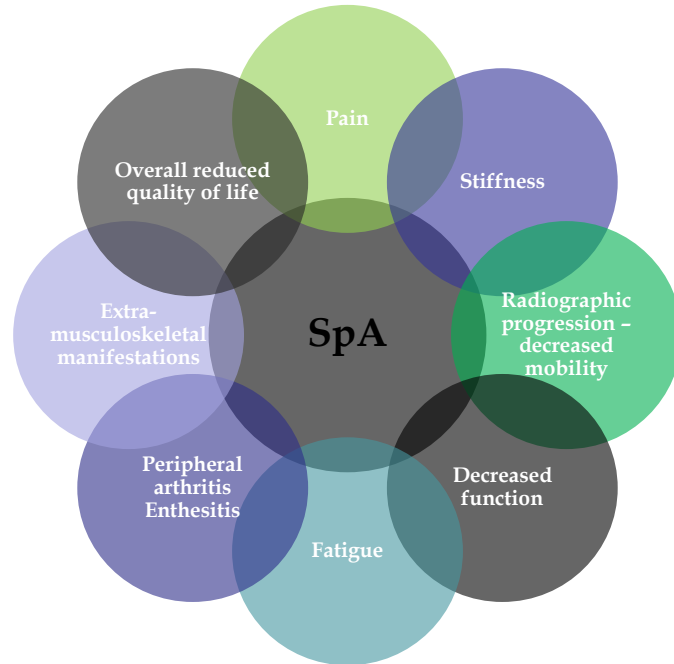
Spondyloarthritis
Clinical manifestations

SpA
Multifaceted disease

Diagram of SpA with surrounding facets: Pain, Stiffness, Radiographic progression – decreased mobility, Decreased function, Fatigue, Peripheral arthritis Enthesitis, Extra-musculoskeletal manifestations, Overall reduced quality of life

- Treatment
  - Non-pharmacological
    - Exercise
    - Physio
  - Pharmacological
  - Extra-articular manifestations
  - Comorbidities

Extra-articular manifestations

Uveitis

- Retrospective study 264 axSpA and 369 PsA patients from 4 centres in Greece (2018-2023)

- In axSpA, uveitis occurred in 11.7%
  - associated with HLA-B27 (OR=4.15, 95%CI 1.16-14.80, p=0.028) and
  - ever-present peripheral arthritis (OR=3.05 (1.10 – 8.41, p=0.031).

- Median uveitis recurrence rate was comparable between axSpA (0.205 episodes/year)
  - No differences between those >0.205 and those with <0.205
  - Permanent ocular damage in 16.1% of AxSpA pts
    - All with recurrent uveitis

Higher frequency but similar recurrence rate of uveitis episodes in axial spondylarthritis compared to psoriatic arthritis. A multicentre retrospective study
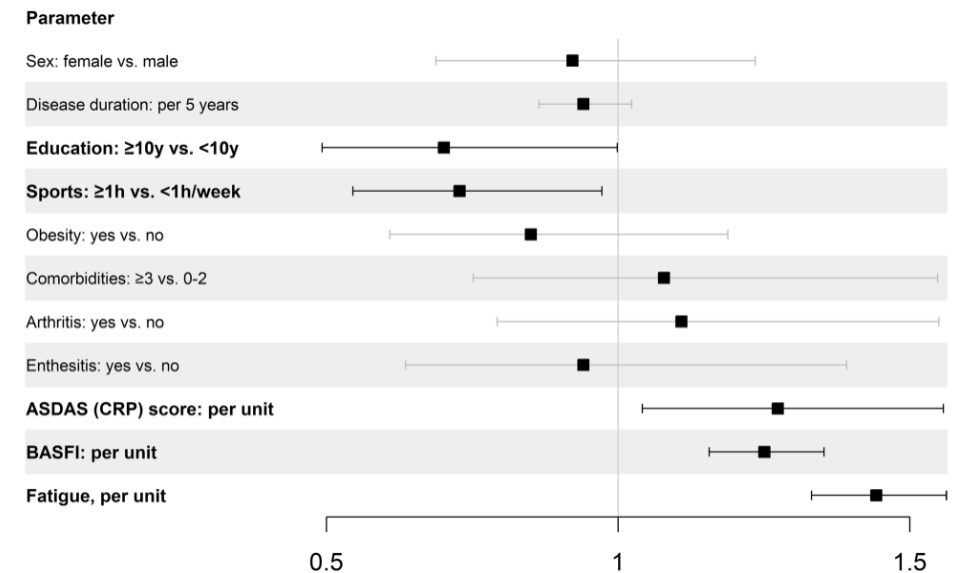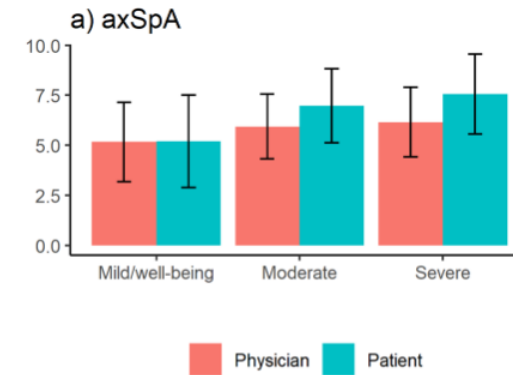
Nikolaos Kougkas[1] · Konstantina Magiouf[2] · Chrysoula G. Gialouri[2,3] · Gerasimos Evangelatos[4] · Maria Pappa[2] · Aikaterini Dimouli[5] · Alexios Iliopoulos[3] · Anastasios Karmanakos[5] · Theodoros Dimitroulas[1] · Maria G. Tektonidou[2] · Petros P. Sfikakis[2] · George E. Fragoulis[2]

Comorbidities

Depression

- RABBIT-SpA cohort

  - WHO-5 Well-Being Index score at baseline were included

  - (1,245 axSpA; 1,225 PsA)

  - Depressive symptoms: 8% and 21%, respectively.

  - AxSpA more likely to patients to experience depressive symptoms

    - higher disease activity

    - a greater functional impairment

  - Less likely

    - more years in education

    - engaging in sports for at least 1 h/week

a) axSpA

Physician / Patient

Parameter

Sex: female vs. male
Disease duration: per 5 years
Education: ≥10y vs. <10y
Sports: ≥1h vs. <1h/week
Obesity: yes vs. no
Comorbidities: ≥3 vs. 0-2
Arthritis: yes vs. no
Enthesitis: yes vs. no
ASDAS (CRP) score: per unit
BASFI: per unit
Fatigue, per unit

Recih et al Arthritis Research & Therapy 2023
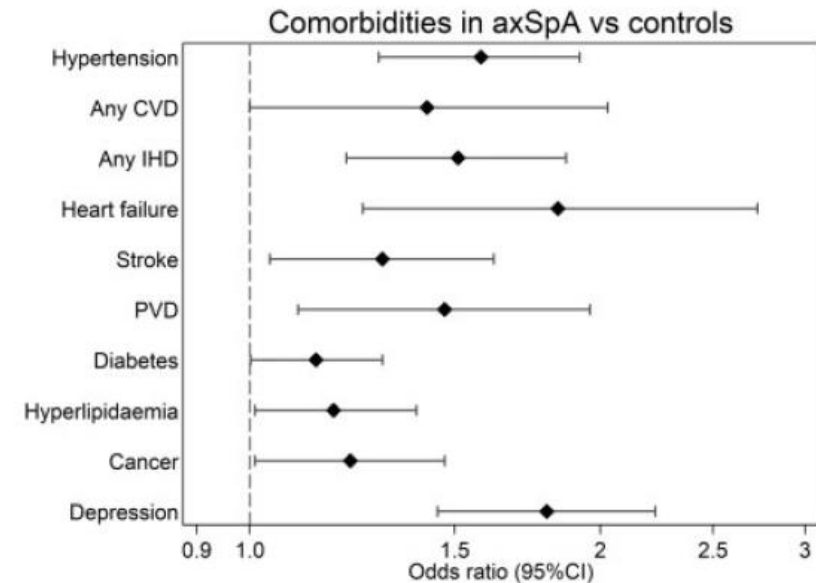
Depression Epidemiology

- RA (meta-analysis)
  - Depression: 15%
  - Anxiety: 19%

- PsA
  - Depression: 30%
    - ✓ 3-5 higher than RA
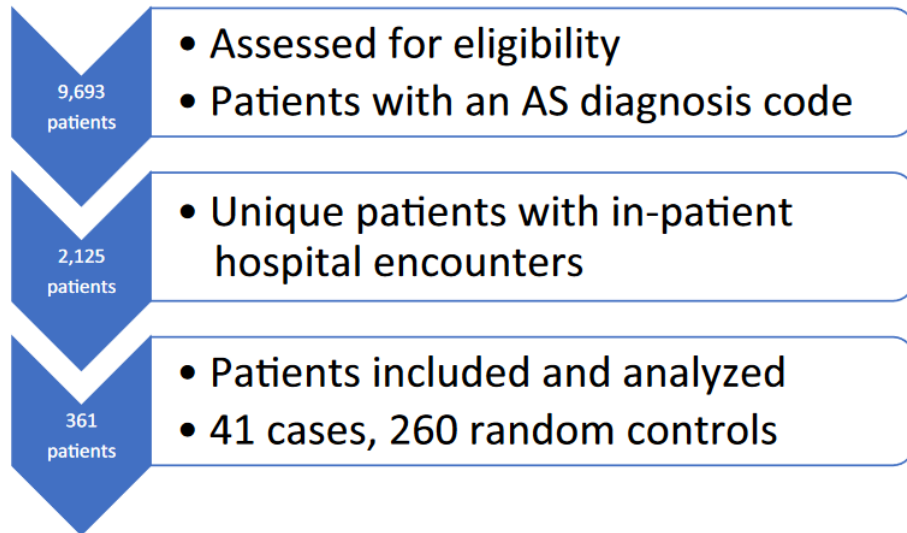   - ✓ 22% higher than general population

- AxSpA
  - Depression (HADS>11): 15% meta-analysis

Comorbidities in axSpA vs controls

Zhao et al Rheumatology (Oxf) 2020
Panagiotopoulos & Fragoulis Clin Ther 2023

AS

Mortality for inpatients

- Case-control study

- Cerner Health Facts® database (US), 2015-2017

9,693 patients
- Assessed for eligibility
- Patients with an AS diagnosis code

2,125 patients
- Unique patients with in-patient hospital encounters

361 patients
- Patients included and analyzed
- 41 cases, 260 random controls

- Leading causes of death

  - CVD

  - Infections

Table 2 Causes of mortality based on the top 5 discharge diagnoses recorded for hospitalized AS patients with mortality outcome

Discharge diagnosis for cause of death	Number of patients
Cardiovascular	15
Infection	14
Respiratory	8
Fracture/trauma	7
Renal	5
Malignancy	3
Drug abuse	1
Intestinal obstruction	1
Unknown/Not recorded	7

	Unadj. OR	95% CI	Adj. OR	95% CI	*p* value
Female sex	0.29	[0.12, 0.70]	0.43	[0.17, 1.10]	0.08
Age	1.04	[1.02, 1.06]	1.02	[0.99, 1.05]	0.14
Elix. Index (dich.)	11.09	[4.24, 29.0]	7.70	[2.82, 21.01]	**<0.0001**
Elix. Index (cont.)	1.20	[1.14, 1.27]	1.18	[1.12, 1.25]	**<0.0001**
NSAID inpatient	0.39	[0.09, 1.76]	0.46	[0.10, 2.17]	0.33
CHF	5.34	[2.19, 13.1]	2.76	[1.04, 7.38]	**0.04**
HTN	2.95	[1.46, 5.99]	1.57	[0.71, 3.47]	0.2634
Kidney disease	3.66	[1.74, 7.70]	2.46	[1.07, 5.69]	**0.035**
Drug abuse	3.90	[1.28, 11.9]	10.9	[2.55, 46.6]	**0.001**
Obesity	1.72	[0.67, 4.43]	1.76	[0.61, 5.1]	0.29

Bittar et al Clin Rheum 2023

Covid-19

- 2 international physician-reported registries

- 5045 cases, 18.3% had PsO, 45.5% PsA and 36.3% axSpA

- Association with severe Covid-19

  - Older Age

  - Male sex (OR 1.54, 95% CI 1.30 to 1.83)

  - Cardiovascular, respiratory, renal, metabolic and cancer comorbidities (ORs 1.25–2.89)

  - Moderate/high disease activity (ORs 1.39–2.23)

Pedro M Machado [1,2,3], Martin Schäfer [4], Satveer K Mahil [5], Jean Liew [6], Laure Gossec [7,8], Nick Dand [9], Alexander Pfeil [10], Anja Strangfeld [4,11], Anne Constanze Regierer [12], Bruno Fautrel [13], Carla Gimena Alonso [14], Carla G S Saad [15], Christopher E M Griffiths [16,17], Claudia Lomater [18], Corinne Miceli-Richard [19,20], Daniel Wendling [21], Deshire Alpizar Rodriguez [22], Dieter Wiek [23], Elsa F Mateus [24,25], Emily Sirotich [26,27,28], Enrique R Soriano [29,30], Francinne Machado Ribeiro [31], Felipe Omura [32], Frederico Rajão Martins [33], Helena Santos [34,35], Jonathan Dau [36], Jonathan N Barker [37], Jonathan Hausmann [38,39], Kimme L Hyrich [17,40], Lianne Gensler [41], Ligia Silva [42], Lindsay Jacobsohn [43], Loreto Carmona [44], Marcelo M Pinheiro [45], Marcos David Zelaya [46], María de los Ángeles Severina [47,48], Mark Yates [49], Maureen Dubreuil [50], Monique Gore-Massy [51], Nicoletta Romeo [52], Nigil Haroon [53,54], Paul Sufka [55], Rebecca Grainger [56], Rebecca Hasseli [57,58], Saskia Lawson-Tovey [17,59], Suleman Bhana [60], Thao Pham [61,62], Tor Olofsson [63,64], Wilson Bautista-Molano [65,66], Zachary S Wallace [67,68], Zenas Z N Yiu [17,69], Jinoos Yazdany [43], Philip C Robinson [70,71], Catherine H Smith [5]
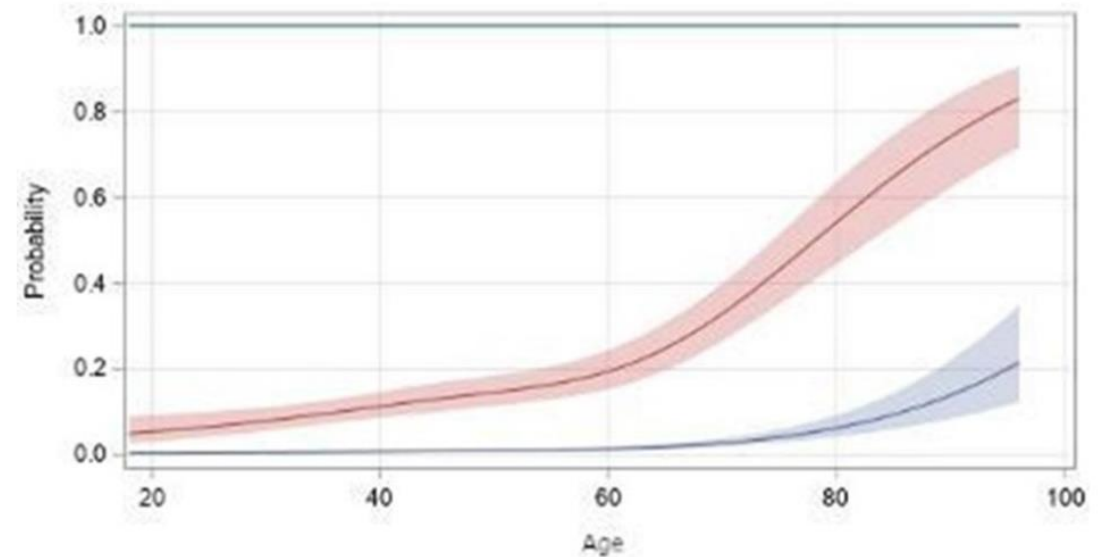
Figure 1 Relationship between age and probability of hospitalisation (red) and death (blue) estimated by four-knot restricted cubic splines, with 95% CIs (primary model, ordinal outcome, all patients).

Lab

HLA-B27

- 2910 patients with axSpA from 24 countries,

- 2269 were tested for HLA-B*27 [1753 HLA-B*27(+) and 516 HLA-B*27(-)].

- B-27+ (males, family History of SpA, Younger age at diagnosis

- HLA-B*27 (-)

  - Enthesitis: OR 1.27 (1.02-1.57)

  - Psoriasis: OR 1.84 (1.36-2.48)

  - IBD: OR 4.84 (3.23-7.30)

  - Uveitis: OR 0.37 (0.27-0.50)

SHORT REPORT

Clinical profile and treatment utilisation based on HLA-B*27 status in axial spondyloarthritis: results from ASAS-PerSpA study

Haseeb Chaudhary [1], Clementina López-Medina [2,3]
Muhammad Asim Khan [4], Maxime Dougados [5] Marina Magrey[1]

Treatment

Residual disease activity despite LDA

- SpANet (monitoring registry for SpA)

- 267 AS pts with ASDAS < 2.1 (LDA) were included

- Indicators of residual disease: fatigue, pain, physical functioning, health-related quality of life (HRQOL), and peripheral symptoms

- Residual disease occurred frequently despite LDA

  - [42.7%] had fatigue scores > 4/10;

  - [17.8%] had pain scores > 4/10, including in those in remission (ASDAS < 1.3).

  - [33%] and [27%] Physical HRQOL was reduced and moderate/poor

  - Multi regression

    - Fatigue more severe and prevalent in women (fatigue severity [0–10]: B_{female} = 0.78, 95% CI 0.18- 1.38; fatigue > 4/10: OR_{female} = 3.29, 95% CI)

Treatment Tapering

- 109 axSpA patients in clinical remission (BASDAI < 40, physician global score < 40) under TNFi for 1 year

  - Tapering: two-thirds of standard dose at baseline, half at week 16, one-third at week 32 and discontinuation at week 48

  - Patients who flared stopped tapering and were escalated to the previous dose.

  - After 2 years

    - 55 patients (52%) had successfully tapered: 23 (22%) receiving two-thirds, 15 (14%) half, 16 (15%) one-third dose and 1 (1%) discontinued

    - Predictor of successful tapering

      - ✓ lower physician global score (OR 0.86 [0.75, 0.98]; P=0.017)

      - ✓ lower Spondyloarthritis Research Consortium of Canada (SPARCC) (OR 0.78 [0.57, 0.98]; P= 0.029)

      - ✓ Current smoker (OR 3.28 [1.15, 10.57]; P =0.026)

Treatment Tapering

- open-label, monocentre, randomised controlled non-inferiority (NI) trial on T2T tapering of TNFi.

- 122 patients (64 PsA and 58 axSpA) on TNFi and LDA for at least 6months were randomised to a T2T strategy

- with (N=81) or without tapering (N=41)
  - Tapering (100%, 66%, 50%, 0%)

- Follow-up for 12 months

- LDA at 12 months was 69% for the tapering and 73% for the no-tapering group
  - Tapering: not inferior

A. Disease activity: PsA   B. Disease activity: AxSpA

—◆— T2T with tapering   – –•– – T2T without tapering
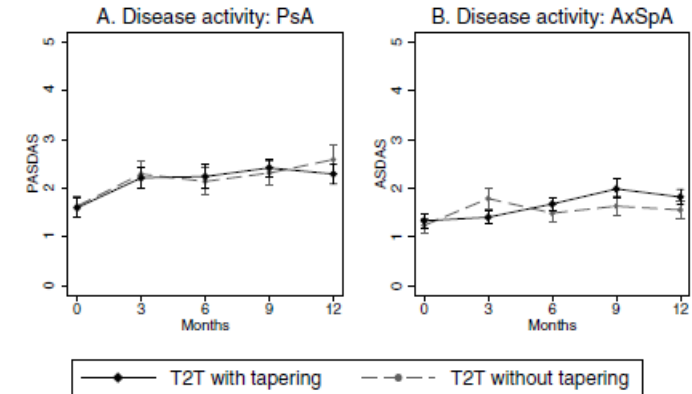
Table 5 Radiographic outcomes in T2T strategy treated patients with PsA with or without tapering

	T2T with tapering (N=42)	T2T without tapering (N=22)	P value
Progression >SDC (1.54), n (%)	5 (13)	2 (10)	0.78
Progression >0.5, n (%)	17 (43)	7 (35)	0.58
Mean progression, mean (SD)	0.8 (1.4)	0.52 (0.82)	0.33*
Median progression, median (IQR)	0.5 (0–1)	0.5 (0–1)	0.77†

Not all patients had complete radiographs (intervention: 2 and control: 2 missing at 12 months).
*Welch T-test.
†Wilcoxon rank-sum test.
PsA, psoriatic arthritis; SDC, smallest detectable change; T2T, treat-to-target.

Michelsen et al Ann Rheum Dis 2022

Treatment & Comorbidities

Cardiovascular

- **French National study**

  - AS included 2010-2013

  - End of follow-up: 12/2018

  - 22.929 patients were included

  - 8-year cumulative incidences

    - MACE: 1.81% [1.61-2.05]

    - Stroke: 0.97% [0.83-1.14],

    - MI: 0.85% [0.71-1.04]

- NSAIDs (SHR: 0.39 [0.32-0.50], p<0.001) and anti-TNF (SHR 0.61 [0.46-0.80], p<0.001), but not anti-IL17 (2.10 [0.79-5.57])

were associated with a lower risk of MACE occurrence.

Table 3: IPTW Analysis with wSHR and its 95% confidence interval stratified by NSAIDs treatment.

	wSHR [95% CI] global	wSHR [95% CI] in patients treated with NSAIDs	wSHR [95% CI] in patients NOT treated with NSAIDs
NSAIDs	0.39*** [0.32-0.50]	N/A	N/A
csDMARDs	0.89 [0.63-1.24]	0.91 [0.58-1.43]	1.02 [0.61-1.71]
Anti-TNF	0.61*** [0.46-0.80]	0.68* [0.47-0.99]	0.57** [0.38-0.85]
Anti-IL17	2.10 [0.79-5.57]	2.88 [0.73-11.3]	1.90 [0.47-7.72]

Anti-IL17

Reduces CVD risk………or Not??

- **Patients:** PsA

- **Database:** Real-world study, French National Health Insurance (2015-9)

- 9510 bDMARD and 1885 apremilast **new users**, without CVD history

- **Primary endpoint**: occurrence of MACEs

- Vs TNFi

  - **IL-12/23: (HR) 2.0, (95% CI 1.3, 3.0)**

  - **IL-17 inhibitors: HR: 1.9, (95% CI 1.2, 3.0)**

  - In a sub-analysis in patients without CV risk factors,

    - MACEs occurred more frequently with IL-17 inhibitors than with TNFi

  (HRw 1.6, 95% CI 1.1, 2.8)

- However…… possible biases (e.g skin involvement and IL-17i)

Fig. 2 Forest plot of risk of major adverse cardiac events by therapeutic drug class in subgroup analyses

Treatments (ref: TNF inhibitors)	HRw
Without active skin psoriasis	
IL12/23 inhibitor	4.7
IL17 inhibitors	3.6
Apremilast	0.9
Without CV comorbidities	
IL12/23 inhibitor*	/
IL17 inhibitors	1.6
Apremilast	0.7
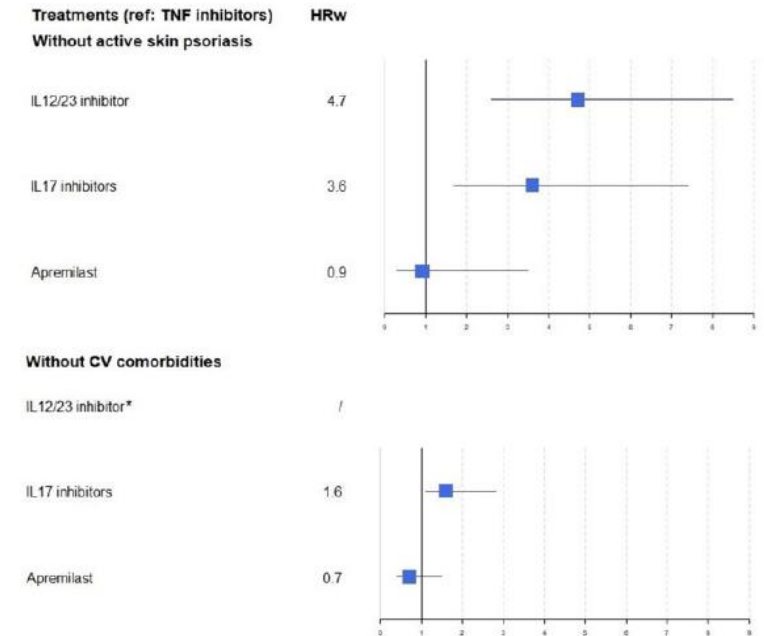
*Not available due to the absence of events in this class. HRw: weighted hazard ratio; CV: cardiovascular.

Treatment & Comorbidities

- 23.333 PsA 11.457 axSpA patients

- Serious infections: 1.09/100py similar between PsA and AxSpA
  - PsA (0.96 per 100 PY 95% CI 0.69 to 1.28)
  - axSpA (1.09 per 100 PY 95% CI 0.76 to 1.46).

- Non-serious infections: 53.0/100 PY
  - PsA (54.08 (95% CI 40.96 to 68.99, I2=98%))
  - axSpA (58.02 per 100 PY (95% CI 44.79 to 72.94, I2=98%))

In PsA patients (IRs)

TNFi 1.36 per 100 PY (95% CI 0.72 to 2.16, I2=55%)
IL-17i 0.97 per 100 PY (95% CI 0.49 to 1.57, I2=47%)
JAKi 1.51 per 100 PY (95% CI 0.00 to 14.74, I2=31%)
IL-23i 0.29 per 100 PY (95% CI 0.00 to 1.03, I2=15%)
PDE4 0.38 per 100 PY (95% CI 0.00 to 1.19, I2=0%)

In axSpA patients,
TNFi 1.24 per 100 PY (95% CI 0.78 to 1.77, I2=28%)
IL-17i 1.20 per 100 PY (95% CI 0.59 to 1.96, I2=40%)
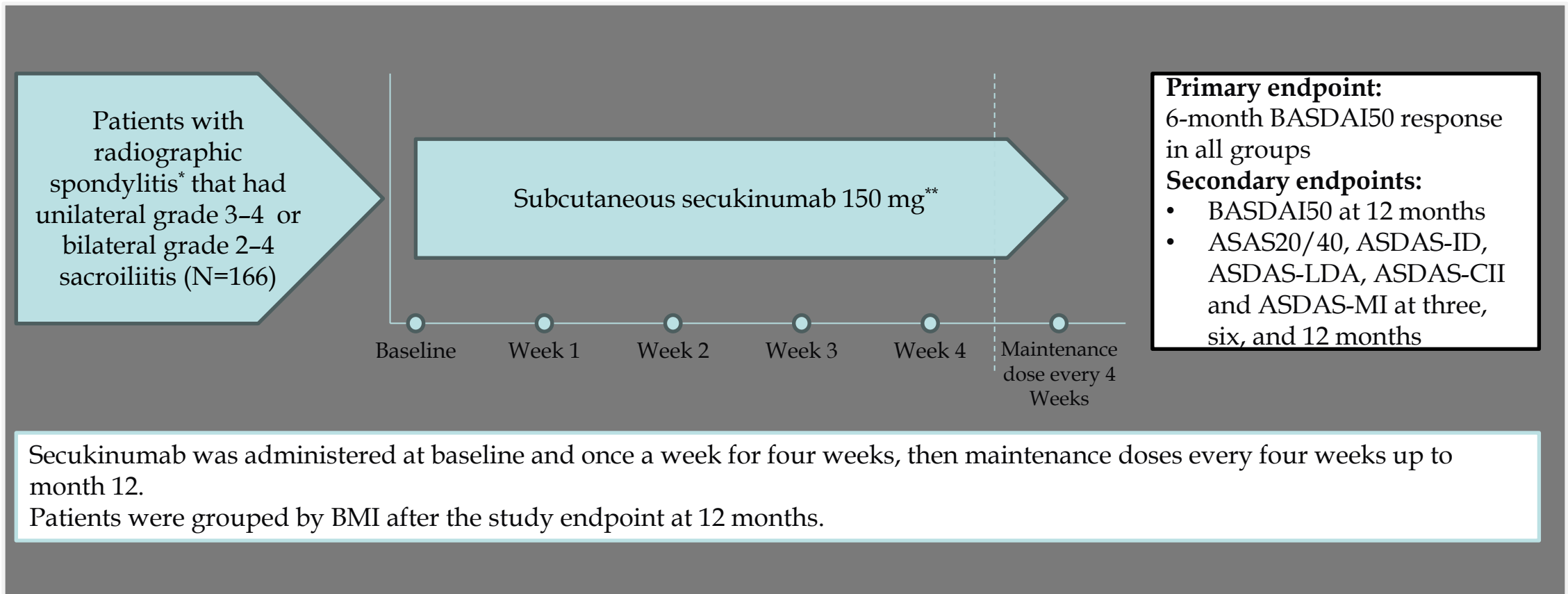JAKi 1.28 per 100 PY (95% CI 0.00 to 13.77, I2=0%) with JAKi

Does Obesity Affect Treatment Response to Secukinumab and its Survival in Ankylosing Spondylitis? Real-life Data from the TURKBIO Registry

Karakaş A, Gulle S, Can G, Dalkılıc G, Akar S, Koca S, Pehlivan Y, Senel S, Tufan A, Ozturk M, Yilmaz S, Yazici A, Cefle A, İnel Y, Erez Y, Sari I, Birlik M, Direskeneli H, Akkoc N, Onen F

Observational cohort study based on the TURKBIO registry
Method

Patients with radiographic spondylitis* that had unilateral grade 3–4 or bilateral grade 2–4 sacroiliitis (N=166)

Subcutaneous secukinumab 150 mg**

Baseline | Week 1 | Week 2 | Week 3 | Week 4 | Maintenance dose every 4 Weeks

Primary endpoint:
6-month BASDAI50 response in all groups
Secondary endpoints:
- BASDAI50 at 12 months
- ASAS20/40, ASDAS-ID, ASDAS-LDA, ASDAS-CII and ASDAS-MI at three, six, and 12 months

Secukinumab was administered at baseline and once a week for four weeks, then maintenance doses every four weeks up to month 12.
Patients were grouped by BMI after the study endpoint at 12 months.

Results: Baseline Disease Activity

Parameter	All patients (N=166)	BMI<25 (n=44)	BMI 25-30 (n=74)	BMI≥30 (n=48)
csDMARD use, mean ± SD	43.0 (25.9)	8.0 (18.2)	24.0 (32.4)	11.0 (22.9)
Biologic naive patients, mean ± SD	47 .0(28.3)	16.0 (36.4)	18.0 (24.3)	13.0 (27.1)
1 prior Anti-TNF, mean ± SD	44.0 (26.5)	13.0 (29.5)	15.0 (20.3)	16.0 (33.1)
2 or more prior Anti-TNF, mean ± SD	75.0 (45.2)	15.0 (34.1)	41.0 (55.4)	19.0 (39.6)
CRP (mg/L), median (IQR)	12.0 (3.0–32.3)	15.0 (3.0–42.5)	10.0 (3.5–23.3)	12.1 (3.3–33)
ESR (mm/h), median (IQR)	26.0 (11.0–45.5)	25.5 (8.3–41.8)	20.0 (11.0–49.0)	28.5 (14.5–45.3)
BASDAI, median (IQR)	4.2 (3.0–5.6)	4.0 (2.5–5.1)	5.2 (3.0–5.9)	4.3 (3.0–5.4)
BASFI, median (IQR)	3.9 (1.9–6.1)	3.9 (1.3–5.7)	2.6 (2.1–5.9)	4.0 (1.9–6.3)
ASDAS, median (IQR)	3.2 (2.7–4.1)	3.8 (2.8–4.2)	3.2 (2.7–4.2)	3.3 (2.5–3.9)
csDMARD use, median (IQR)	43.0 (25.9)	8.0 (18.2)	24.0 (32.4)	11.0 (22.9)

Baseline disease activity is comparable among treatment groups

Results: BASDAI50 Response over Time
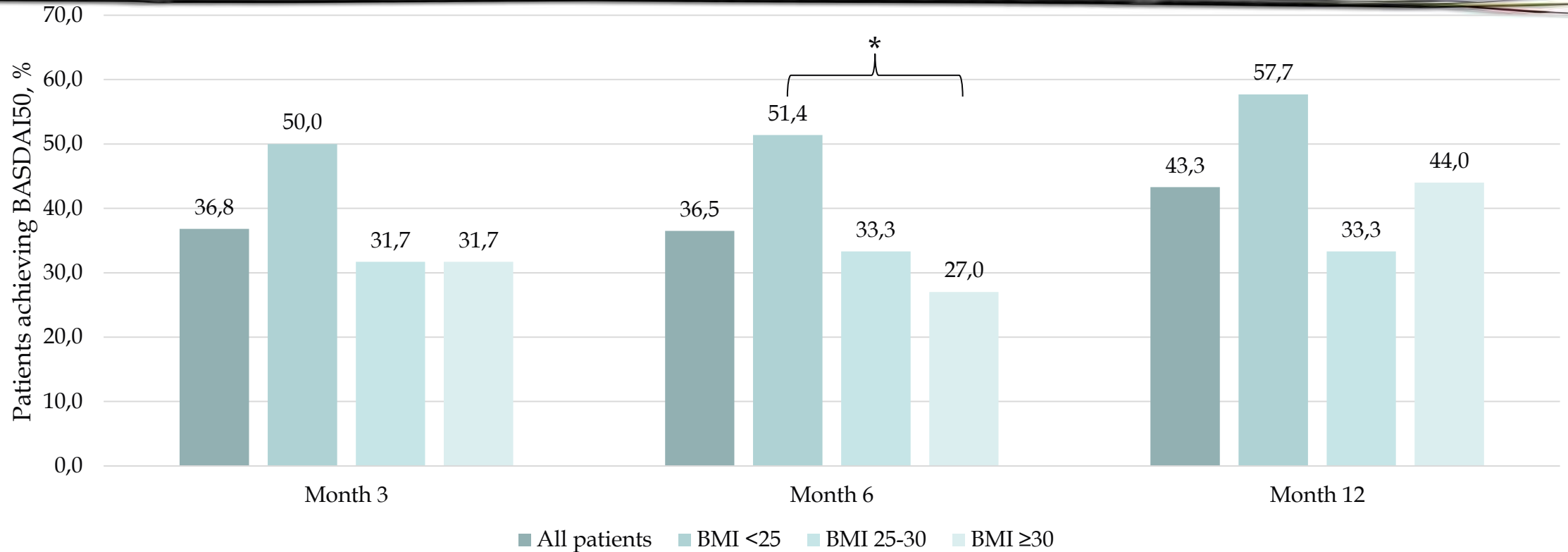
The primary outcome shows that the BMI ≥30 group is achieving BASDAI50 at a significantly lower rate

*Difference between BMI <25 group and BMI ≥30 group, $p<0.05$
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

Results: Regression Analysis Model for BASDAI50 Response at 6 Months

Variable	Univariate analysis, OR (95% CI)	*p* value	Multivariate analysis, OR (95% CI)	*p* value
Age	1.018 (0.985 - 1.052)	0.283	1.035 (0.993 - 1.078)	0.104
Gender (F)	0.616 (0.293 - 1.294)	0.201	0.881 (0.369 - 2.105)	0.776
Smoking	1.870 (0.868 - 4.027)	0.110	1.755 (0.723 - 4.260)	0.214
Disease duration	1.022 (0.974 - 1.073)	0.379	1.010 (0.956 - 1.067)	0.732
Baseline CRP (mg/L)	1.000 (0.989 - 1.012)	0.958	0.999 (0.987 - 1.012)	0.921
BMI ≥30 (ref: BMI<30)	0.545 (0.235 - 1.263)	0.157	0.512 (0.199 - 1.320)	0.166
Biologic naïve	0.485 (0.221- 1.062)	0.070	0.432 (0.180 - 1.037)	0.060

The low BASDAI50 response in the BMI ≥30 treatment group is not significantly affected by obesity

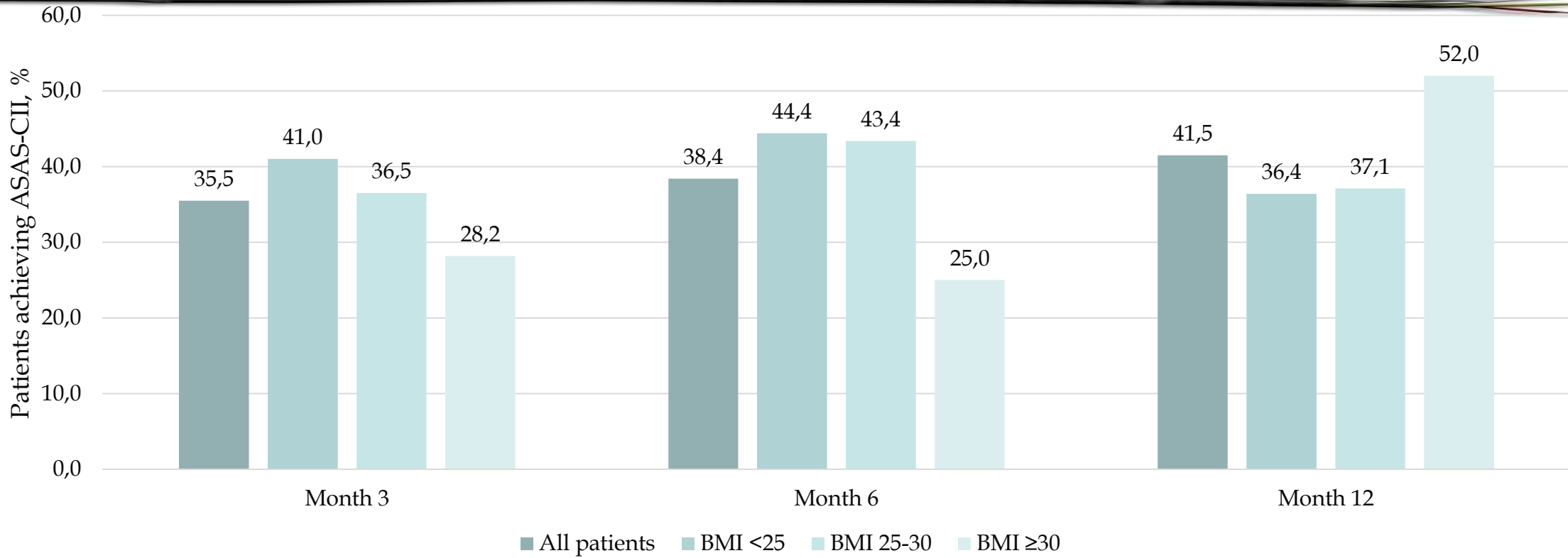BASDAI, Bath Ankylosing Spondylitis Disease Activity Index

Results: ASDAS Low Disease Activity over Time
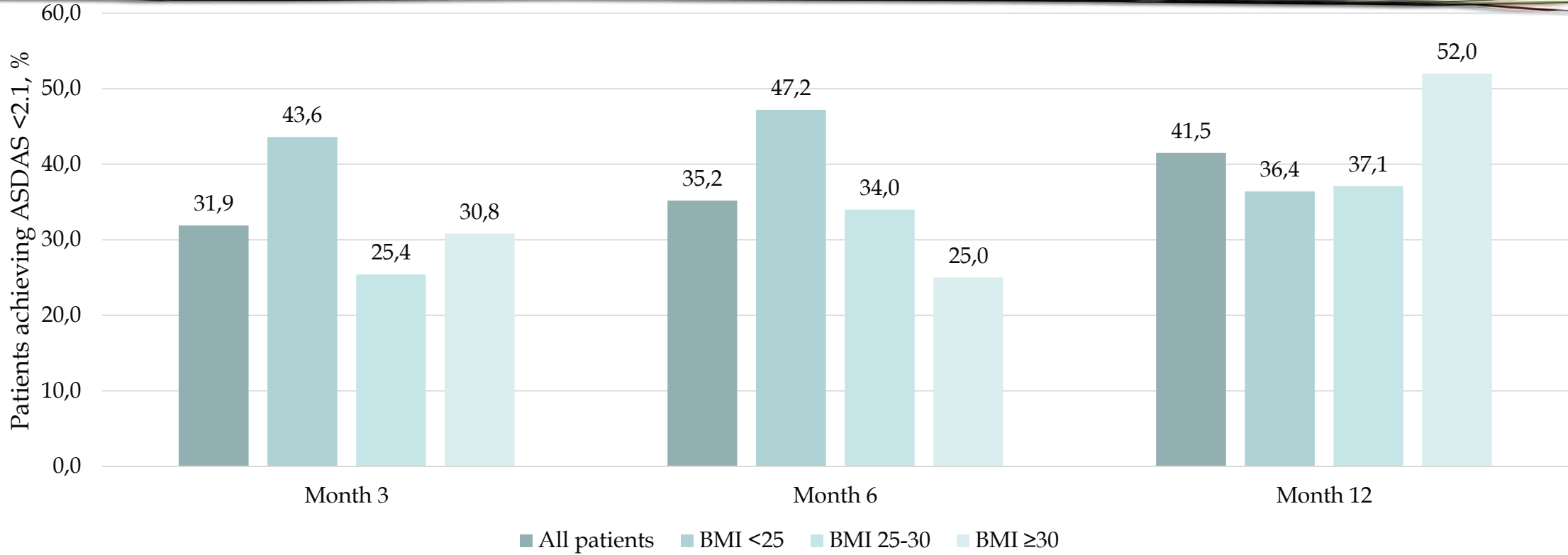
There was no significant difference in ASDAS low disease activity response between each BMI groups

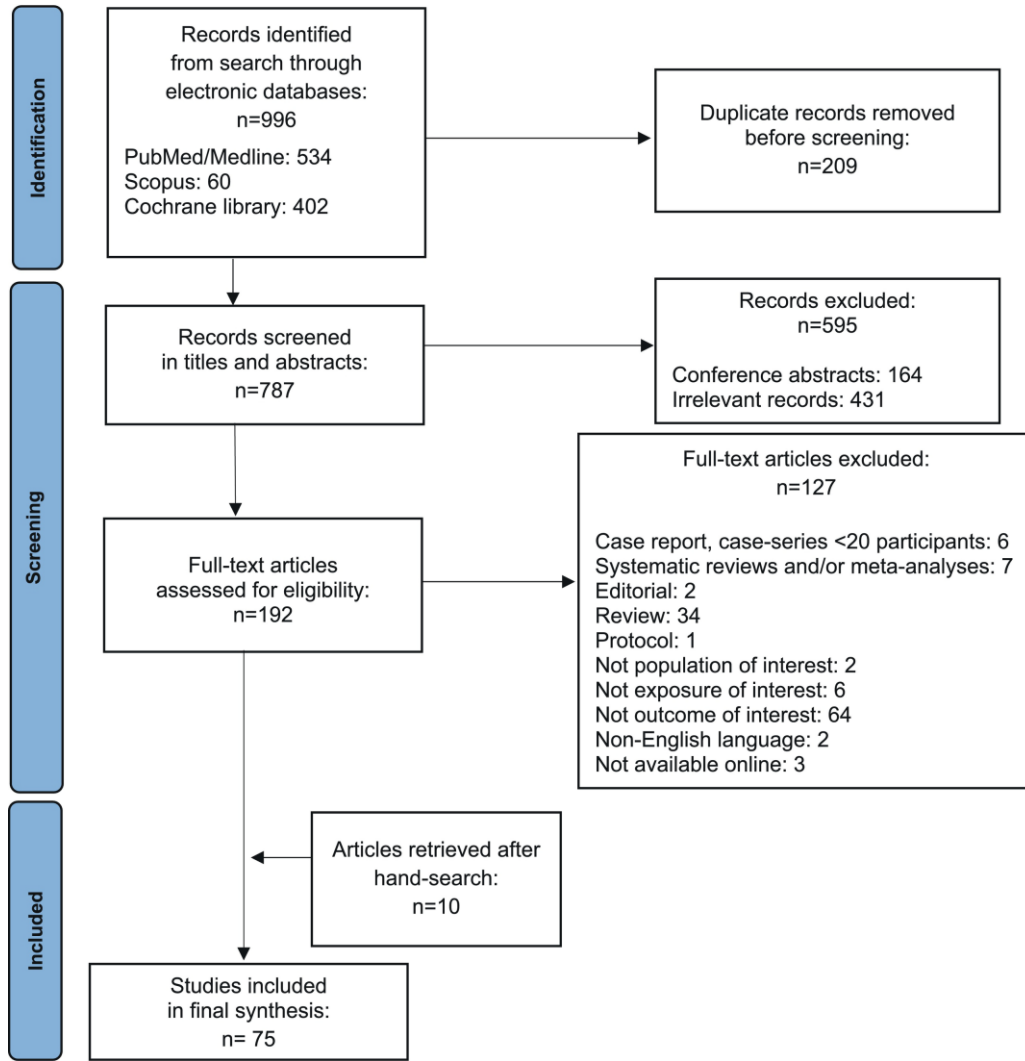# Results: ASDAS Clinically Important Improvement over Time

There was no significant difference in ASDAS-CII between the BMI groups

Effect of BMI in treatment efficacy b-ts-DMARDs

- Effect more pronounced for TNFi across IA

- IL 17i and IL-23i: less affected

Drug category	RA	PsA	SpA
Abatacept			
JAK inhibitors			
IL-17 inhibitors			
IL-23 inhibitors			
IL-6R inhibitors			
Rituximab			
TNF inhibitors			

Gialouri et al Autoimmunity Reviews 2023

Conclusions

- Comorbidities Important
  - Cardiovascular
  - Infections
  - Mental-health
- Factors affecting treatment
  - BMI
  - Cardiovascular
- Tapering?