Ερμηνεύοντας τον όρο «συννοσηρότητες»

George E Fragoulis,

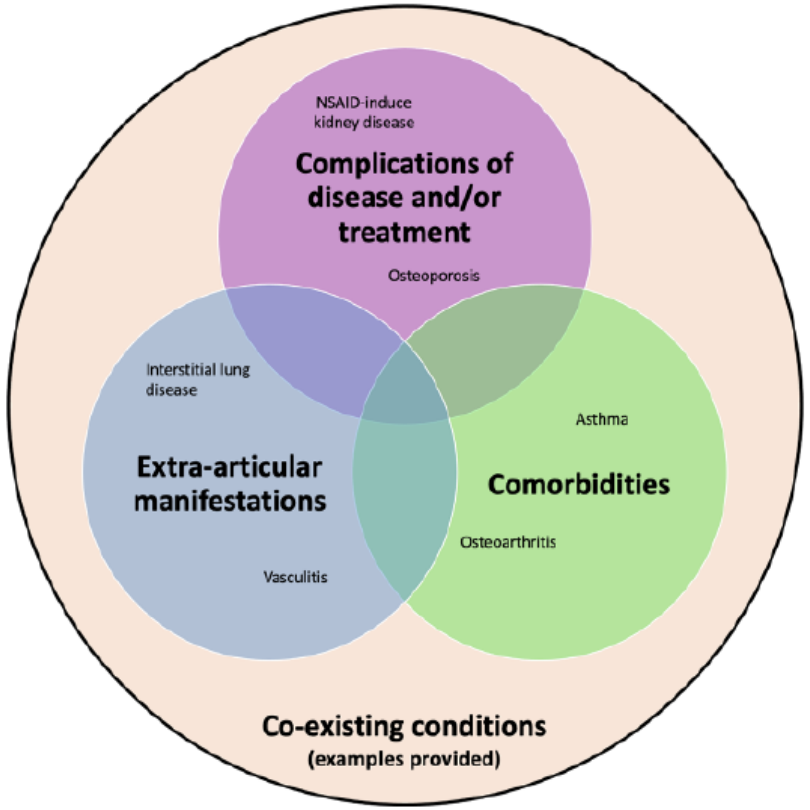
Rheumatologist, “Laiko” Hospital

Conflicts of Interest

Speaker fees/consultancies: Abbvie, Pfizer, UCB, Novartis, Janssen, Aenorasis, Farran, Lilly, Genesis

Co-morbidities.....or co-existing conditions?

- Co-existing Clinical Conditions
  - Can be seen as
    - Comorbidities
    - Extra-articular manifestations
  - Nomenclature
    - Still scarce
    - Needs to be defined for clinical & research purposes
      - ✓ Relation to the underlying pathophysiology?
  - Negative Impact on Disease's outcomes
    - Can lead to difficult to treat (D2T) disease

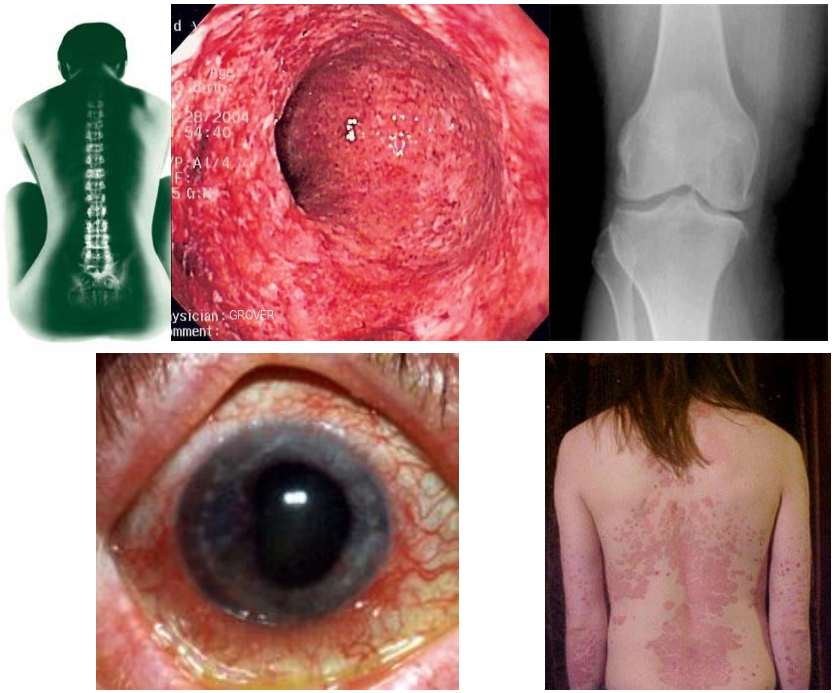


Dey et al Rheumatology (Oxf) 2022

Co-existing conditions

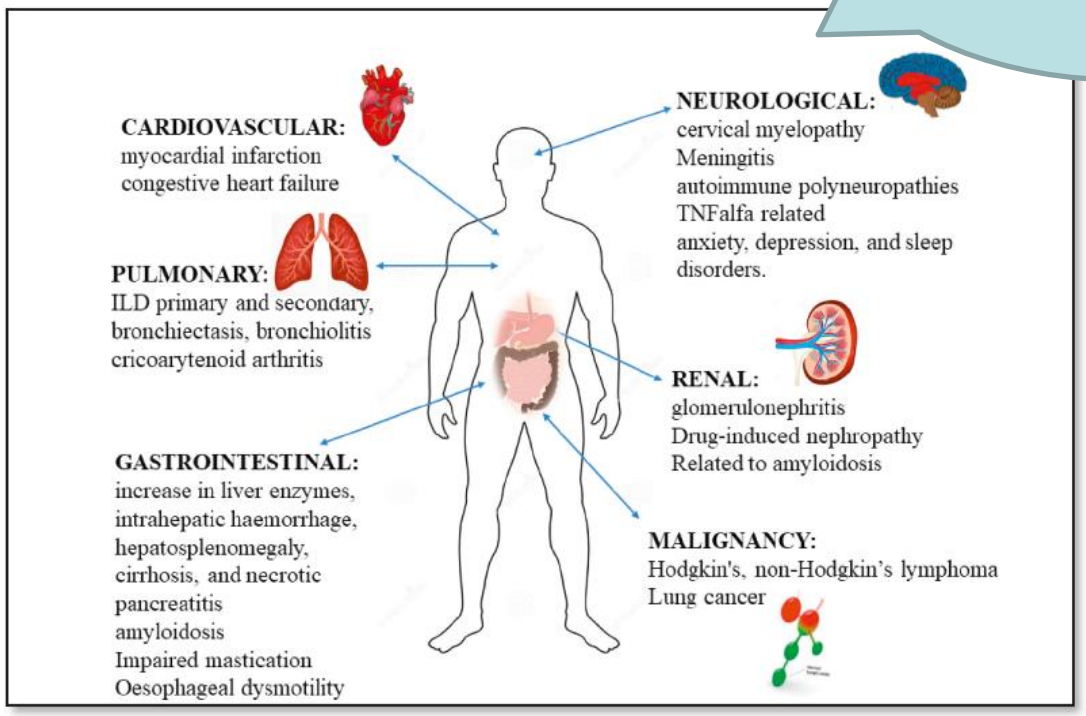
General remarks

- Spondyloarthritis (SpA)



- Rheumatoid Arthritis

An average RA patient has 1.6 co-existing clinical conditions and approximately 60% of patients have multiple comorbidities



Chandran et al J Autoimmun 2010
Figus et al Autoim. Reviewes 2021

Psoriatic arthritis

...or psoriatic disease

- Metabolic component
  - Diabetes (11-20%)
  - Obesity (16-60%)
    - Associates with PsA development and worse prognosis
  - Hypertension/CVD (28-47%/21-62%)
    - ⇧ CVD risk
      - ✓ Does not fully explained by classic CVD risk factors
  - Mental disorders
    - Depression (9-27%)
    - Anxiety (6-37%)
- Inflammatory Bowel Disease
  - Crohn (not for UC)
    - Risk Ratio
      - Vs Healthy: 2.96 (1.40 - 6.00)
      - Vs Psoriasis 3.60 (1.83 – 7.10)
- Ocular manifestations
  - Risk Ratio
    - Vs Healthy: 3.35 (2.21 - 5.70)
    - Vs Psoriasis 2.13 (1.40 – 3.24)

Kimball AB J Am Acad Dermatol. 2008
Krishnadas R Brain Behav Immun 2016
Nikiphorou E, Fragoulis GE Ther Adv Musculoskelet Dis. 2018

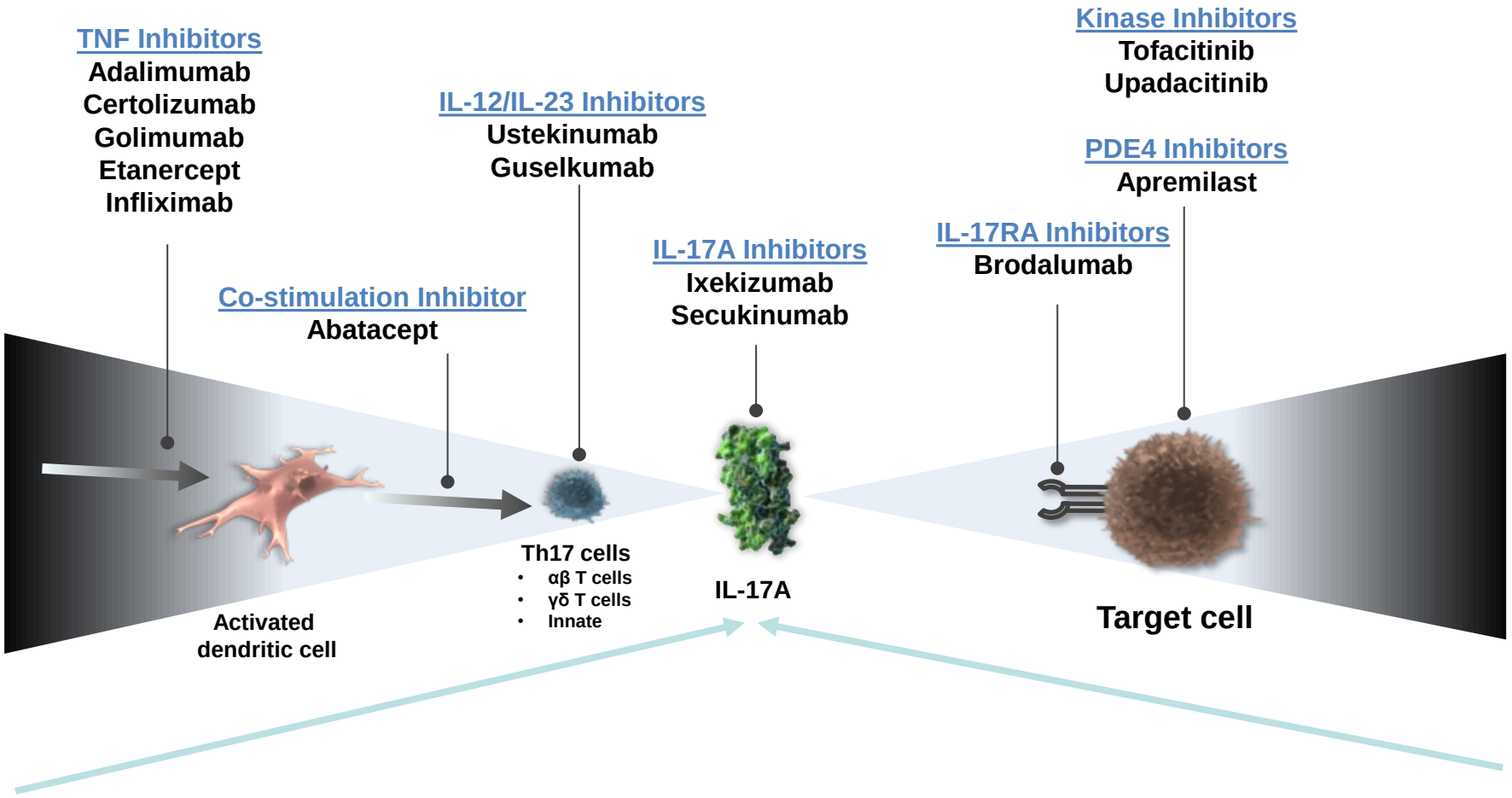
Charlton R et al Ann Rheum Dis 2018
McDonough E et al J Rheum 2014
Khraishi M et al Clin Rheum 2014
Husted JA et al Arthritis Care and Res 2014

Outline

- Co-morbidities
  - What are they?
- SpA specific
- Comorbidities common in RA/SpA
  - Cardiovascular risk
  - Mental health disorders

Treatment – the major players

tsDMARDs & Biologics



Nestle F et al. *N Engl J Med.* 2009
Kopf M et al. *Nat Rev Drug Discov.* 2010
Garber K. *Nat Biotechnol.* 2011

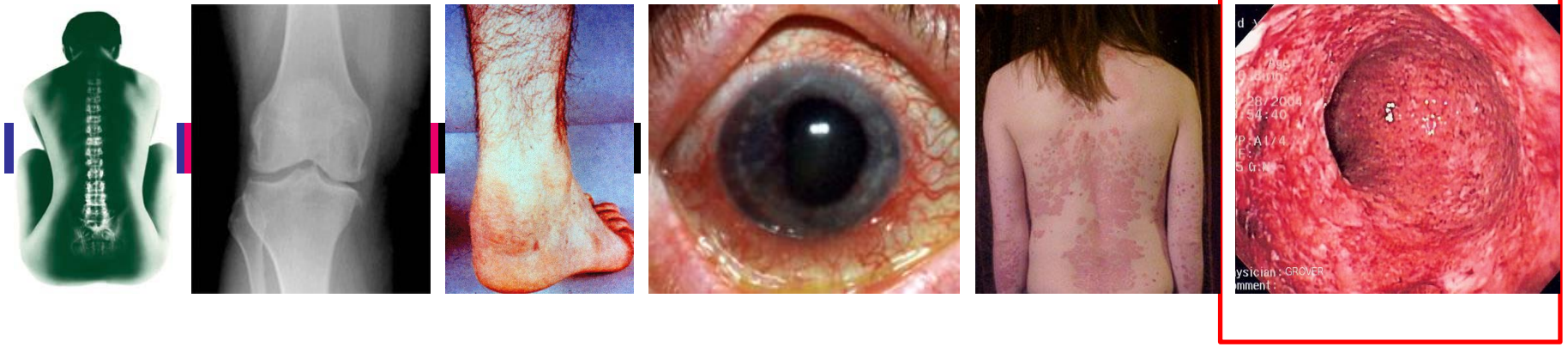
PsA - Co-existing conditions

What else we should check?

- Bowel
- Uveitis
- CVD
- Mental health disorders
- Others

EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update

F When managing patients with psoriatic arthritis, non-musculoskeletal manifestations (skin, eye and gastrointestinal tract) should be taken into account; comorbidities such as metabolic syndrome, cardiovascular disease or depression should also be considered.



Gossec L et al, ARD 2020

Treatment

Safety & Co-morbidities

- Inflammatory bowel disease
  - Efficacy
    - Infliximab
    - Adalimumab
    - Ustekinumab
    - Certolizumab
    - Risankizumab (phase II)
  - Contra-indication
    - Anti-IL-17
    - Etanercept

Whitlock SM et al J Am Acad Derm 2018
Feagan BG et al Lancet 2017

Sharma S et al Best clin Prac & Res Clin Rheum 2018

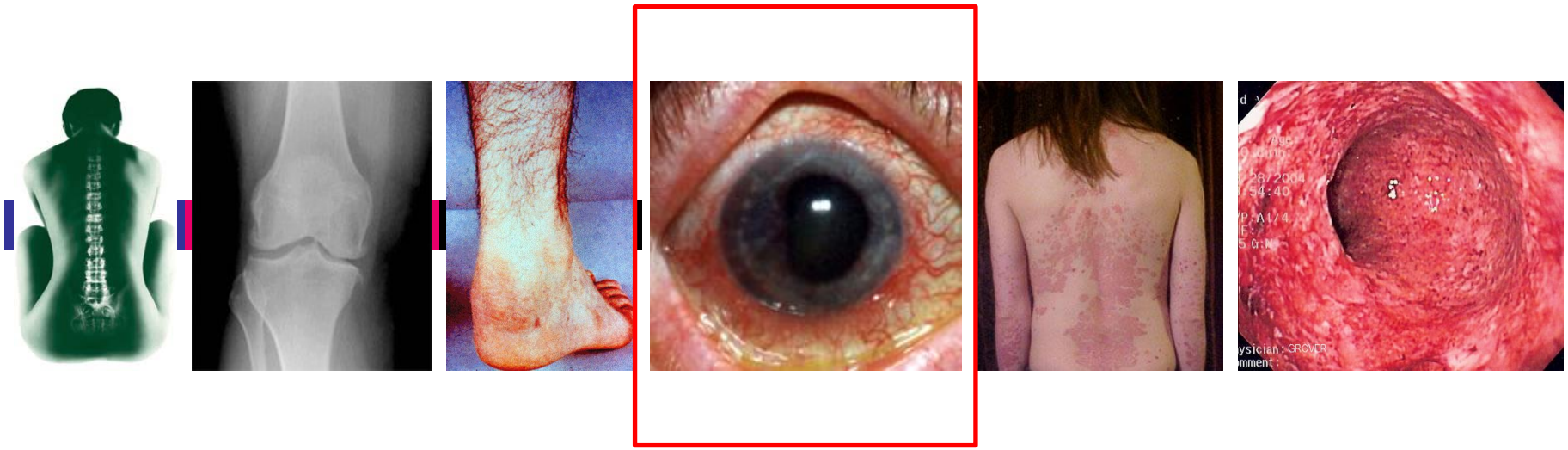
PsA - Comorbidities

What else we should check?

- Bowel
- Uveitis
- CVD
- Mental health disorders
- Others

EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update

F When managing patients with psoriatic arthritis, non-musculoskeletal manifestations (skin, eye and gastrointestinal tract) should be taken into account; comorbidities such as metabolic syndrome, cardiovascular disease or depression should also be considered.



Gossec L et al, ARD 2020

AAU Treatment

EULAR and ACR recommendations

- EULAR recommendations for PsA
  - "……Importantly, however, in case of concomitant inflammatory bowel disease or uveitis, a TNFi (monoclonal antibody) would be preferred."
- ACR/SPARTAN recommendations for SpA
  - axSpA patients with recurrent uveitis: TNFi > other bDMARDs

Ward et al Arthritis Rheumatol 2019
Gossec et al Ann Rheum Dis 2020

PsA - Uveitis

Treatment options – b-ts-DMARDs

- Adalimumab
  - Approved for uveitis (non-anterior)
- Certolizumab, infliximab, golimumab
  - Have also good results
- Etanercept, Secukinumab
  - Not-effective (mainly in other diseases)
- Ustekinumab, Tofacitinib, Filgotinib, Baricitinib
  - Unknown

Rademacher J et al Ther Adv Mus Dis 2020
Fragoulis & Siebert Rheumatology 2020

Treatment options in SpA

Condition	Monoclonal TNF inhibitors	Etanercept	IL-17-inhibitors	IL-23-inhibitors	JAK-inhibitors
AxSpA	++	++	++	-	++
Uveitis	++	- (?)	-	(?)	(?)
IBD	++	-	-	++	CD(?)/UC++
Psoriasis	++	+	+++	+++	++

modif from Fragoulis GE & Siebert S Rheumatology (Oxf 2020)

Outline

- Co-morbidities
  - What are they?
- SpA specific
- Comorbidities common in RA/SpA
  - Cardiovascular risk
  - Mental health disorders
  - Infections

Autoimmune Rheumatic Diseases

Cardiovascular (CV) risk

- CV risk & mortality
  - ⇧ compared to the general population

Kurmann RD and Mankad R, Clin Cardiology 2018
Alhusain A and Bruce I, Clin Med 2013
Vd Hoek et al Clin Exp Rheum 2016

EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome

George C Drosos [1], Daisy Vedder [2], Eline Houben,[3] Laura Boekel [2], Fabiola Atzeni,[4] Sara Badreh,[5] Dimitrios T Boumpas [6,7] Nina Brodin,[8,9] Ian N Bruce,[10,11] Miguel Ángel González-Gay [12], Søren Jacobsen [13,14] György Kerekes,[15] Francesca Marchiori,[16] Chetan Mukhtyar [17], Manuel Ramos-Casals,[18] Naveed Sattar,[19] Karen Schreiber,[20] Savino Sciascia [21], Elisabet Svenungsson [22], Zoltan Szekanecz [23], Anne-Kathrin Tausche,[24] Alan Tyndall,[25] Vokko van Halm,[26] Alexandre Voskuyl,[27] Gary J Macfarlane [28], Michael M Ward [29], Michael T Nurmohamed,[2,30] Maria G Tektonidou [1,7]

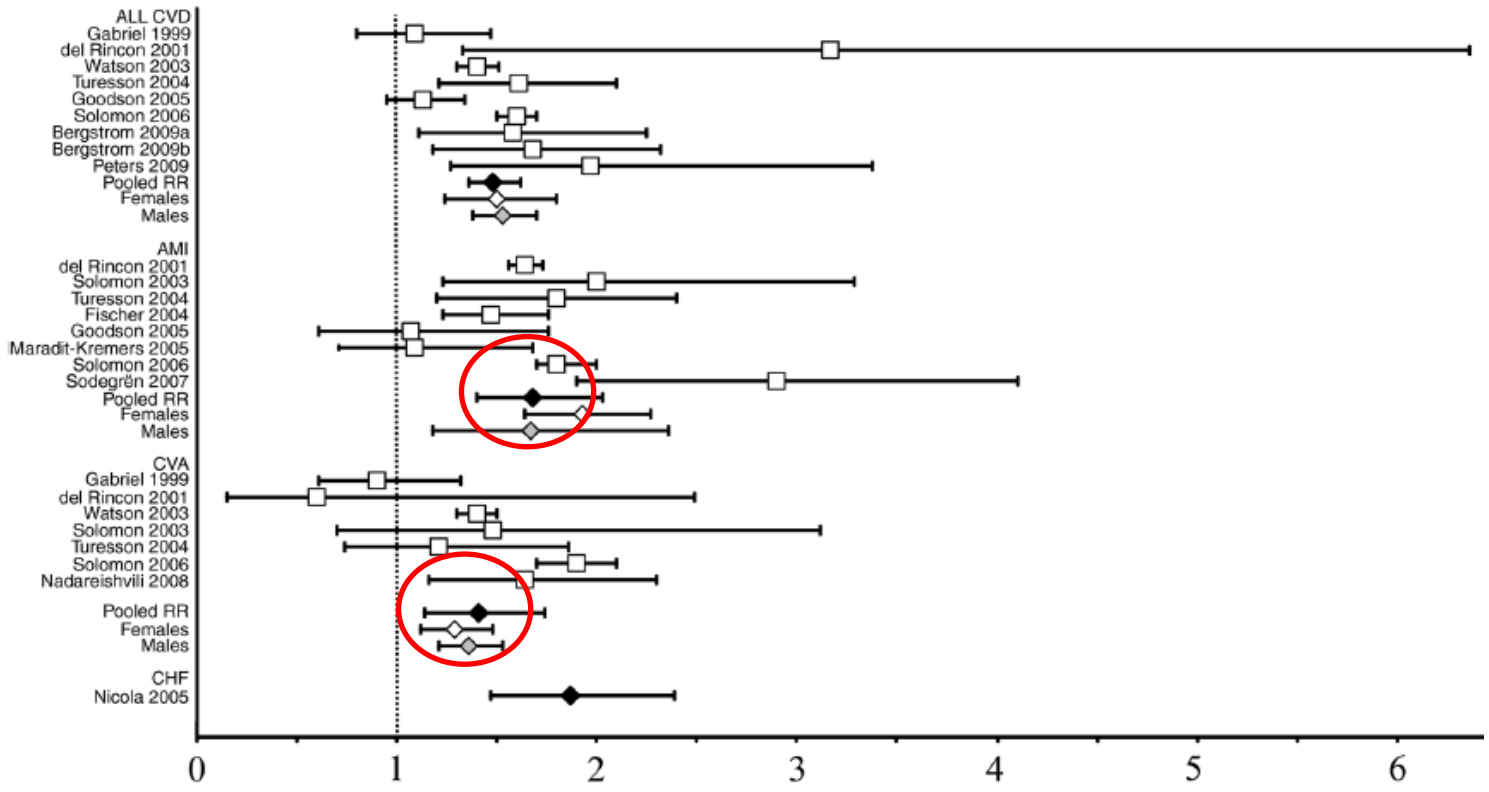
EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update

R Agca,[1] S C Heslinga,[1] S Rollefstad,[2] M Heslinga,[1] I B McInnes,[3] M J L Peters,[4] T K Kvien,[5] M Dougados,[6] H Radner,[7] F Atzeni,[8] J Primdahl,[9,10,11] A Södergren,[12] S Wallberg Jonsson,[12] J van Rompay,[13] C Zabalan,[14] T R Pedersen,[15] L Jacobsson,[16,17] K de Vlam,[18] M A Gonzalez-Gay,[19] A G Semb,[20] G D Kitas,[21] Y M Smulders,[4] Z Szekanecz,[22] N Sattar,[23] D P M Symmons,[24] M T Nurmohamed[25]

RA and CVD risk

Epidemiology & outcomes

- Meta-analysis for RA
  - 14 studies/41.490 patients
  - In RA
    - 48% ⇧ risk of incident CVD
    - 68% ⇧ risk of MI
    - 41% ⇧ CVA



Avina-Zubieta JA et al Ann Rheum Dis 2012

SpA/PsA and CVD risk

- Less evidence compared to RA
  - However…..PsA: worse metabolic profile compared RA
    - Many data derived from psoriasis studies
  - Lack of evidence for newer drugs

Fragoulis et al, Ther Adv M. Dis 2020

PsA

Comparable CVD-burden with DM?

- Study comparing PsA vs RA Vs DM

Table 3. Comparison of comorbidities between psoriatic arthritis, rheumatoid arthritis and diabetes mellitus patients.

Comorbidity	PsA *n* = 215	RA *n* = 215	DM n = 215	PsA *versus* RA		PsA *versus* DM	
				Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Smoking	76 (35.4)	62 (28.8)	85 (39.5)	1.35 (0.90–2.03)		0.84 (0.57–1.24)	
Hyperlipidaemia	101 (47.0)	67 (31.2)	101 (47.0)	1.96 (1.32–2.90)	–	1	–
Hypertension	62 (28.8)	51 (23.8)	97 (45.1)	1.30 (0.84–1.99)	–	0.49 (0.33–0.74)	–
Obesity	50 (29.4)	24 (12.8)	79 (36.7)	2.83 (1.65–4.86)		0.72 (0.47–1.10)	
Coronary disease	10 (4.7)	10 (4.7)	16 (7.4)	1 (0.41–2.45)	1.05 (0.31–3.57)[a]	0.61 (0.27–1.37)	0.66 (0.23–1.91)[a]
Stroke	8 (3.7)	2 (0.9)	7 (3.3)	4.12 (0.86–19.6)	5.06 (0.80–32.1)[a]	1.15 (0.41–3.22)	1.20 (0.35–4.12)[a]
MACEs	12 (5.6)	12 (5.6)	22 (10.2)	1 (0.44–2.28)	1.20 (0.40–3.63)[a]	0.52 (0.25–1.08)	0.42 (0.16–1.10)[a]
Osteoporosis	12 (5.6)	24 (11.2)	2 (0.9)	0.46 (0.21–1.03)	0.67 (0.28–1.64)[b]	6.22 (1.33–29.2)[b]	–
Depression[c]	42 (19.5)	15 (7.0)	12 (5.6)	3.24 (1.74–6.04)	3.02 (1.57–5.81)[d]	4.11 (2.10–8.05)	4.85 (2.37–9.93)[d]
Malignancy	12 (5.6)	7 (3.3)	–	1.76 (0.68–4.55)	1.60 (0.60–4.26)[e]	–	–

Fragoulis Ther Adv M Dis 2021

PsA

Increased CVD risk

- SLR
- ⇧ CVD morbidity and mortality risk
- ⇧ rates of risk factors for CVD
  - (e.g hypertension, overweight)

Table 5 Cardiovascular risk factors in PsA

Cardiovascular risk factor	No of studies	Findings
Dyslipidaemia*	6	Dyslipidaemia was more prevalent in PsA patients than in controls[18 24 26 28–30] • Reduced total cholesterol and HDL-cholesterol levels[26 28 30] • Reduced LDL-cholesterol levels[28 30] • Increased LDL and triglycerides levels[26]
Hypertension	6	Hypertension was more prevalent in PsA patients than in controls[17 18 24 26 28 29]
Obesity or BMI	3	Patients with PsA had higher BMI than controls[24 26 28]
Diabetes mellitus	4	Diabetes mellitus was more prevalent in PsA patients than in controls[18 24 28 29]
Smoking	3	There was no statistical differences between patients and controls.[24 28 29]

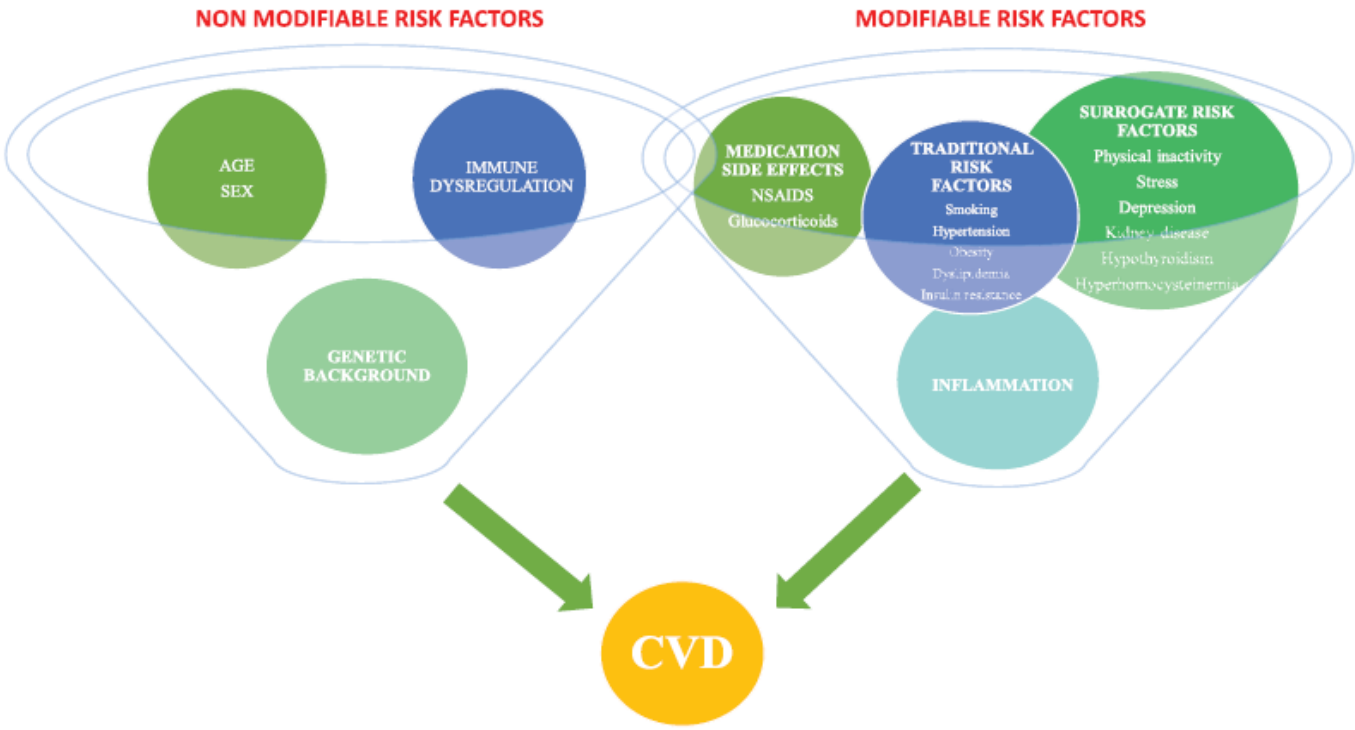
*Dyslipidaemia is defined as abnormalities in lipid profile predisposing to cardiovascular diseases.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PsA, psoriatic arthritis.

Jamnitski et al ARD 2013

CVD risk

Why?

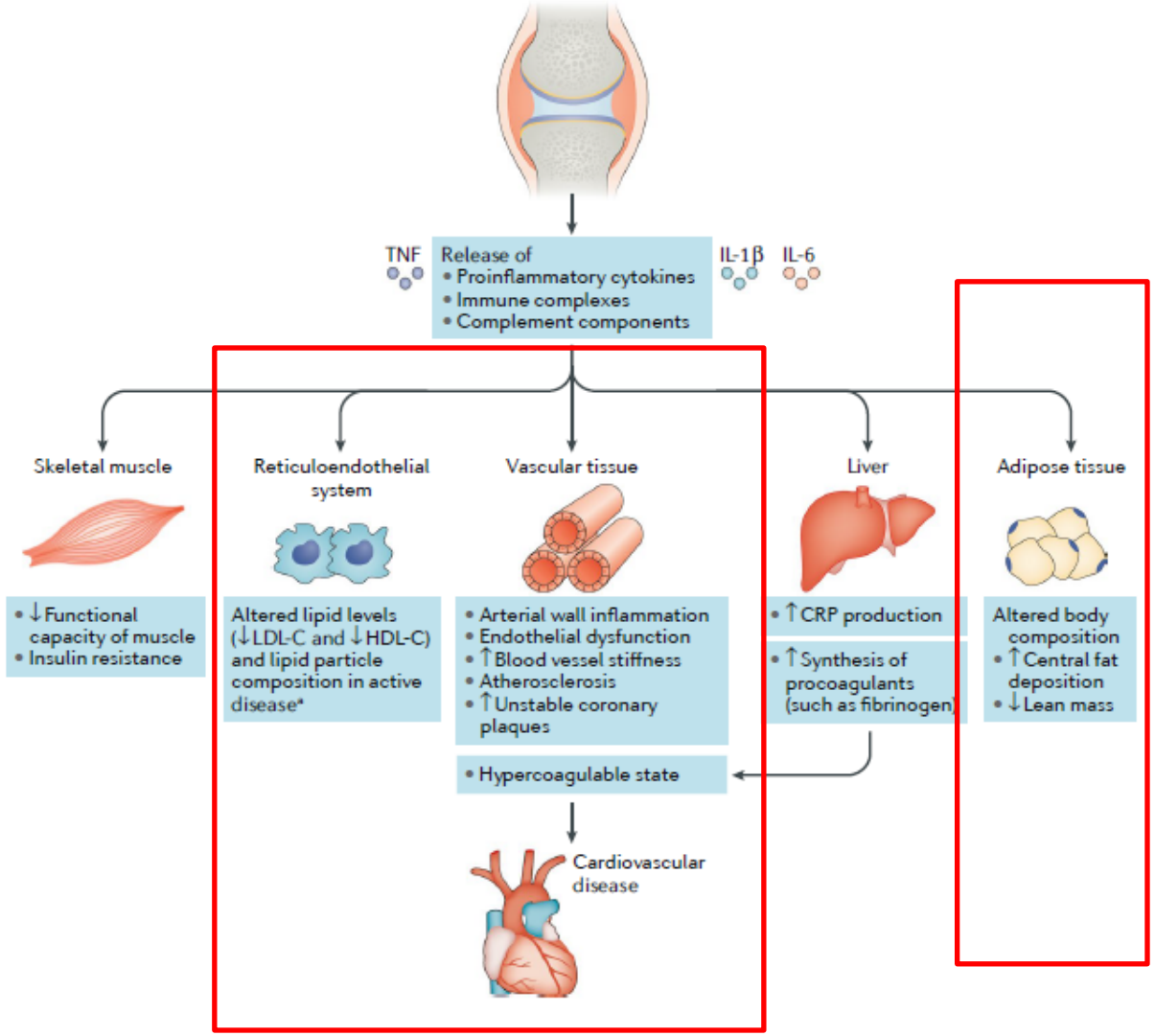
- Traditional risk factors
- Newly identified risk factors
  - **Inflammation**
  - others



Solomon et al Ann Rheum Dis 2010
Zegkos and Kitas Ther Adv M Dis 201

Cytokines and Comorbidities

Cardiovascular risk – the big picture



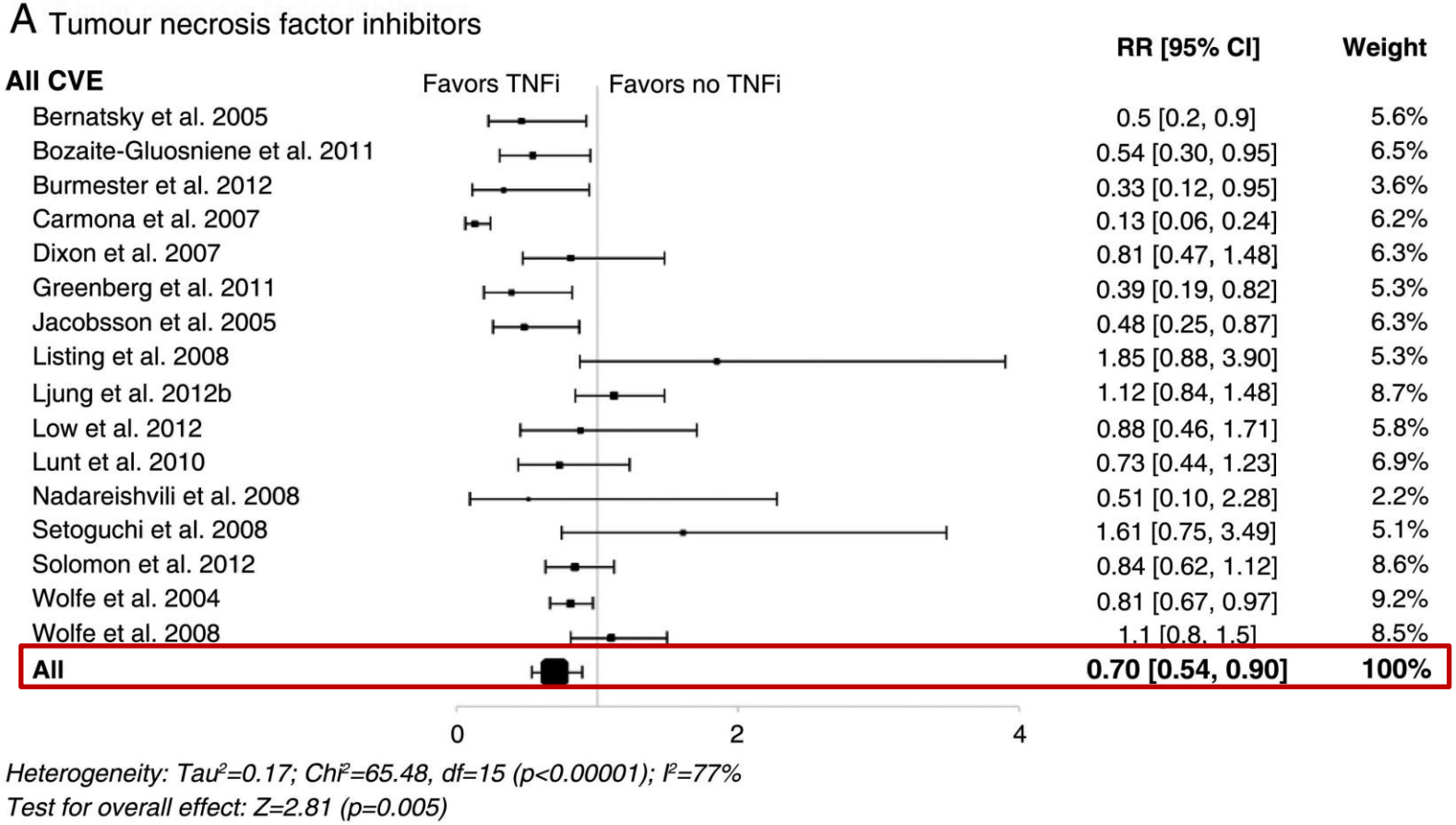
Feguson L et al, Nat Rev Rheum 2019

Any Differential effect of the various bDMARDs in CVD?

RA

RA - TNFi

Meta-analysis

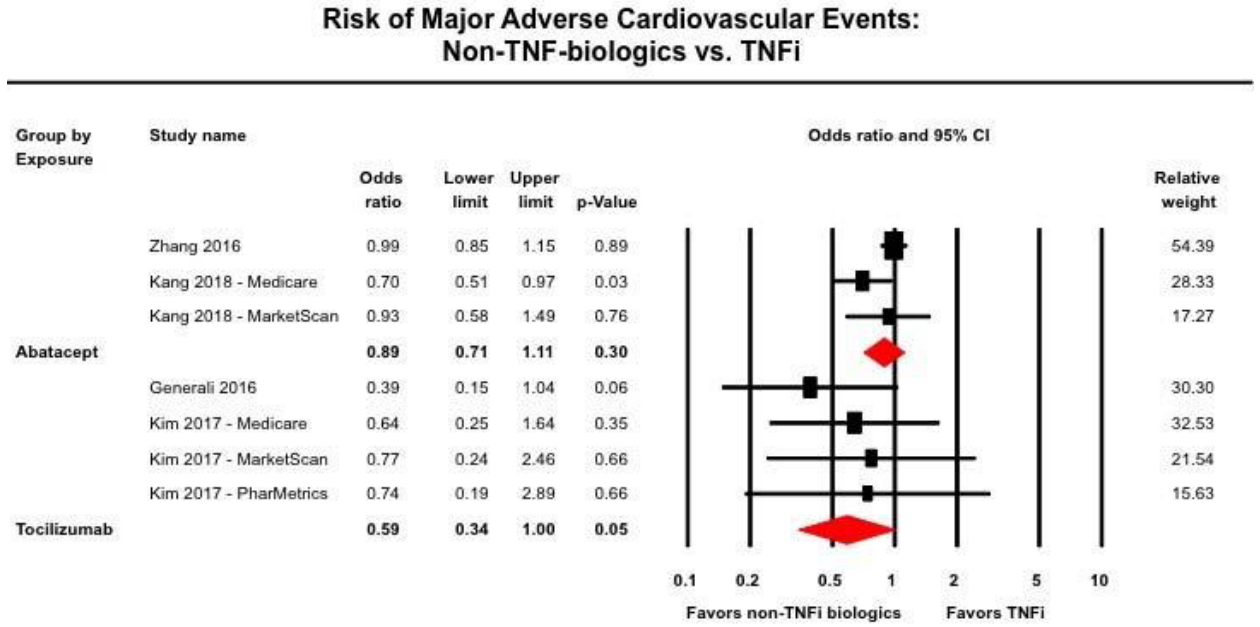


Roubille et al. 2015 ARD

RA - Cardiovascular risk

Treatment – Tocilizumab

- MediCare and Marketscan
  - CVD risk for tocilizumab
    - Similar as abatacept, rituximab and TNF-inhibitors
- SLR and meta-analysis: Tocilizumab ⇩ reduced risk of MACE *Vs* anti-TNF

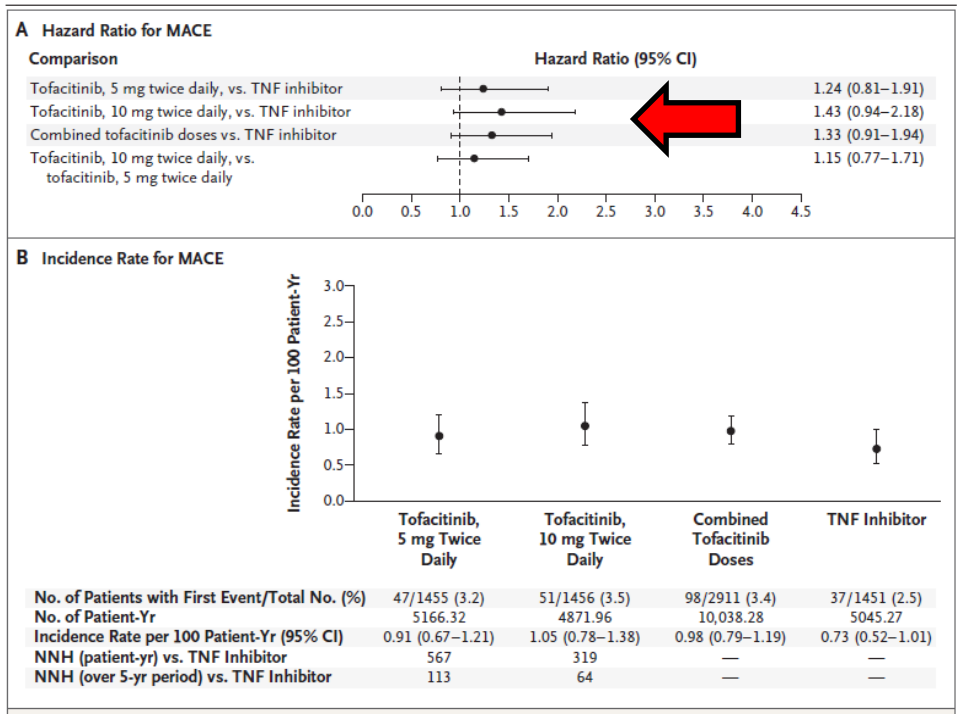


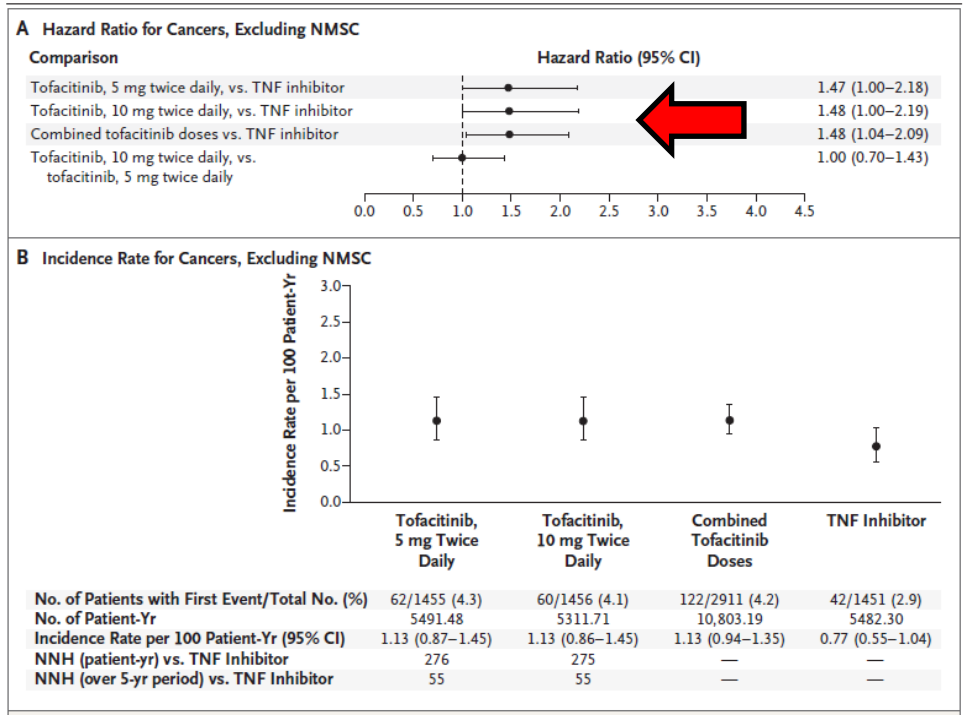
Singh S et al, Arth C Res 2019
Xie F et al, Arth C Res 2019

Oral – surveillance

Tofacitinib and MACE

- 4362 patients, median follow-up: 4 years





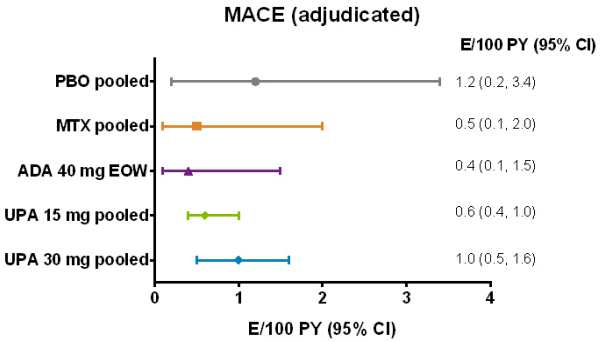
The licensed dose of tofacitinib in RA is 5 mg BID

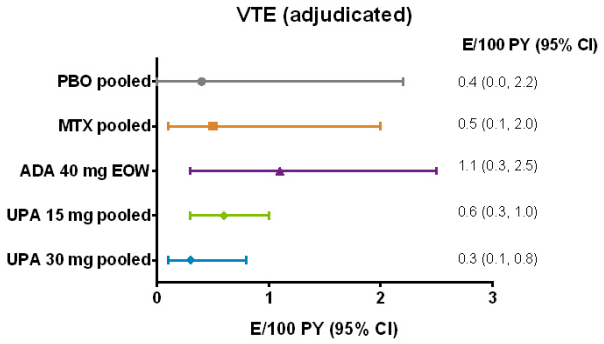
Ytterberg et al NEJM 2022

Other JAKs

Thromboembolic

- Baricitinib
  - Pooled data from 9 RA studies
  - Numerically more VTE observed in patients who received baricitinib 4mg
    - 6/997 patients, all of them having other cardiovascular risk factors) compared to placebo (0/1070 patients)
    - IR of DVT/PE were stable over time
- Upadacitinib
  - Integrated analysis of phase III trials and an FDA review
    - MACE and VTE rates (RA)
      - ✓ Comparable to MTX & Adalimumab
- Need to clarify whether this is a class effect





Taylor et al Arthr Rheumatol 2019
Cohen et al ARD 2021

Other JAKs Thromboembolic…

- Nationwide (Sweden 2010-2021)
  - Initiators of a JAKi, a TNFi, or a non-TNFi bDMARD (n=32.737) Vs
  - General population cohort (1:5) and “overall RA” (n=85 722)
  - Outcome: VTE, DVT, PE
  - 559 VTE events, age and sex-matched IR
    - 5.15/1000py (TNFi)
    - 11.33/1000py JAKi (**Bari, Tofa**)
    - 5.86/1000py overall RA
    - 3.28/1000py in the general population.
  - The fully adjusted HR JAK Vs TNFi
    - 1.73 (1.24 to 2.42) VTE
    - **3.21 (2.11 to 4.88) PE**
    - 0.83 (0.47 to 1.45) DVT

when restricting the study population to mimic that of ORAL surveillance, the VTE incidence generally increased by some 50% but the HR for JAKi versus TNFi remained largely the same as in our overall analysis

Molander et al Ann Rheum Dis 2022

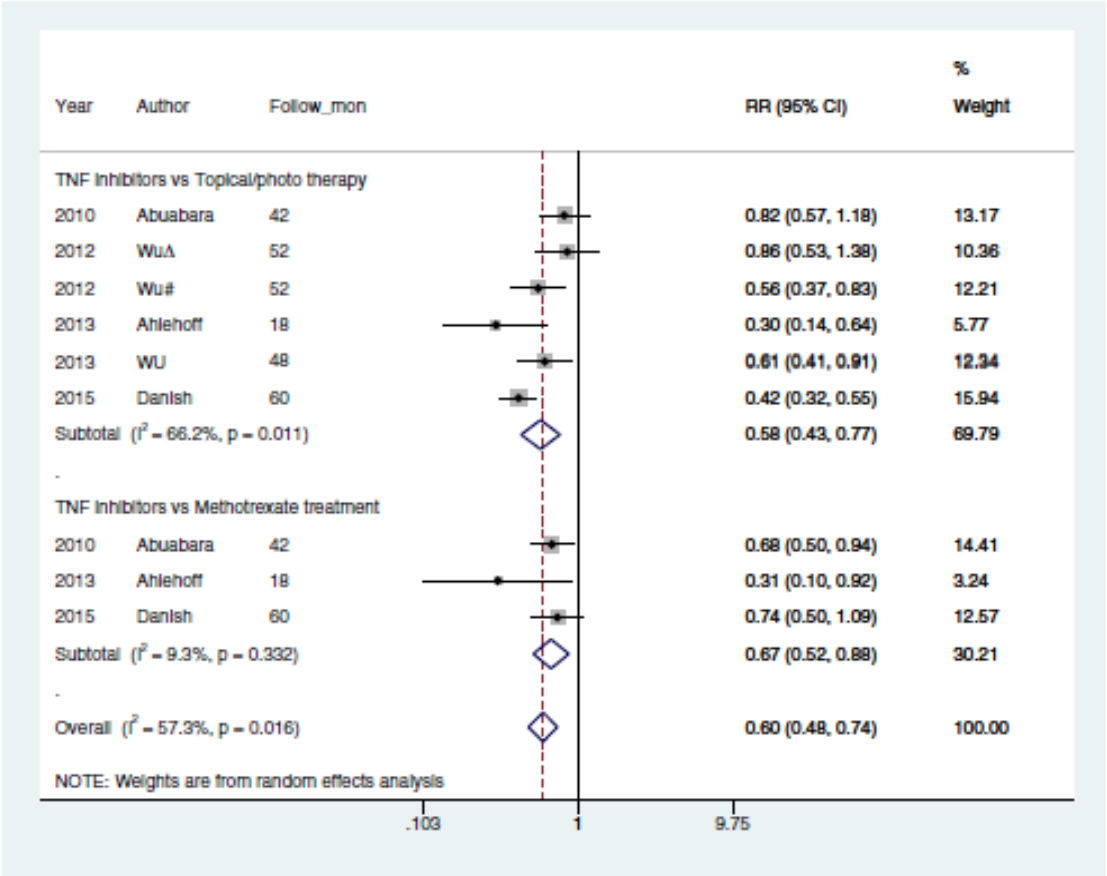
Any Differential effect of the various bDMARDs in CVD?

PsA

PsA (PsO) – TNFi clinical outcomes

- Meta-analysis TNFi Vs topical therapy (psoriasis)
  - ⇩ risk for all CVD
    (RR, 0.58; 95 % CI, 0.43 to 0.77; P < 0.001)
  - ⇩ risk for MI
    (RR, 0.73; 95 % CI, 0.59 to 0.90; P = 0.003)
- Meta-analysis TNFi Vs MTX
  - ⇩ risk risk for CVD
    (RR, 0.67; 95 % CI, 0.52 to 0.88; P = 0.003)
  - ⇩ risk for MI

    (RR, 0.65; 95 % CI, 0.48 to 0.89; P = 0.007)



Yang ZS et al, Clin Rev All Immun 2016
Roubille C et al, ARD 2015
Lee MP et al, JAMA Dermatol 2019

Anti-IL17

Reduces CVD risk?

- 150 psoriasis patients
  - 1:1:1
    - Secukinumab
    - Cyclosporine
    - Methotrexate
  - Examined
    - LV global longitudinal strain, GLS rate (GLSR), GLSR at early diastole, LV twisting, coronary flow reserve, pulse wave velocity and oxidative stress.
- Anti-IL-17 Vs MTX Vs Cyclosporine
  - Better in a greater improvement of vascular and myocardial function

Makavos et al Can J Card 2020

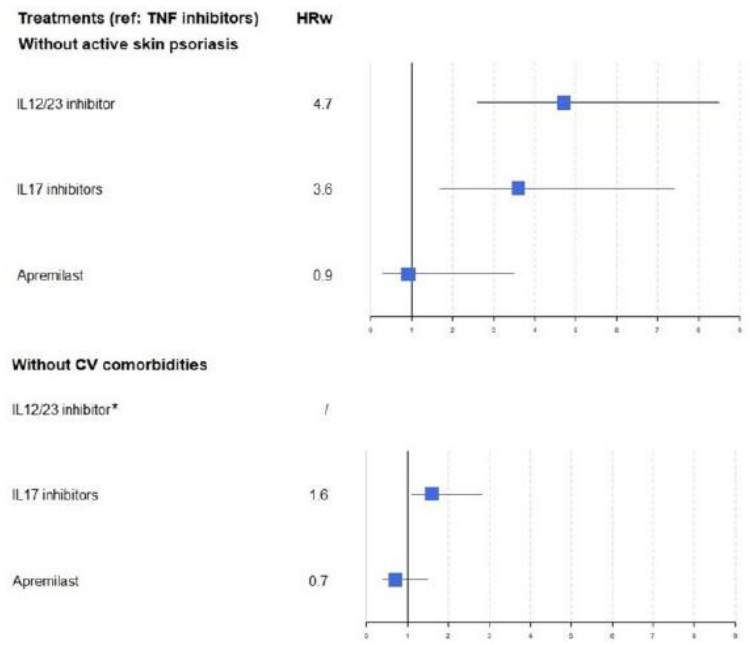
Anti-IL17

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

    (HR: 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



*Not available due to the absence of events in this class. HR_w: weighted hazard ratio; CV: cardiovascular.

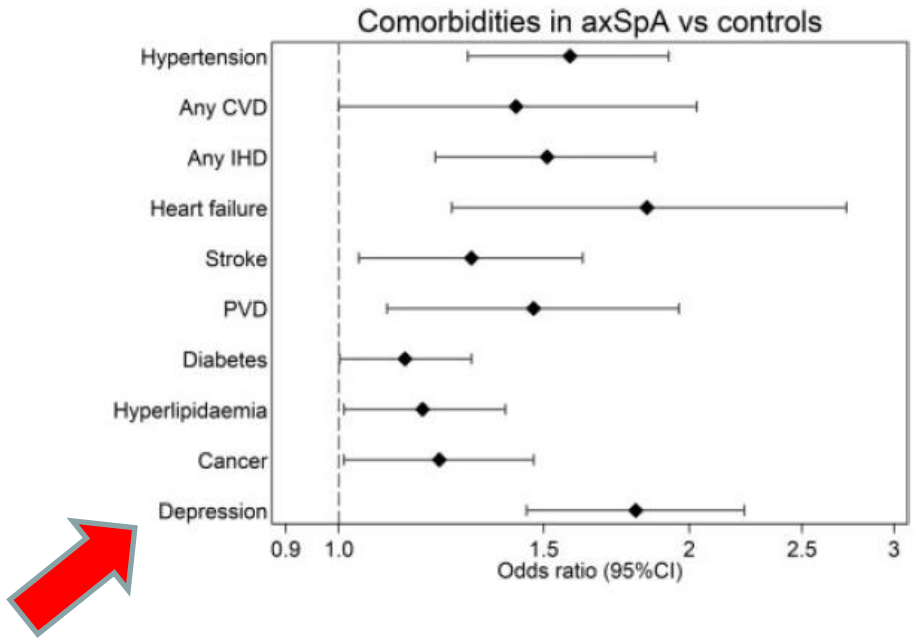
Pina Vegas Rheumatology (Oxf) 2021
Gialouri et al Rheumatology (Oxf) 2021

Outline

- Co-morbidities
  - What are they?
- SpA/PsA specific
- Comorbidities common in RA/PsA
  - Cardiovascular risk
  - Mental health disorders
  - Infections

Depression Epidemiology

- RA (meta-analysis)
  - Depression: 15%
  - Anxiety: 19%
- PSA
  - Depression: 30%
    - ✓ 3-5 higher than RA
    - ✓ 22% higher than general population



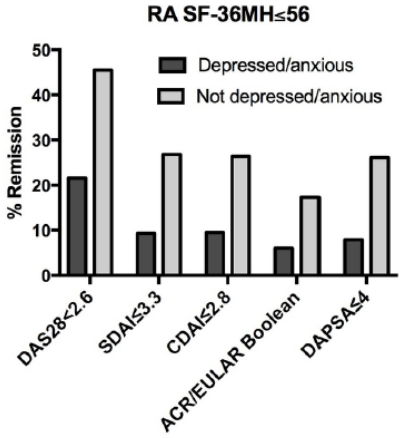
Pooled OR: 1.80

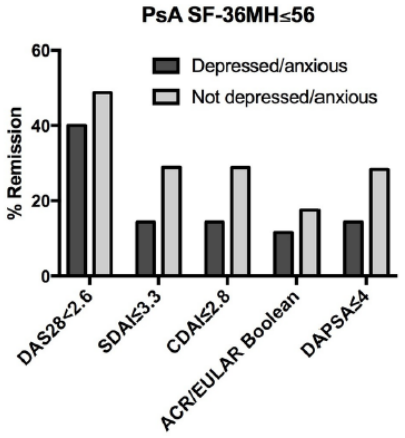
Zhao et al Rheumatology (Oxf) 2020
Panagiotopoulos & Fragoulis (under review)

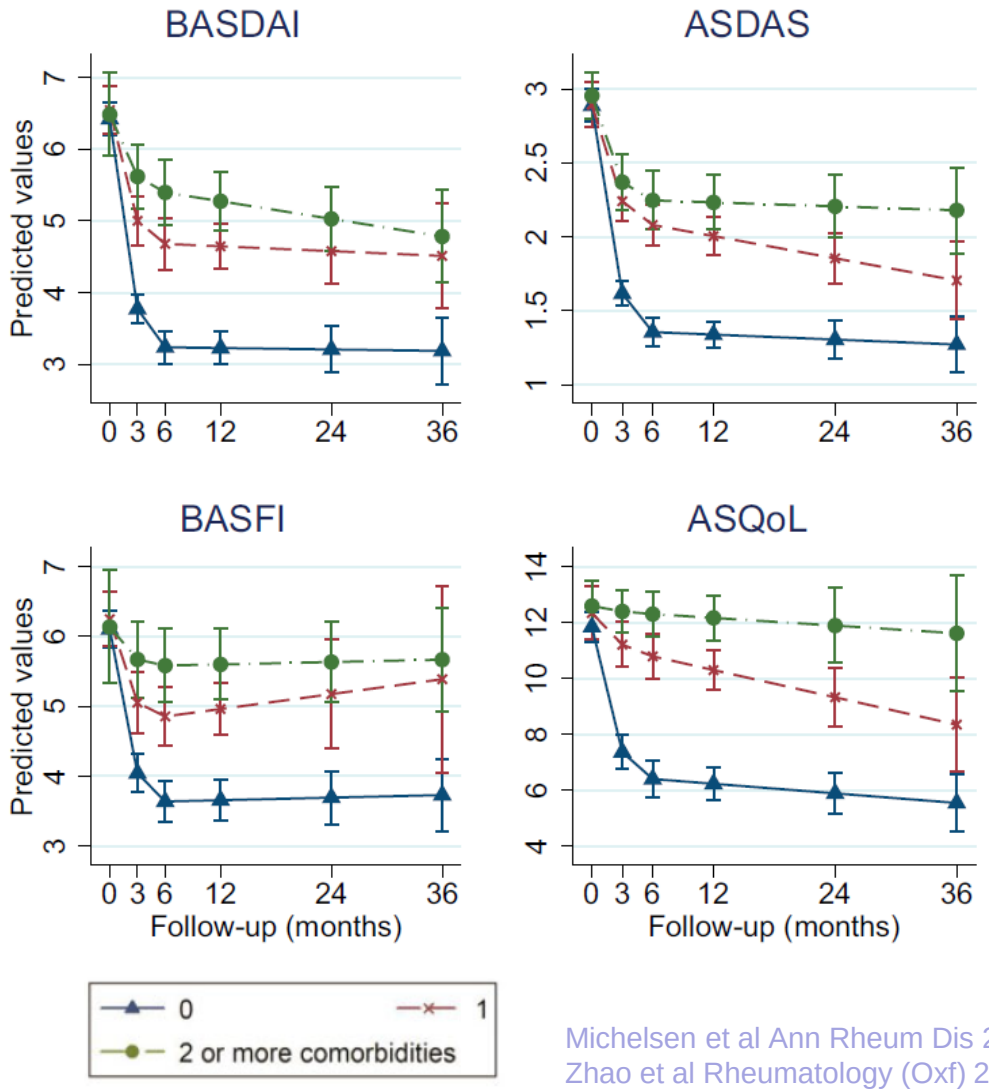
Depression

Why is it important?

- Effect on Treatment
  - Baseline depression and anxiety was associated with adverse outcomes in
  - RA
  - PsA
  - SpA







Michelsen et al Ann Rheum Dis 2017
Zhao et al Rheumatology (Oxf) 2021

bDMARDs

…& anti-depressants

- IDIKA database
  - RA, PsA, SpA who received bDMARDs (8/2016–7/2018)
  - concomitant antidepressant/anxiolytic medication use was documented
- bDMARD introduction OR switching was associated with use of
  - antidepressant [OR: 1.24, 1.15 to 1.35] and [OR: 1.50, 1.37 to 1.6]
  - Anxiolytic [OR: 1.17, 1.09 to 1.26] and [OR: 1.16, 1.07 to 1.26]

*independent of age, gender, underlying disease diagnosis and concomitant glucocorticoid

or csDMARD medication use.

Bournia et al. RMDOpen 2020

Depression & Inflammation
A bidirectional relationship

- In humans
  - Plasma TNF-α correlated significantly with 5-HTT (serotonin transporter-SERT) availability (rho=0.6; p=0.03)
  - Etanercept for 6-8weeks
    - ↓↓ in 5-HTT availability (Z=2.09; p=0.03; r=0.6) consistent with a functional link (SPECT)
    - Similar results after 4 weeks with Adalimumab (in arthritis patients)

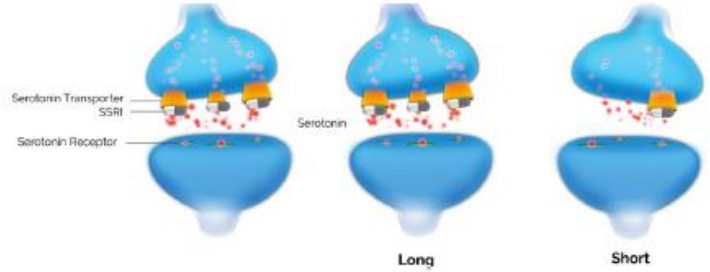
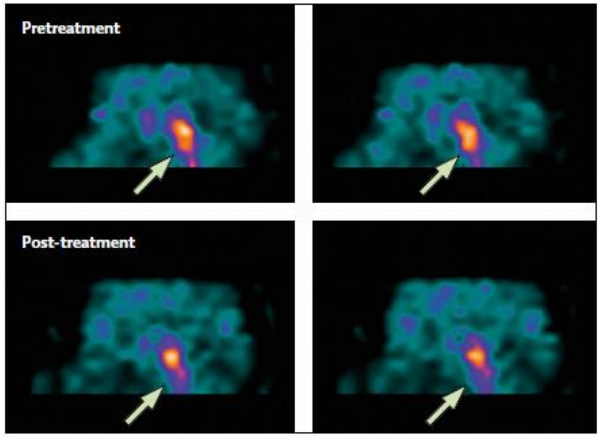


Figure 1: The SLC6A4 5-HTTLPR



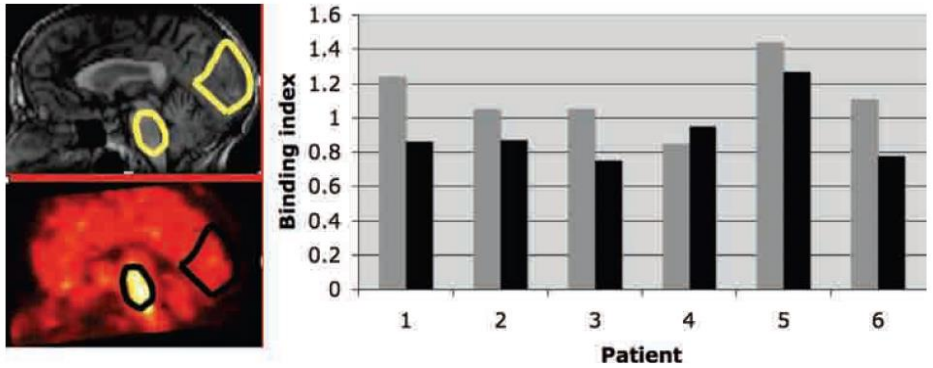
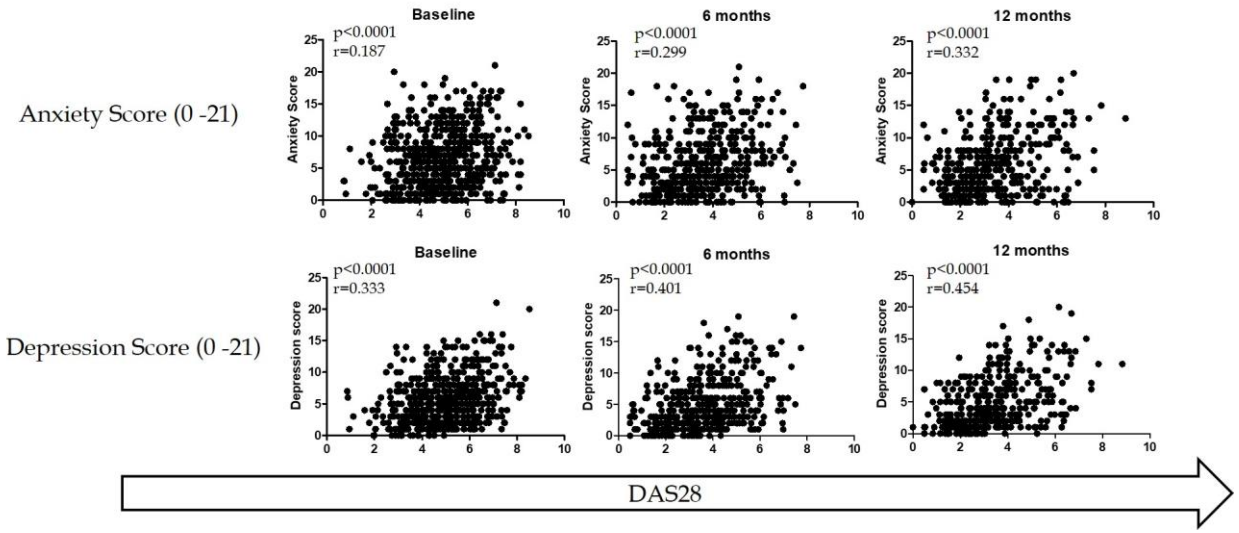


Figure 1 Binding index of β-carbomethoxy-3-β-(4-[^{123}I]iodophenyl)tropane before (grey) and after (black) 4 weeks on adalimumab.

Cavanagh J et al Ann Rheum Dis 2010
Krishnadas R et al, *Brain Behav Immun* 2016

Depression & Inflammation
A bidirectional relationship

- In early RA (n=848)
  - Close association with CRP



In PsA (n=128)

- No association with CRP

Table IV. Correlation of changes between values at first and second visit, in depression and anxiety scores with respective changes in disease activity parameters.

Variable	Depression score		Anxiety score	
	r	*p*-value	r	*p*-value
ESR	0.18	0.132	0.1	0.42
CRP	0.127	0.225	-0.083	0.34
TJC	0.204	**0.049**	-0.044	0.68
SJC	0.1	0.35	-0.038	0.72
PtG	0.236	**0.023**	-0.006	0.95
PtP	0.266	**0.01**	-0.089	0.34
DAPSA	0.286	**0.005**	-0.035	0.74

Gialouri CG et al Clin Exp Rheum 202
Fragoulis GE et al RMD Open 2020

Any Differential effect of the various bDMARDs in Mental health disorders?

PsA

Depression in SpA
any drugs differential effect?

- Brodalumab
  - pooled safety data from 5 phase 2/3 trials of in PSO (8.891 patient-years)
    - absence of association with suicidal ideation – behavior
    - NO Increased depression and anxiety

Suicidal ideation and behaviour

Suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with brodalumab. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with brodalumab and increased risk of suicidal ideation and behaviour has not been established.

The risk and benefit of treatment with brodalumab should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment.

- Apremilast
  - A pooled safety analysis of three Phase 3 RCTs
    - Rates of depression remained low in apremilast users

Psychiatric disorders

Apremilast is associated with an increased risk of psychiatric disorders such as insomnia and depression. Instances of suicidal ideation and behaviour, including suicide, have been observed in patients with or without history of depression (see section 4.8). The risks and benefits of starting or continuing treatment with apremilast should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended. Patients and caregivers should be instructed to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation. If patients suffered from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue treatment with apremilast.

Reich et al Acta Derm Venereol 2020
Panagiotopoulos &Fragoulis (under review)
Mease et al ACROpen 2020

Depression in PsA
any data? (Apremilast)

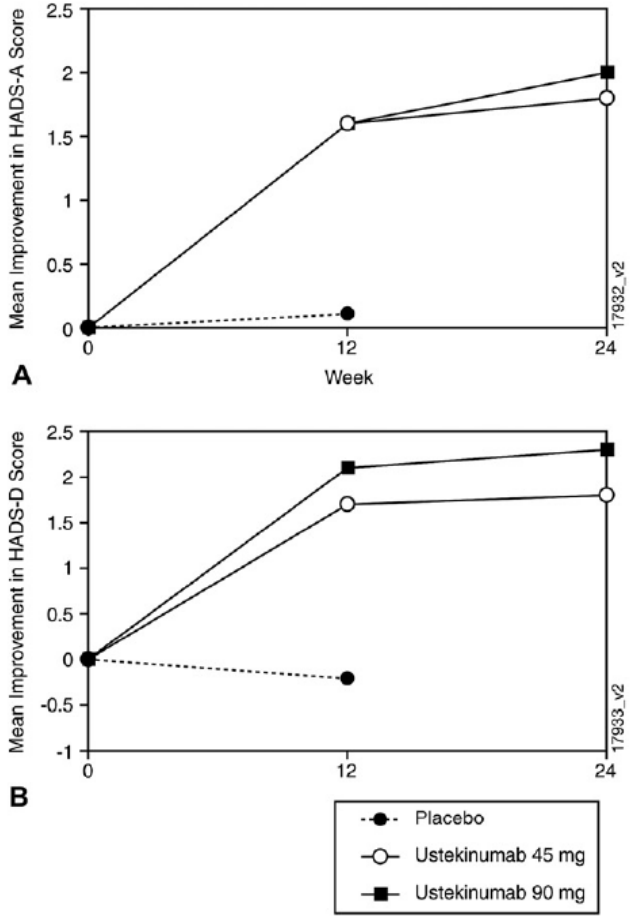
- US Marketscan [PsO (31.274) or PsA (30.426)]
  - To estimate risk for anxiety and depression (code + prescription)

  Apremilast Vs other bDMARDs
- IRs for each outcome were similar between exposure categories
- PsA cohort
  - ⇧⇧ Anxiety among users of apremilast
  - Depression: similar

C. Vasilakis-Scaramozza et al JEADV 2020

Depression in PsA
any data? (Ustekinumab)

- Ustekinumab
- Psoriasis (n = 1230, 1:1:1) 45 mg, 90 mg ustekinumab, PBO
  - Depression: 26.7%
  - Anxiety: 40.3%
- UST Vs Placebo: ⇧ improvement @w12 in
  - Mean HAD-depression (13.9%)
  - Mean HAD-anxiety (29.3%)
  - Association between anxiety/depression improvement and PASI (r = 0.24; P<.0001) and (r = 0.32; P <.0001)



Langley et al J Am Acad Dermatol 201(

Depression in SpA
any drugs differential effect?

- Few data
  - TNF-inhibitors
    - Conflicting data from meta-analyses
      - ✓ Studies specifically examining this issue are lacking
  - IL-17-inhibitors, JAK-inhibitors
    - No data yet….but an emerging field of research

Lemos et al Rheum Int 2014
Panagiotopoulos & Fragoulis (under revie

Outline

- Co-morbidities
  - What are they?
- SpA/PsA specific
- Comorbidities common in RA/PsA
  - Cardiovascular risk
  - Mental health disorders
  - Infections

Dey et al Rheumatology (Oxf) 2022

bDMARDs

Infections (Tuberculosis)

Are IL-17 better??

Table 6. Comparative presentation of active tuberculosis (TB) incidence rates (IR) between different biologic and targeted synthetic DMARDs.

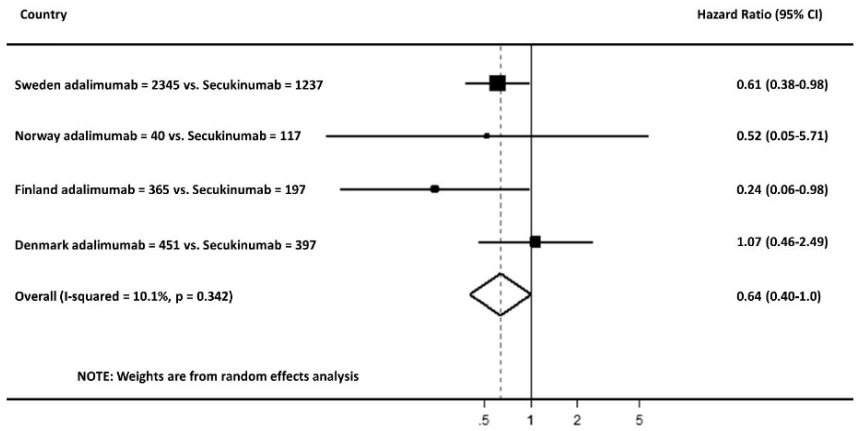
Drug	Disease	Study type	IR§	Reference
Infliximab	RA, AS, PsA, PsO, CD, UC	LTE, RLS	52.5–2558.0	Askling *et al.*[2]; Seong *et al.*[6]; Wolfe *et al.*[8]; Dixon *et al.*[9]; Gomez-Reino *et al.*[10]; Souto *et al.*[27]; Tubach *et al.*[28]
Certolizumab	RA	LTE	474.29	Souto *et al.*[27]
Adalimumab	RA, AS, PsA, PsO, CD, UC	LTE, RLS	90.0–215.0	Dixon *et al.*[9]; Souto *et al.*[27]; Tubach *et al.*[28]
Golimumab	RA, AS, PsA	LTE	172.13	Souto *et al.*[27]
Etanercept	RA, AS, PsA, PsO	RLS, LTE	9.3–80.0	Askling *et al.*[2]; Dixon *et al.*[9]; Souto *et al.*[27]; Tubach *et al.*[28]
Apremilast	PsA, PsO	RCT, LTE, RLS	0.0	Cutolo *et al.*[35]; Edwards *et al.*[36]; Kavanaugh *et al.*[37]; Wells *et al.*[38]; Crowley *et al.*[39]; Abignano *et al.*[40]; Favalli *et al.*[41]
Tofacitinib	RA	RCT, LTE	200.0–210.0	Winthrop *et al.*[47]; Cohen *et al.*[49]
Baricitinib	RA	RCT, LTE	150.0–230.0	Smolen *et al.*[56]; Chen *et al.*[57]
Ustekinumab	PsA, PsO, CD	RCT, LTE, RLS	0.0–22.12	Ghosh *et al.*[76]; Lopez-Ferrer *et al.*[77]; Tsai *et al.*[78]; Hsiao *et al.*[79]
Secukinumab	AS, PsA, PsO	RCT, LTE	0.0–5.0	Deodhar *et al.*[95]; van de Kerkhof *et al.*[96]
Ixekizumab	PsA, PsO	RCT	0.0	Mease *et al.*[98]; Romiti *et al.*[99]

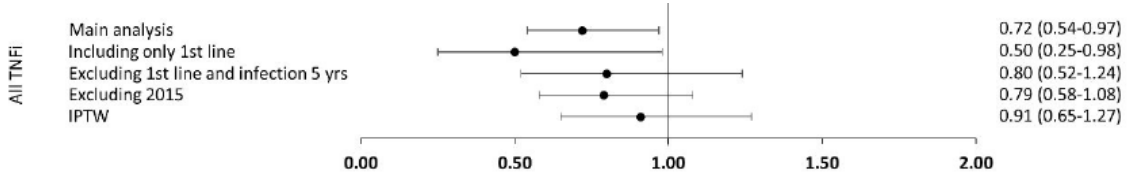
Evangelatos G et al TAMD 2020

bDMARDs

Serious Infections

- 4 Nordic registries (2015-2018)
- SpA (n=7708) and PsA (n=5760)
  - starting secukinumab or TNFi
  - First-year risk of hospitalized infection was
    - SEC: 3.5% (IR 5.0; 3.9-6.3)
    - ADA: 1.7% (IR 2.3; 1.7-3.0)
    - Other TNFi: similar to ADA
- This excess risk seemed largely explained by confounding by indication





Glintborg et al. Rheumatology 2022

bDMARDs

Serious Infections

- Insurance Data - USA (PsA & PSO)
  - 11.560 new treatment episodes with 190 serious infections (9264 person-years)
  - Class-specific IRs
    - Similar among IL-17 and TNF, yet significantly lower for IL-12/23
  - In biologic-experienced individuals
    - no difference in infection risk across TNF, IL-17 or IL-12/23 inhibitors.

	Unadjusted	Adjusted for propensity score and imbalanced covariates
Total cohort		
IL-17 vs TNF	0.86 (0.58 to 1.27)	0.89 (0.48 to 1.66)
IL-12/23 vs TNF	0.55 (0.37 to 0.80)	0.59 (0.39 to 0.90)
IL-17 vs IL-12/23	1.53 (0.94 to 2.51)	1.12 (0.62 to 2.03)
Biologic-naive		
IL-17 vs TNF	1.45 (0.70 to 3.00)	2.02 (0.94 to 4.33)
IL-12/23 vs TNF	0.41 (0.22 to 0.76)	0.46 (0.23 to 0.89)
IL-17 vs IL-12/23	3.63 (1.44 to 9.12)	3.34 (1.10 to 10.12)
Biologic experienced		
IL-17 vs TNF	0.68 (0.42 to 1.12)	0.72 (0.40 to 1.32)
IL-12/23 vs TNF	0.62 (0.37 to 1.04)	0.72 (0.42 to 1.26)
IL-17 vs IL-12/23	1.05 (0.59 to 1.90)	0.92 (0.49 to 1.74)

Li et al. Ann Rheum Dis 2020

Take home messages

- Co-morbidities
  - Broad term that could include many different conditions
- CVD: common and preventable in IA
- Mental-health: relatively common especially in PsA
  - Could affect outcomes
  - Should be considered
- Differential effect of bDMARDs in these conditions
  - Research still needed

Thank you a lot for your attention ☺

https://spondyloarthritis.gr/