ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΑΣΦΑΛΕΙΑ ΜΕ JAK inhibitors

ΔΗΜΗΤΡΟΥΛΑΣ ΘΕΟΔΩΡΟΣ

Δ’ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΑΠΘ

Disclosures and Acknowledgments

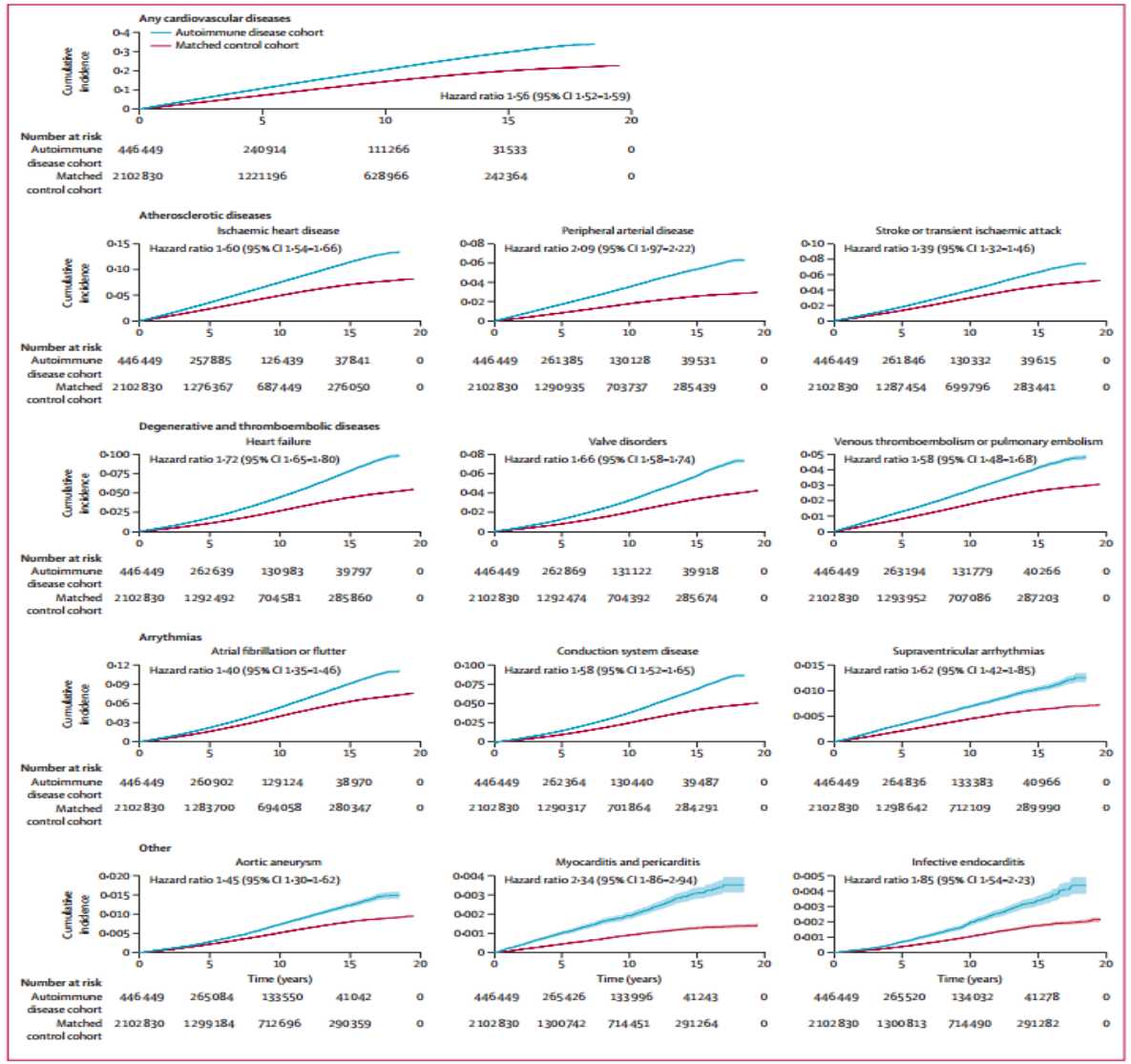
Current presentation: **No conflict**

THE LANCET

Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK

Nathalie Conrad, Geert Verbeke, Geert Molenberghs, Laura Goetschalckx, Thomas Callender, Geraldine Cambridge, Justin C Mason, Kazem Rahimi, John J V McMurray, Jan Y Verbakel

	Cohort		Events		Hazard ratio (95% CI)
	Autoimmune disease	Matched controls	Autoimmune disease	Matched controls	
Any autoimmune disease	446449	2102830	68413	231410	1·56 (1·52–1·59)
Number of autoimmune diseases					
1	404547	1902682	55301	198769	1·41 (1·37–1·45)
2	37226	177676	11005	28570	2·63 (2·49–2·78)
≥3	4676	22472	2107	4071	3·79 (3·36–4·27)
Connective tissue diseases	160217	761918	36846	118391	1·68 (1·63–1·74)
Ankylosing spondylitis	9864	46121	1423	3822	1·97 (1·65–2·35)
Polymyalgia rheumatica	48102	231802	15390	55870	1·47 (1·40–1·54)
Rheumatoid arthritis	66796	318456	15520	46594	1·83 (1·74–1·92)
Sjögren's syndrome	9933	47330	2327	6139	2·08 (1·81–2·39)
Systemic lupus erythematosus	10483	49402	2204	4227	2·82 (2·38–3·33)
Systemic sclerosis	2159	10310	752	1320	3·59 (2·81–4·59)
Vasculitis	37940	178494	7839	22658	1·87 (1·73–2·01)
Organ-specific diseases	407078	1909992	53706	175205	1·60 (1·56–1·64)
Addison's disease	2548	12055	604	1218	2·83 (1·96–4·09)
Coeliac disease	24895	115692	2507	8618	1·50 (1·33–1·69)
Type 1 diabetes	50264	235540	9697	23568	2·36 (2·21–2·52)
Inflammatory bowel disease	49214	230236	6470	19532	1·71 (1·59–1·85)
Graves' disease	44001	207508	6409	20535	1·61 (1·49–1·74)
Hashimoto's thyroiditis	7630	35650	822	2364	1·76 (1·41–2·19)
Multiple sclerosis	12006	56523	1356	3876	1·85 (1·56–2·20)
Myasthenia gravis	2171	10319	544	1812	1·61 (1·21–2·15)
Pernicious anaemia	32910	156887	8228	27099	1·61 (1·50–1·73)
Psoriasis	185178	869184	21197	73465	1·47 (1·41–1·53)
Primary biliary cirrhosis	4612	21973	1086	3060	2·00 (1·66–2·41)
Vitiligo	23709	109914	1791	6526	1·38 (1·19–1·60)

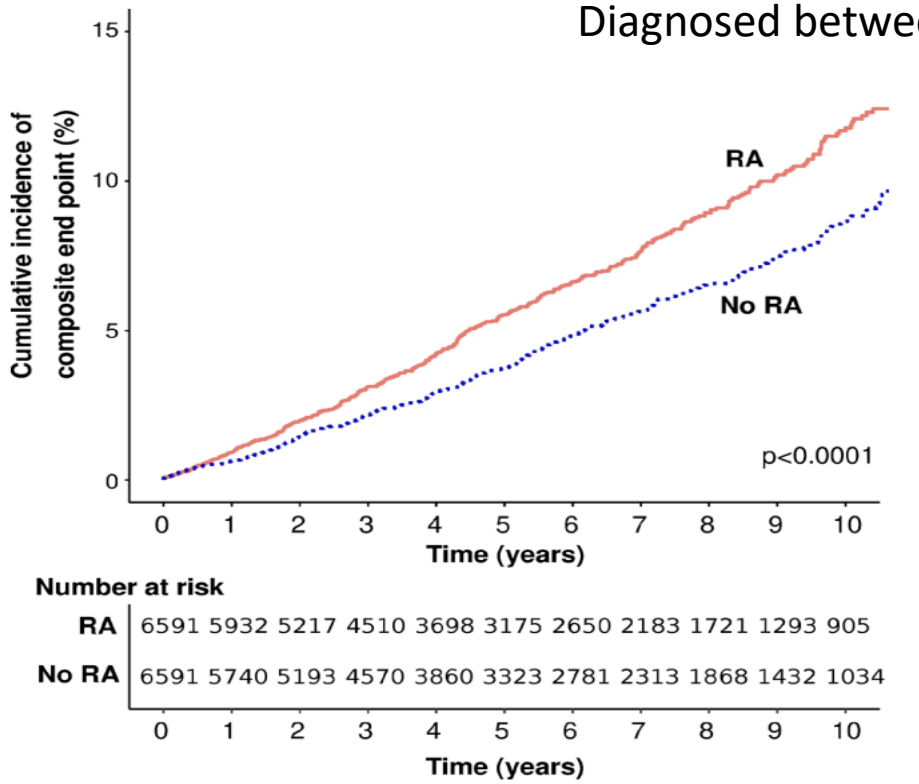


Conrad N et al, Lancet 2022

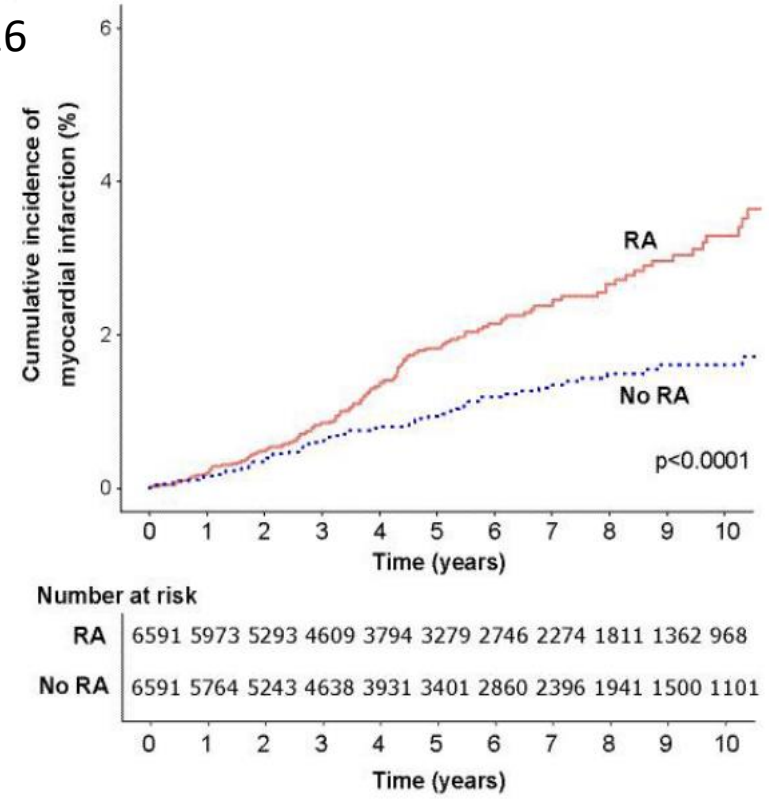
BMJ Journals
Heart

Cardiovascular risk factors and outcomes in early rheumatoid arthritis: a population-based study

Diagnosed between 2004 and 2016



Cumulative incidence of the composite endpoint (myocardial infarction, stroke or heart failure) in people with rheumatoid arthritis (RA) and matched controls without RA.



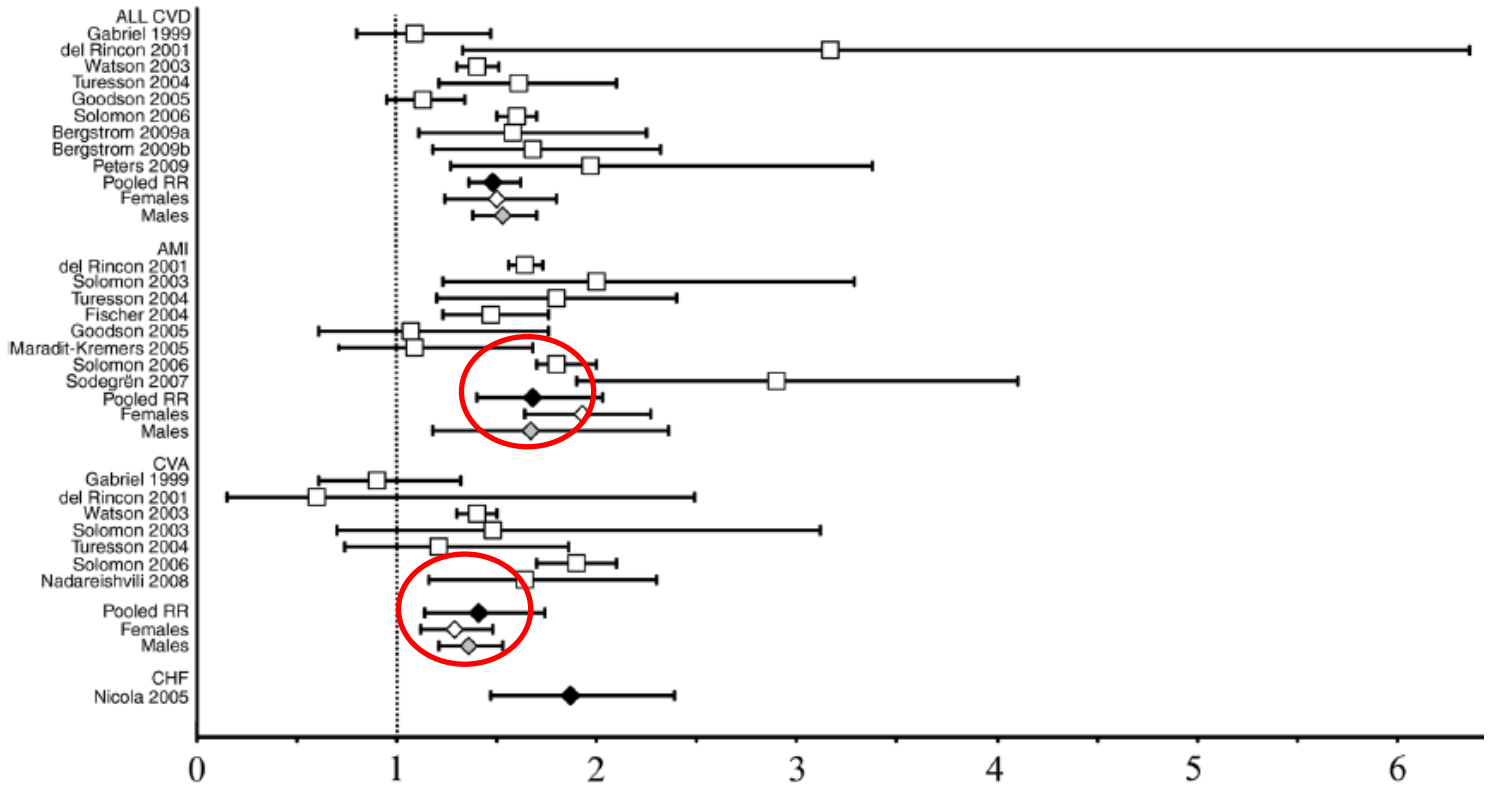
Cumulative incidence of myocardial infarction in people with rheumatoid arthritis (RA) and matched controls without RA.

Nikiphorou E, et al. *Heart*. 2020;106(20):1566-1572.

RA and CVD risk
Epidemiology & outcomes

The risk of incident CVD is increased by 48% in patients with RA compared to the general population

- Meta-analysis for RA
  - 14 studies comprising 41 490 patients
  - 48% ⇧ risk of incident CVD in RA (RR 1.48 (95% CI 1.36 to 1.62)
  - 68% ⇧ risk of MI and 41% CVA
  - CHF risk was assessed in only one study (RR 1.87 (95% CI 1.47 to 2.39)

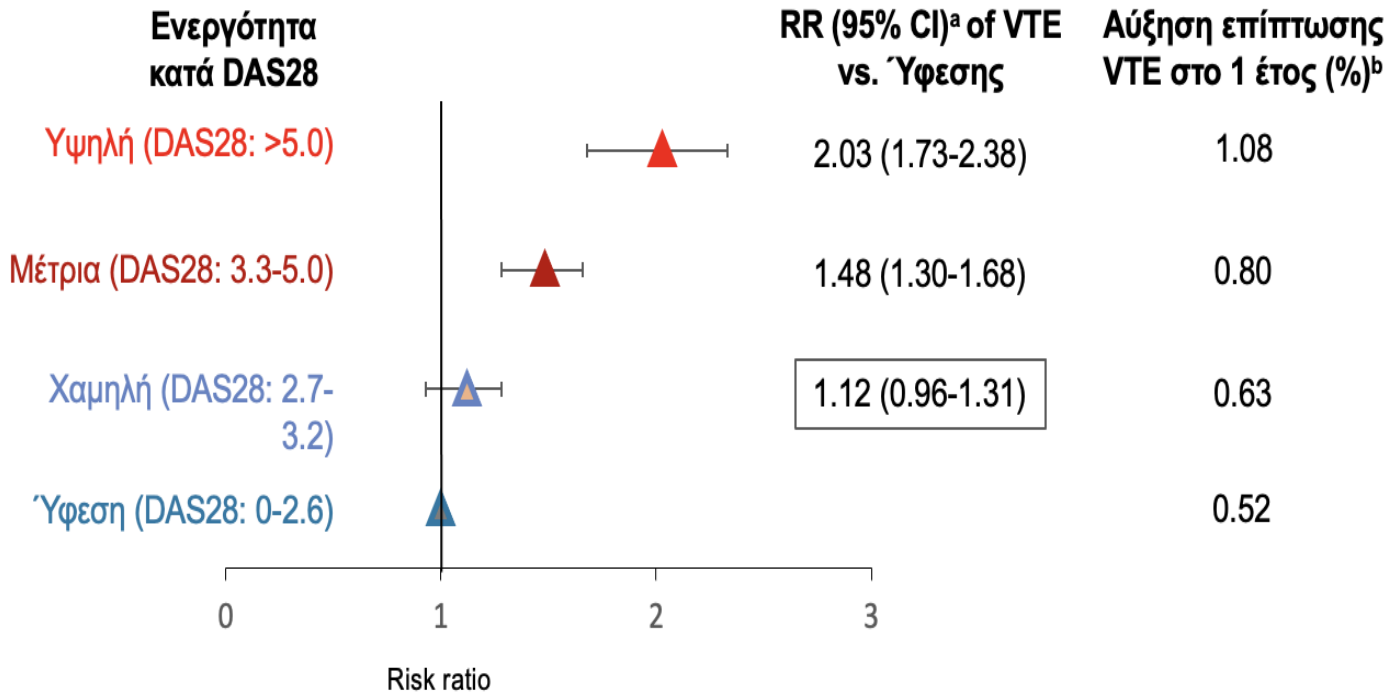


Avina-Zubieta JA et al Ann Rheum Dis 2012

Risk of VTE and disease activity score in RA (DAS28)

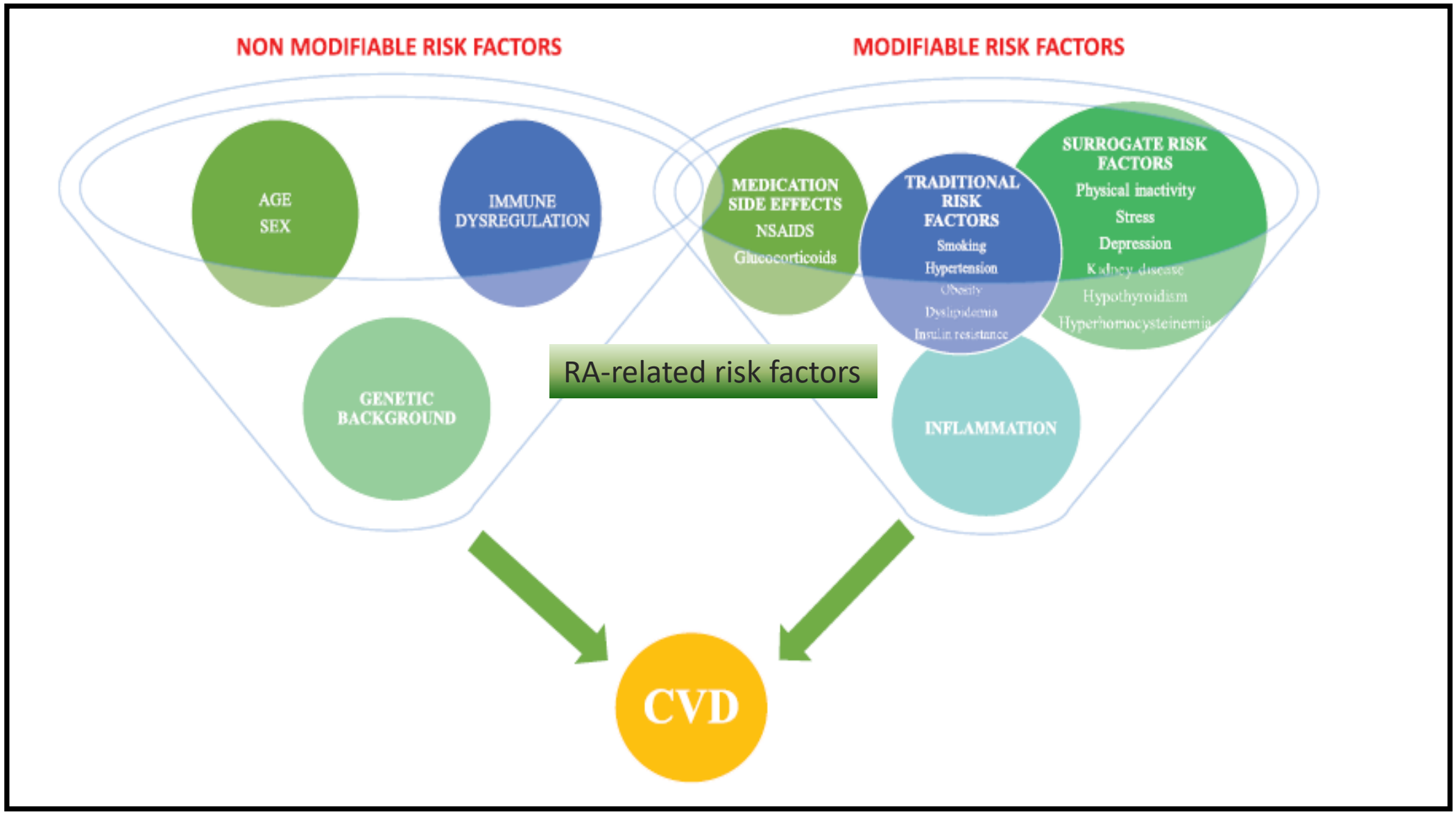
Data from the Swedish Rheumatology Quality Register

A nationwide register-based cohort study 2006 through 2018 using the Swedish Rheumatology Quality Register (46 316 patients, 322 601 visits)
–
2257 incidents VTE (1391 DVT and 866PE) in RA VS 5301 VTE events in the general population cohort, the risk ratio for VTE in RA was 1.88 (95% CI 1.65 to 2.15).



[a]Adjusted for age (restricted cubic spine), sex, and calendar year of the visit year. [b]Absolute risk calculated from observed data.

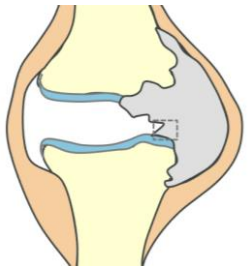
Molander V, et al. Ann Rheum Dis. 2021;80:169–175



Zegkos et al, Ther Adv Musculoskelet Dis 2016

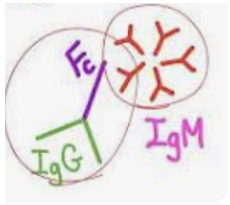
RA poor prognostic factors contribute to overall increased CVD

Data from a combination of 13 cohorts from patients with RA from 10 countries 5638 patients mean follow-up 5,8 years



Disease activity DAS> 3,2

Accounts for 13% of the risk



Seropositivity

Accounts for 12 % of the risk

ESR and CRP

Each account for about 5% of the risk

Up to 30% of CVD risk in RA patients is attributed to RA-related characteristics

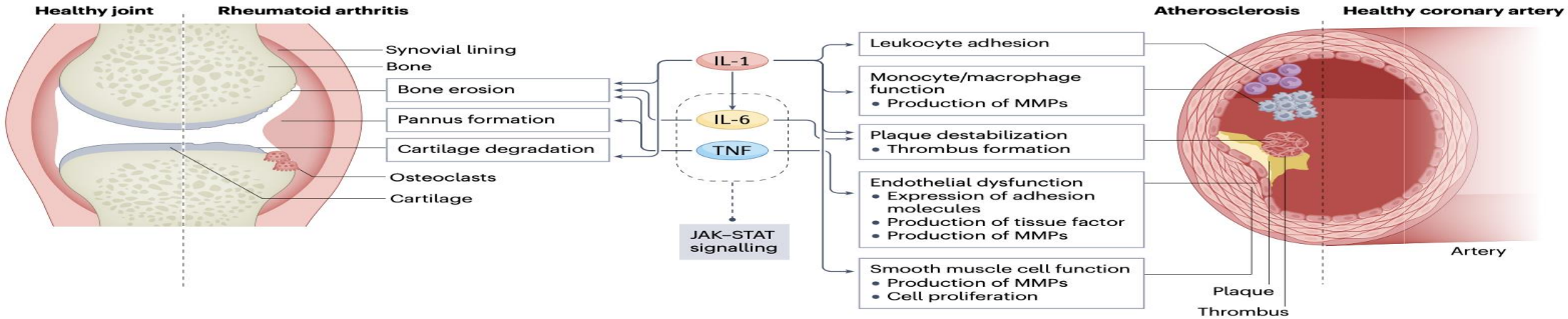
Effective disease control is fundamental for the reduction of CV risk

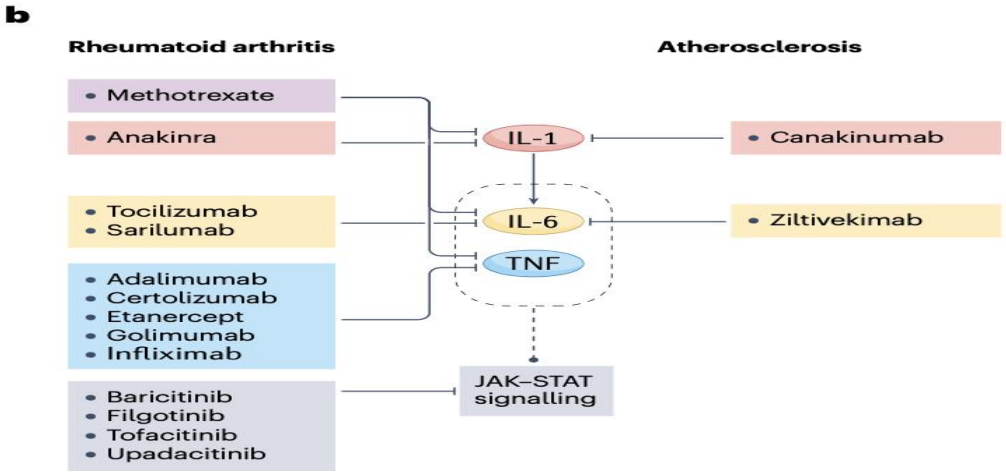
Cynthia S Crowson et al, Ann Rheum Dis 2018

nature REVIEWS RHEUMATOLOGY

Shared inflammatory pathways of rheumatoid arthritis and atherosclerotic cardiovascular disease

Brittany N. Weber[1], Jon T. Giles[2] & Katherine P. Liao[3,4]

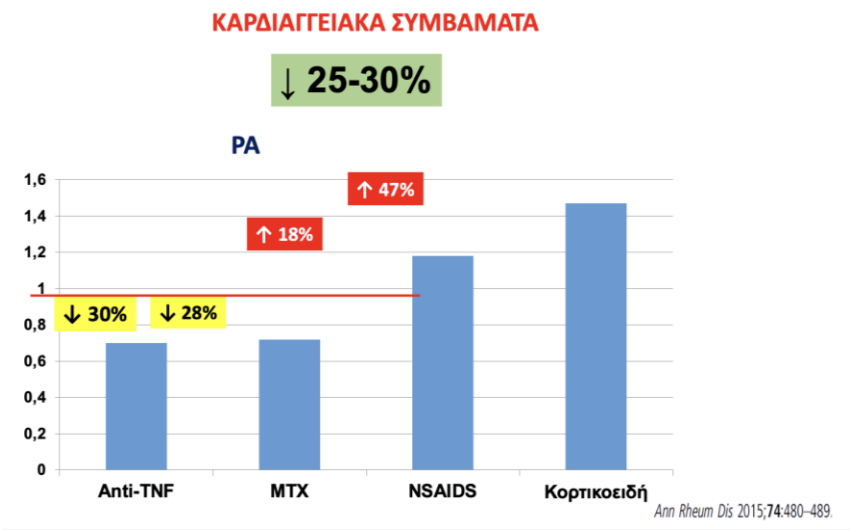




Waber B et al, Nat Rev Rheumatol 2023

The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis

Camille Roubille,[1] Vincent Richer,[2] Tara Starnino,[3] Collette McCourt,[4] Alexandra McFarlane,[5] Patrick Fleming,[6] Stephanie Siu,[7] John Kraft,[8] Charles Lynde,[8] Janet Pope,[7] Wayne Gulliver,[9] Stephanie Keeling,[5] Jan Dutz,[4] Louis Bessette,[10] Robert Bissonnette,[11] Boulos Haraoui[12]



Ann Rheum Dis 2015;17:480-489

Relationship between exposure to tumour necrosis factor inhibitor therapy and incidence and severity of myocardial infarction in patients with rheumatoid arthritis

Audrey S L Low,[1] Deborah P M Symmons,[1,2] Mark Lunt,[1] Louise K Mercer,[1] Chris P Gale,[3,4] Kath D Watson,[1] William G Dixon,[1] Kimme L Hyrich,[1] on behalf of the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) and the BSRBR Control Centre Consortium

Table 2 Risk of MI compared between sDMARD and TNFi cohorts

	sDMARD; n=3058	TNFi; n=11 200
Median duration of follow-up per patient, years (IQR)	3.5 (1.8, 4.9)	5.3 (3.6, 6.4)
Total person-years of exposure, pyrs	10 337	55 636
Primary drug exposure model: on-TNFi+90 days		
Number of verified first MIs	58	194
Crude incidence rate of verified first MI per 10 000 pyrs (95% CI)	56 (43 to 73)	35 (30 to 40)
Unadjusted HR (95% CI)	Referent	0.78 (0.58 to 1.05)
HR adjusted for age and gender (95% CI)		1.19 (0.89 to 1.59)
HR after adjusting for PD* (95% CI)		0.61 (0.41 to 0.89)
Sensitivity analyses		
In subjects ever exposed to TNFi; PD-adjusted HR (95% CI)		0.67 (0.46 to 0.96)
Trimming the PD at 5%; PD-adjusted HR (95% CI)		0.56 (0.34 to 0.93)

*Deciles of propensity score (PD). The PD included age, gender, DAS28, disease duration, health assessment questionnaire score, whether the patients used four or more sDMARDs prior to study registration (yes/no), whether the patients were recruited to the register before or after 30 June 2004, hypertension, diabetes, chronic lung disease, smoking (ever/never), antiplatelet therapy, NSAID/COX-2 inhibitor use, glucocorticoid use and statin use.

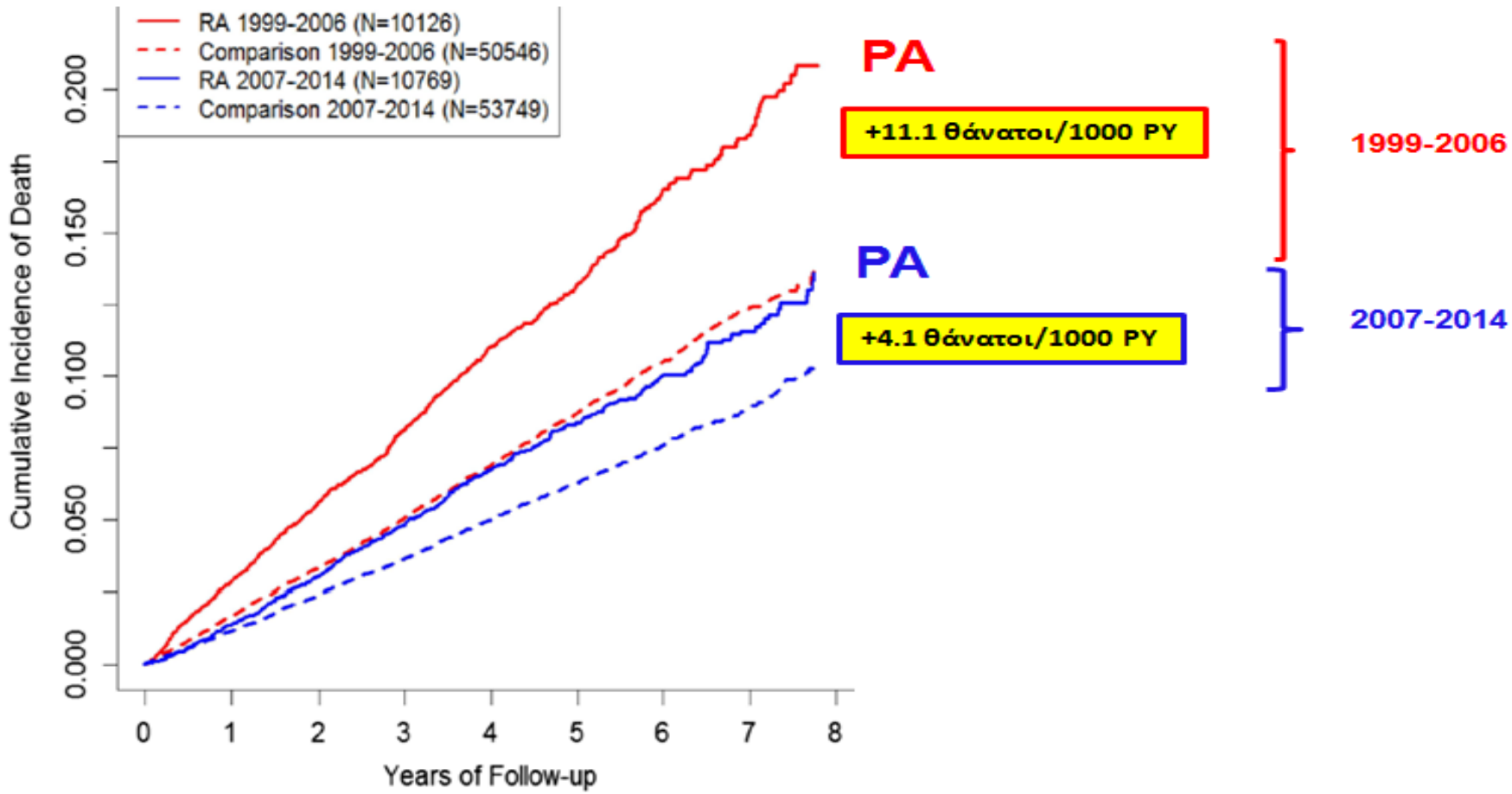
Ann Rheum Dis 2017 Apr;76(4):654-660

BMJ Journals

Annals of the Rheumatic Diseases

Clinical and epidemiological research
Extended report

Improved survival in rheumatoid arthritis: a general population-based cohort study



PA

+11.1 θάνατοι/1000 PY

1999-2006

PA

+4.1 θάνατοι/1000 PY

2007-2014

↓ ~ 50%

*Zhang Y et al, Ann Rheum Dis2017;*76:408–413.

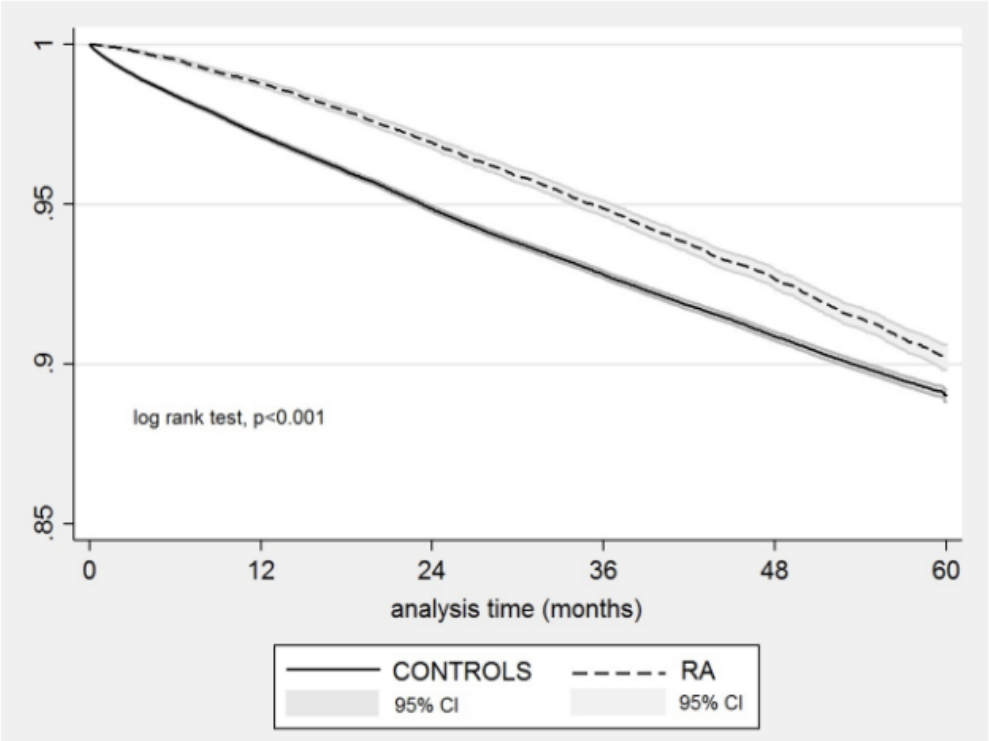
RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

All-cause mortality in systemic rheumatic diseases under treatment compared with the general population, 2015–2019

Vasiliki-Kalliopi Bournia ,[1] George E Fragoulis ,[1] Panagiota Mitrou,[2] Konstantinos Mathioudakis,[3] Anastasios Tsolakidis,[3] George Konstantonis,[1] Georgia Vourli,[4] Dimitrios Paraskevis,[4] Maria G Tektonidou ,[1] Petros P Sfikakis[1]

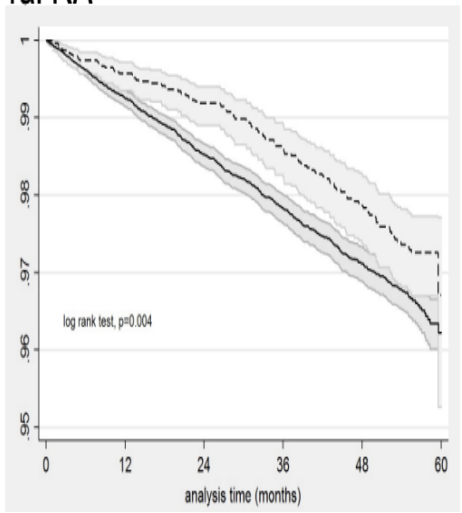
Panel 1. RA



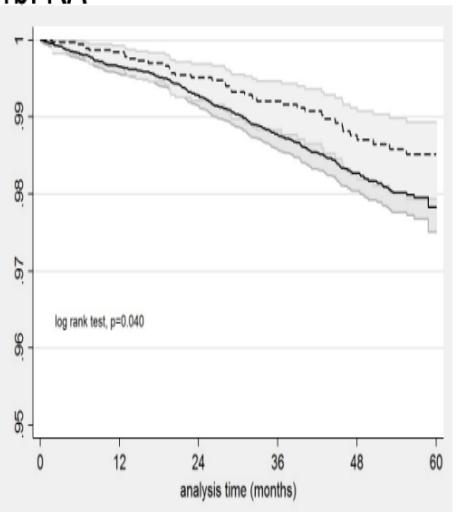
a. Males

b. Females

1a. RA



1b. RA



Bournia et al, RMD Open 2021

TRANSLATIONAL SCIENCE

Cardiovascular effects of biological versus conventional synthetic disease-modifying antirheumatic drug therapy in treatment-naïve, early rheumatoid arthritis

Sven Plein,[1] Bara Erhayiem,[1] Graham Fent,[1] Sarah Horton,[2] Raluca Bianca Dumitru ,[3] Jacqueline Andrews,[3] John P Greenwood,[1] Paul Emery ,[3,4] Elizabeth MA Hensor,[3,4] Paul Baxter,[1] Sue Pavitt,[5] Mava H Buch [3,4,6]

81 patients with early RA, treatment naïve, no history of CVD, no symptoms randomly assigned to receive MTX or MTX+ETA

Table 1 Summary of baseline demographic, disease activity and comorbidity data for controls and patients

Variable	Controls n=30	All patients with ERA n=81	ETN-MTX n=40	MTX-TT n=41
Demographics*				
Female % (n/N)	63 (19/30)	69 (55/81)	60 (24/40)	76 (31/41)
Age, years median (IQR)	54 (23)	51 (21)	48.5 (13.5)	54 (23)
BMI, median (IQR)	27.0 (7.1)	24.9 (5.4)	25.6 (5.5)	24.6 (5.2)
RA profile, % (n/N)				
CCP positive	N/A	84 (64/76)	82 (31/38)	87 (33/38)
RF positive	N/A	75 (57/76)	68 (26/38)	82 (31/38)
RA disease activity profile, median (IQR)		n=77	n=39	n=38
Baseline DAS28 score	N/A	5.3 (1.4)	5.5 (1.6)	5.3 (1.4)
ESR	N/A	30 (30)	31 (33.5)	30 (28.3)
CRP	N/A	8 (23)	8 (27)	8 (17.8)
Traditional CV risk factors, % (n/N; unless otherwise stated)				
Hypertension	N/A	7 (6/81)	3 (1/40)	12 (5/41)
Hypercholesterolaemia	N/A	2 (2/81)	0 (0/40)	5 (2/41)
Diabetes	0 (0/30)	0 (0/81)	0 (0/40)	0 (0/41)
Family history IHD	N/A	5 (4/81)	5 (2/40)	5 (2/41)
Systolic blood pressure, mm Hg median (IQR)	120.5 (13.5)	121 (26)	122 (24.5)	120 (23)
Pack years smoking, years median (IQR)	0 (0.4)	0.1 (10)	0 (5.3)	3 (17.5)
Smoking status	n=30	n=76	n=38	n=38
Current	13 (4/30)	22 (17)	16 (6)	29 (11)
Former	17 (5/30)	33 (25)	29 (11)	37 (14)
Never	70 (21/30)	45 (34)	55 (21)	34 (13)

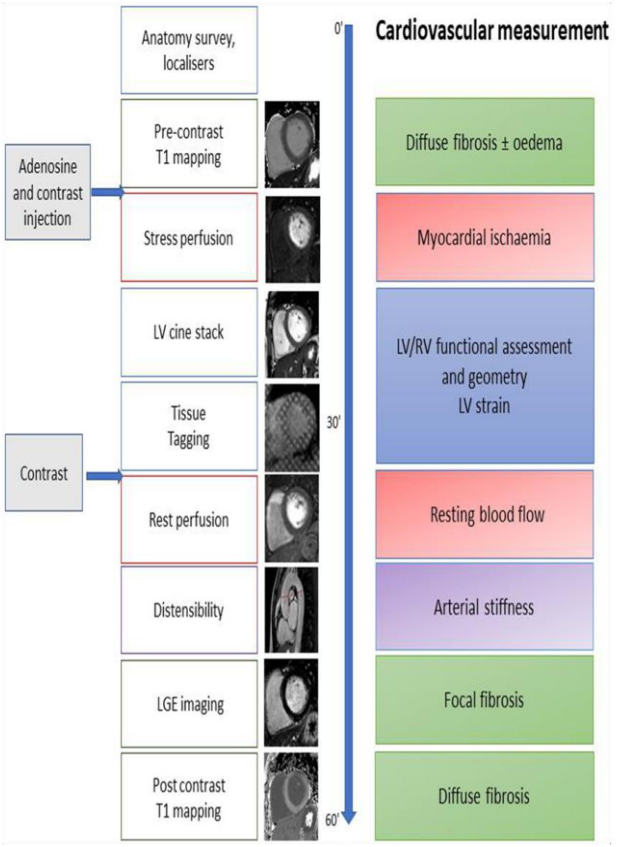
*Denominator that is less than n=81 indicates missing data (not retrieved or original imputation

Table 3 Summary of baseline to year 1 outcomes for the whole early rheumatoid arthritis group

Outcome	Geometric mean (95% CI) Baseline	Geometric mean (95% CI) 1 year	Ratio (95% CI), P value
AD (10^{-3} mm Hg^{-1})	3.0 (2.7 to 3.4)	3.6 (3.1 to 4.1)	1.2 (1.1 to 1.3), <0.01
LVEF (%)	60.3 (59.1 to 61.6)	59.9 (58.5 to 61.5)	1.0 (1.0 to 1.0), 0.54
LVLS (cm/s)	1.1 (1.1 to 1.2)	1.1 (1.1 to 1.2)	1.0 (1.0 to 1.1), 0.84
PLVTw (°)	14.9 (13.9 to 15.8)	14.6 (13.7 to 15.7)	1.0 (0.9 to 1.1), 0.69
LV mass (g)	78.2 (73.7 to 82.9)	81.4 (76.3 to 86.9)	1.0 (1.0 to 1.1), 0.01
Native T1 (ms)	1183.92 (1174.44 to 1193.48)	1185.39 (1168.99 to 1202.02)	1 (0.99 to 1.02), 0.87
ECV (%)	27.2 (26.4 to 28.1)	26.4 (25.6 to 27.1)	1.0 (0.9 to 1.0), 0.06

n=81 with imputation for missing baseline or follow-up values.

AD, aortic distensibility; ECV, myocardial extracellular volume; LVEF, left ventricular ejection fraction; LVLS, left ventricular longitudinal strain; LV mass, left ventricular mass; PLVTw, peak left ventricular twist



Plein S et al, Ann Rheum Dis 2020

CLINICAL SCIENCE

Reducing cardiovascular risk with immunomodulators: a randomised active comparator trial among patients with rheumatoid arthritis

Daniel H Solomon ,[1] Jon T Giles,[2] Katherine P Liao,[1] Paul M Ridker,[1] Pamela M Rist,[1] Robert J Glynn,[1] Rachel Broderick,[2] Fengxin Lu,[1] Meredith T Murray,[1] Kathleen Vanni,[1] Leah M Santacroce,[1] Shady Abohashem,[3] Philip M Robson,[4] Zahi Fayad,[4] Venkatesh Mani,[4] Ahmed Tawakol,[3] Joan Bathon,[2] TARGET Trial Consortium

115 patients with active RA on MTX received were randomly assigned to receive TNF inhibitor or HCQ + SLS (triple therapy)

Baseline and follow-up 18F- fluorodeoxyglucose-positron emission tomography/CT scans were assessed for change in arterial inflammation, measured as an arterial target-to- background ratio (TBR) in the carotid arteries and aorta.

Table 2 Results of FDG-PET/CT scans target to background ratio comparing subjects randomised to TNF inhibitors versus triple therapy

	Baseline		Follow-up		Differences (Δ=baseline to follow-up)			
	TNFi	Triple therapy	TNFi	Triple therapy	ΔTNFi	ΔTriple therapy	TNFi versus triple therapy	
Arterial location assessed	Mean (SD)						β (95% CI)	P value
Primary outcome								
MDS of index vessel*	2.72 (0.75)	2.62 (0.51)	2.47 (0.68)	2.43 (0.51)	−0.24 (0.51)	−0.19 (0.51)	−0.02 (−0.19 to 0.15)	0.79
Secondary outcomes†								
MDS of aorta	2.67 (0.79)	2.64 (0.50)	2.50 (0.69)	2.47 (0.42)	−0.17 (0.52)	−0.17 (0.39)	0.01 (−0.14 to 0.17)	0.87
Aorta	2.46 (0.66)	2.48 (0.43)	2.45 (0.74)	2.42 (0.38)	−0.02 (0.43)	−0.06 (0.34)	0.03 (−0.11 to 0.18)	0.64
Bilateral carotids	2.13 (0.36)	2.21 (0.44)	2.07 (0.51)	2.11 (0.46)	−0.06 (0.48)	−0.10 (0.51)	−0.003 (−0.20 to 0.19)	0.98
Index vessel	2.51 (0.62)	2.45 (0.45)	2.43 (0.74)	2.38 (0.47)	−0.09 (0.43)	−0.07 (0.47)	−0.01 (−0.17 to 0.16)	0.94

Follow-up value is at study conclusion (approximately 24 weeks). Triple therapy refers to the use of weekly methotrexate, sulfasalazine 1000 mg two times per day, and hydroxychloroquine 200–400 mg per day. Counts of the number of individuals included in each analysis: TBR MDS—TNFi=58, triple therapy=57; aorta—TNFi=56, triple therapy=52; left carotid—TNFi=44, triple therapy=41; right carotid—TNFi=43, triple therapy=42; average carotid—TNFi=45, triple therapy=43.
*When vessel is not specified, the measurement refers to the index vessel with the most diseased segment.
†P values for the secondary outcomes are nominal and not corrected for multiple testing. All β estimates and p values are from ANCOVA models that estimate the change in TBR as a function of the baseline TBR, treatment group and the randomisation strata.
ANCOVA, analysis of covariance; FDG-PET/CT, 18F-fluorodeoxyglucose positron emission tomography/CT scan; MDS, most disease segment examining right and left carotid arteries and aorta; TBR, target to background ratio; TNFi, TNF inhibitor.

Solomon D et al, Ann Rheum Dis 2023

Randomized Controlled Trial > Arthritis Rheumatol. 2020 Jan;72(1):31-40.
doi: 10.1002/art.41095.

Cardiovascular Safety of Tocilizumab Versus Etanercept in Rheumatoid Arthritis: A Randomized Controlled Trial

Jon T Giles [1], Naveed Sattar [2], Sherine Gabriel [3], Paul M Ridker [4], Steffen Gay [5], Charles Warne [6], David Musselman [7], Laura Brockwell [6], Emma Shittu [6], Micki Klearman [7], Thomas R Fleming [8]

Comparative Study > Semin Arthritis Rheum. 2018 Dec;48(3):399-405.
doi: 10.1016/j.semarthrit.2018.03.012. Epub 2018 Mar 22.

No difference in cardiovascular risk of tocilizumab versus abatacept for rheumatoid arthritis: A multi-database cohort study

Seoyoung C Kim [1], Daniel H Solomon [2], James R Rogers [3], Sara Gale [4], Micki Klearman [4], Khaled Sarsour [4], Sebastian Schneeweiss [3]

Observational Study > J Am Heart Assoc. 2018 Jan 24;7(3):e007393.
doi: 10.1161/JAHA.117.007393.

Comparative Cardiovascular Risk of Abatacept and Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis With and Without Diabetes Mellitus: A Multidatabase Cohort Study

Eun Ha Kang [1 2], Yinzhu Jin [1], Gregory Brill [1], Jennifer Lewey [1 3], Elisabetta Patorno [1], Rishi J Desai [1], Seoyoung C Kim [4 5]

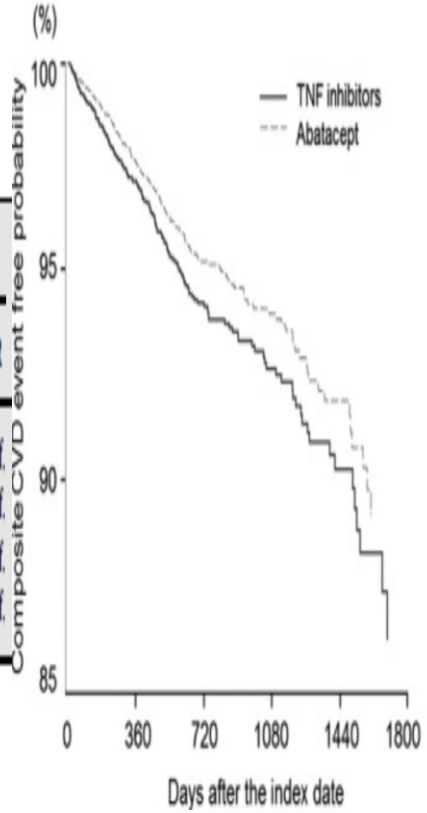
- **HR for MACE tocilizumab vs. etanercept**
  - **1.05 (95% CI 0.77, 1.43) for intention to treat population**
    - MACE rate 1.82/100 patient years for tocilizumab group
    - MACE rate 1.70/100 patient-years for etanercept group
  - **1.11 (95% CI 0.78, 1.62) for on-treatment population**

Table 3

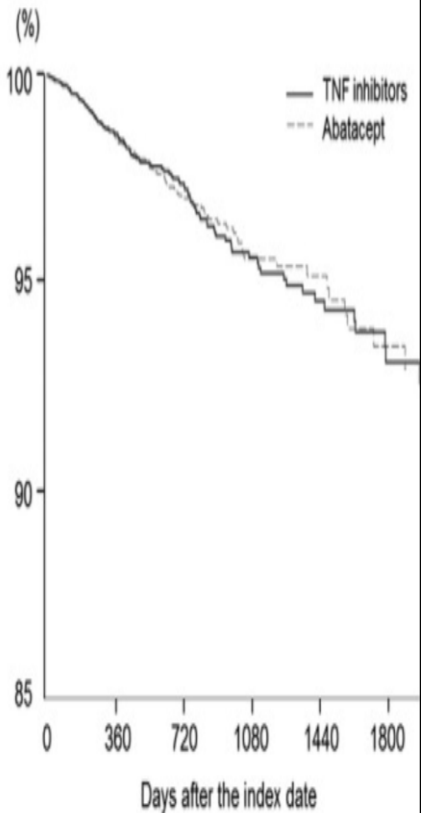
Incidence rate and hazard ratio of the composite cardiovascular endpoint in tocilizumab users versus abatacept, propensity score-matched with a 1:3 variable ratio

	Tocilizumab					Abatacept				
	No. of subjects	Events	Person-years	IR[a] (95% CI)	HR	No. of subjects	Events	Person-years	IR[a] (95% CI)	HR
Medicare	1516	18	1097	1.64 (1.01-2.54)	0.96 (0.56-1.63)	4075	59	3497	1.69 (1.30-2.16)	Ref.
PharMetrics	1735	5	1336	0.37 (0.14-0.82)	0.67 (0.25-1.84)	3840	18	3061	0.59 (0.36-0.91)	Ref.
MarketScan	2986	9	2163	0.42 (0.21-0.76)	0.68 (0.32-1.42)	6770	35	5126	0.68 (0.48-0.94)	Ref.
Combined	6237	32	4596	0.70 (0.49-0.97)	0.82[b] (0.55-1.22)	14,685	112	11,684	0.96 (0.79-1.15)	Ref.

A. Medicare

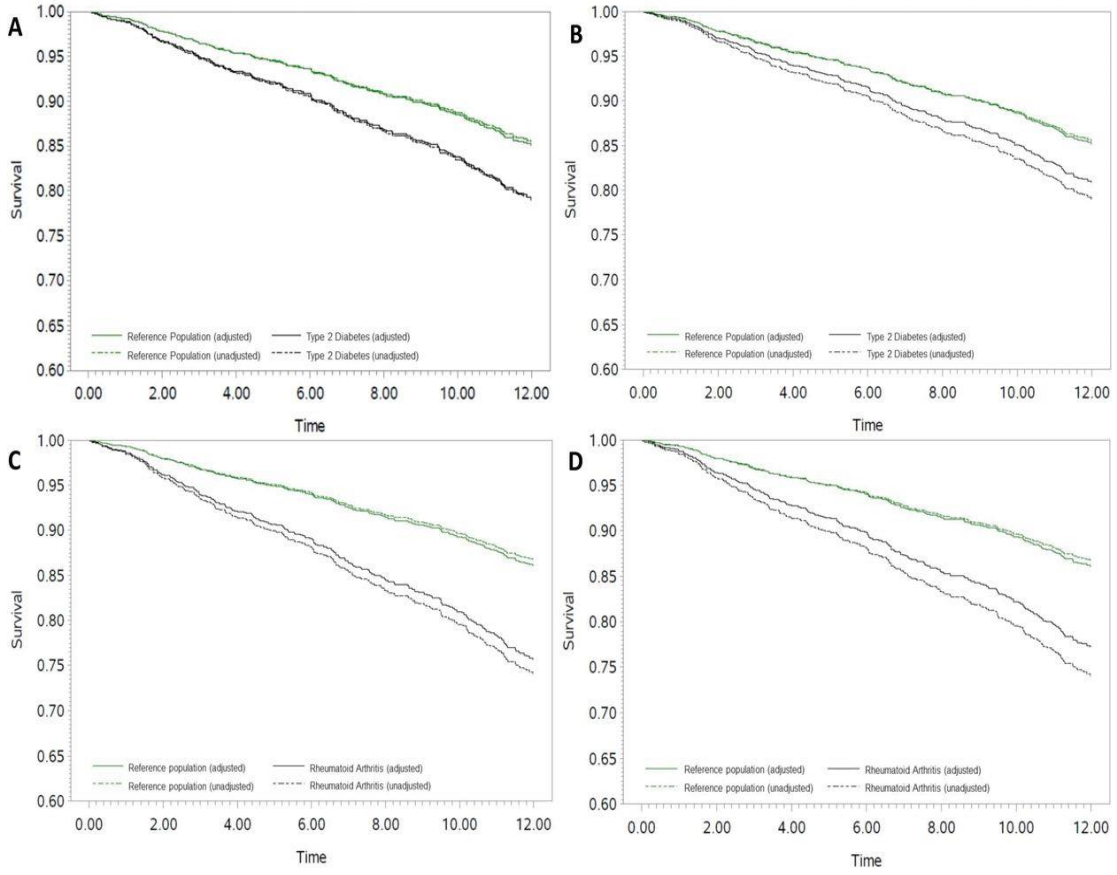


B. Market Scan



Cardiovascular Event Risk in Rheumatoid Arthritis Compared with Type 2 Diabetes: A 15-year Longitudinal Study

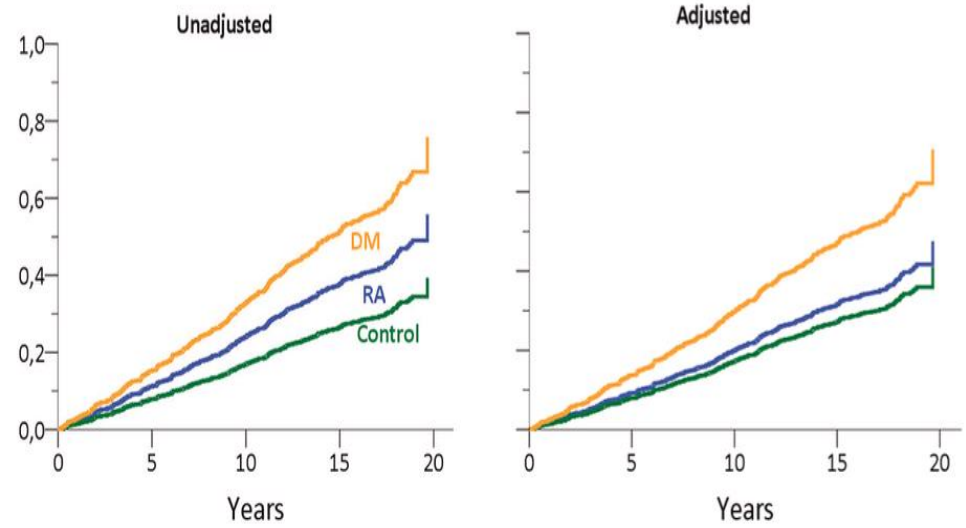
Rabia Agca, Luuk H.G.A. Hopman, Koen J.C. Laan, Vokko P. van Halm, Mike J.L. Peters, Yvo M. Smulders, Jacqueline M. Dekker, Giel Nijpels, Coen D.A. Stehouwer, Alexandre E. Voskuyl, Maarten Boers, Willem F. Lems and Michael T. Nurmohamed



Rabia Agca et al. J Rheumatol 2020

In RA patients without prevalent CVD, incident CVD is mainly associated with traditional risk factors: A 20-year follow-up in the CARRÉ cohort study

R. Raadsen[a,*], R. Agca[a,b], M. Boers[a,b,c], V.P. van Halm[d], M.J.L. Peters[e], Y. Smulders[f], J.W.J. Beulens[c], M.T. Blom[c], C.D.A. Stehouwer[g,h], A.E. Voskuyl[a,b], W.F. Lems[a,b], M. T. Nurmohamed[a,b]



Patients at risk				
RA	192	144	94	1
DM	80	59	38	0
Controls	1147	968	802	4

Raadsen R et al, Semin Arthritis Rheum 2023

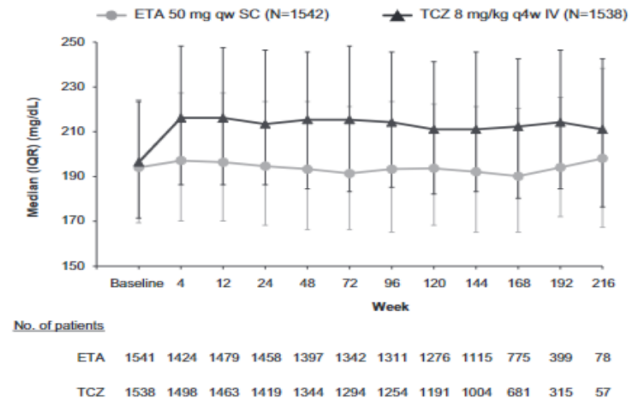
Randomized Controlled Trial > Arthritis Rheumatol. 2020 Jan;72(1):31-40.
doi: 10.1002/art.41095.

Cardiovascular Safety of Tocilizumab Versus Etanercept in Rheumatoid Arthritis: A Randomized Controlled Trial

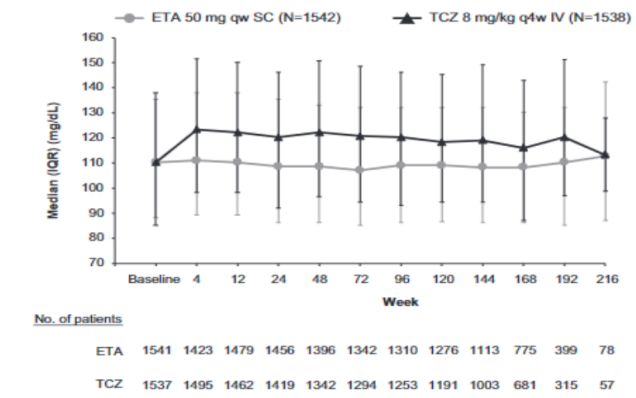
Jon T Giles [1], Naveed Sattar [2], Sherine Gabriel [3], Paul M Ridker [4], Steffen Gay [5], Charles Warne [6], David Musselman [7], Laura Brockwell [6], Emma Shittu [6], Micki Klearman [7], Thomas R Fleming [8]

- FDA Mandated Phase 4 Safety Trial
- Primary outcome was major adverse CVD events (MACE)
  - Fatal and non-fatal MI and CVA, sudden cardiac death including unknown cause of death
- RA patients with active disease on background DMARDs
  - randomized 1:1 to tocilizumab (IV; n=1538) or etanercept (SQ; n=1542)
- Treatment not blinded
- Mean follow-up 3.2 years with 96% completing
- CVD events independently adjudicated
- Non-inferiority margin of 1.8 pre-specified
- **HR for MACE tocilizumab vs. etanercept**
  - **1.05 (95% CI 0.77, 1.43) for intention to treat population**
    - MACE rate 1.82/100 patient years for tocilizumab group
    - MACE rate 1.70/100 patient-years for etanercept group
  - **1.11 (95% CI 0.78, 1.62) for on-treatment population**

Total Cholesterol

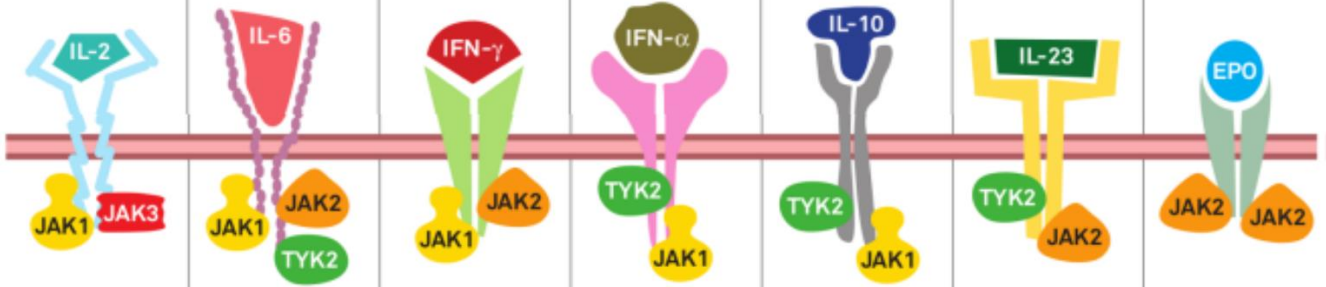


LDL-C



Giles JT et al. Arthritis Rheumatol 2020;72(1):31-40.

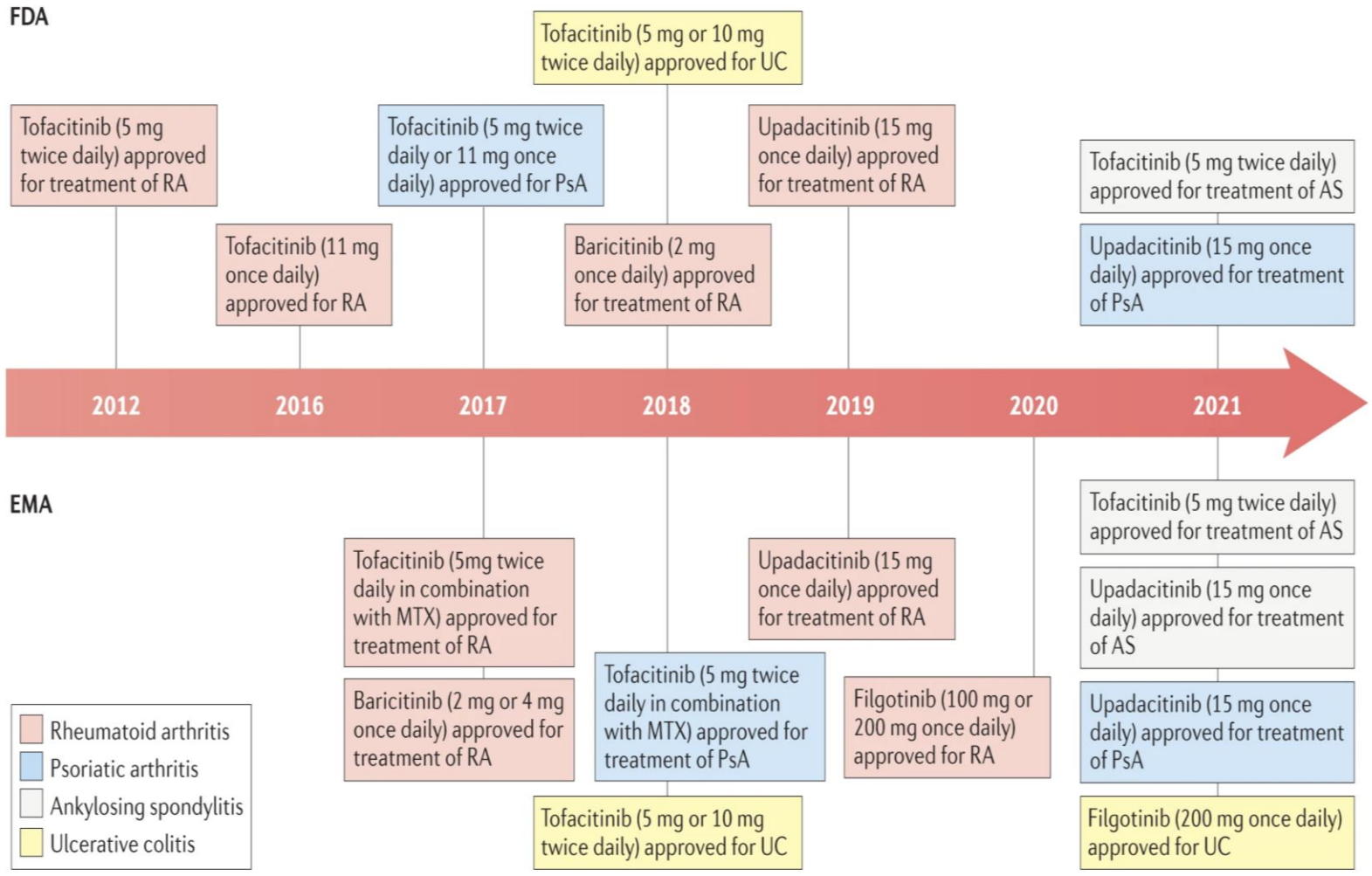
JAK Inhibitor Mechanism of Action

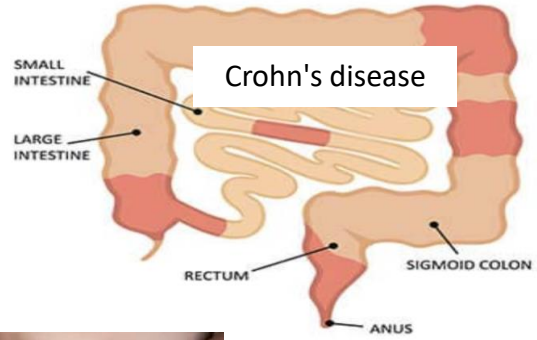
Cytokine and cytokine receptor families	*Cytokine* receptor sharing the γ-chain (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21)	Cytokine receptor sharing the gp130 (IL-6, IL-11, IL13, IL-25, IL-27, IL-31)	IFN-γ receptor	Type I IFN Receptor (IFN α/β)	IL-10 family receptor (IL-10, IL-22)	Receptors for Cytokine sharing the IL-12Rβ1 (IL-12,IL-23)	Homo-dimeric cytokine receptor (GM-CSF, EPO, TP, IL-3, IL-5)
							
	STAT 1, 3, 5, 6	STAT 1, 3, 5	STAT 1, 3, 5	STAT 1, 2, 3	STAT 1, 3, 5	STAT 3, 4	STAT 5

Drug	Selectivity*						
Baricitinib	JAK1, 2	+	+	+	+	+	+	+
Filgotinib	JAK1	+	+	+	+	+	-	-
Peficitinib	JAK1, 2, 3	+	+	+	+	+	+	+
Tofacitinib	JAK1, 2, 3	+	+	+	+	+	+	+
Upada-citinib	JAK1, (2)	+	+	+	+	+	+	+

From Nash P, et al. Ann Rheum Dis. 2021 Jan;80(1):71-87.

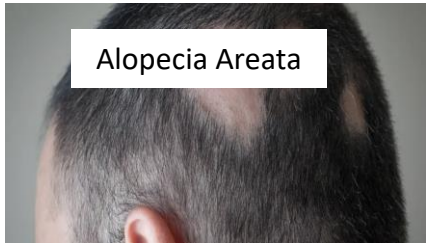
JAK INHIBITORS - EXPANDING INDICATIONS

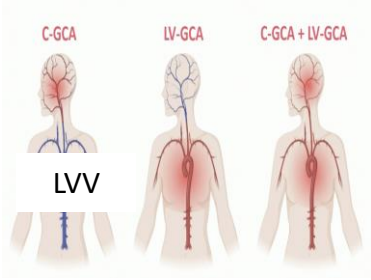




Crohn's disease

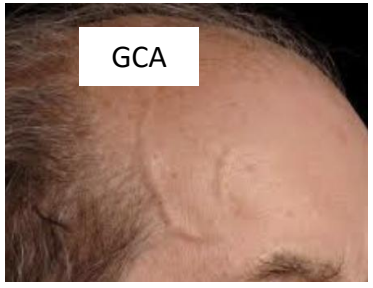

Atopic dermatitis

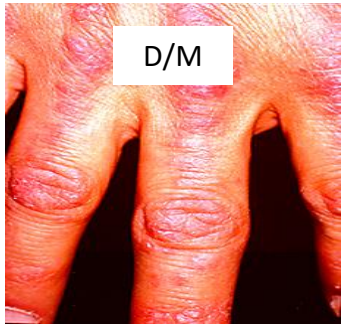

Alopecia Areata



LVV


Skin psoriasis

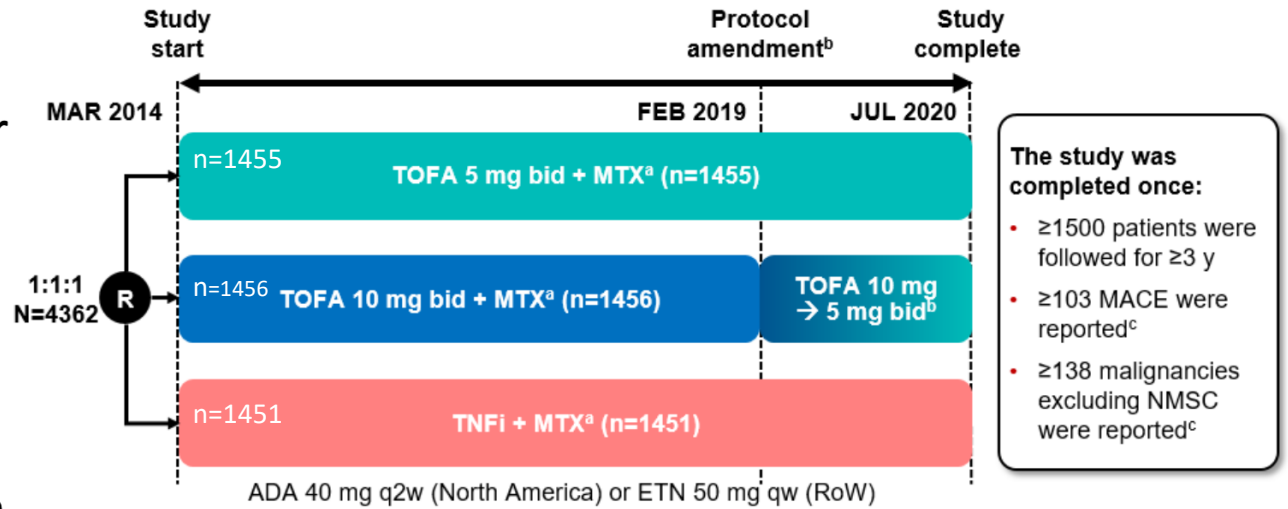

GCA


D/M

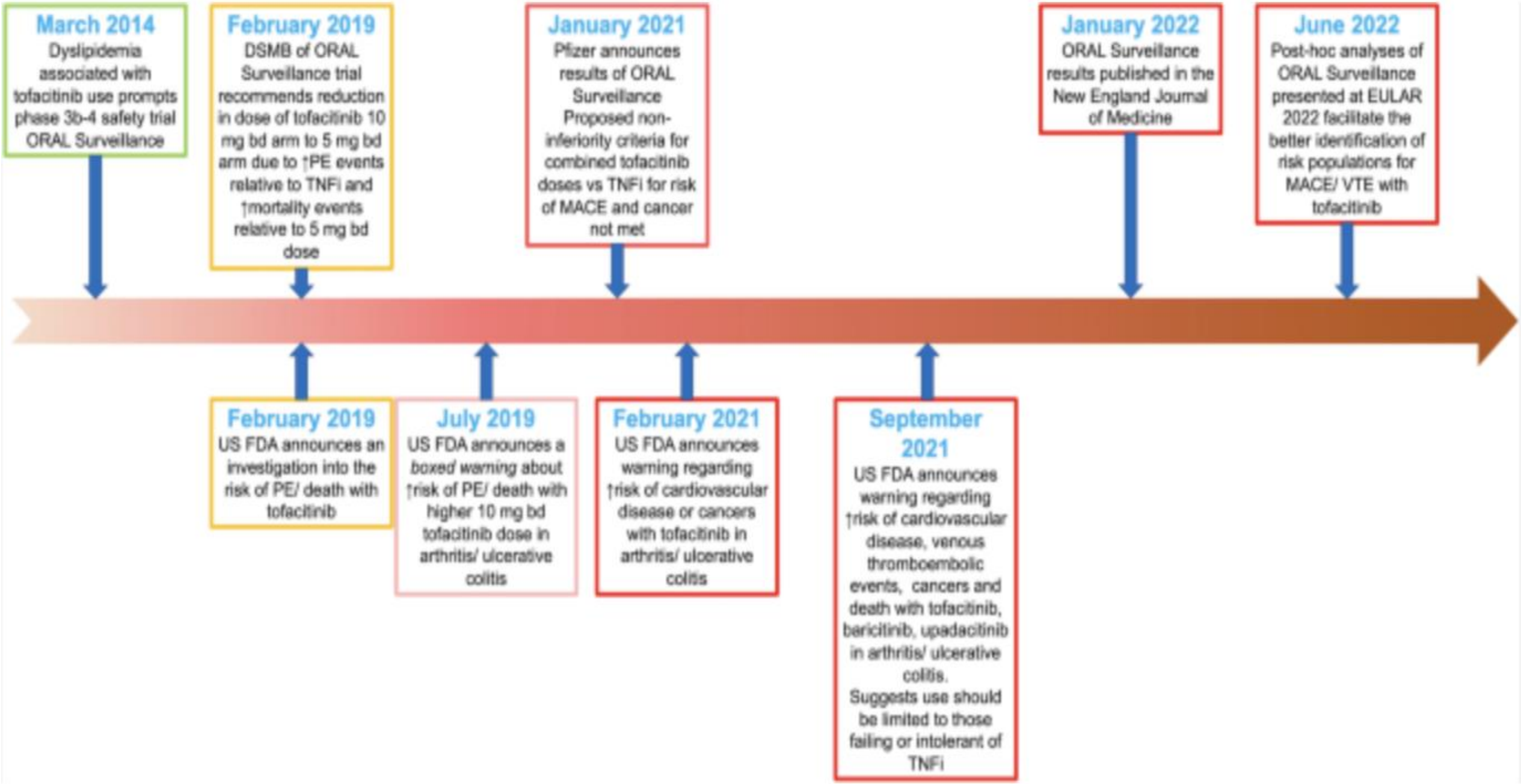
Winthrop K & Cohen S Nature Rev Rheumatol 2022

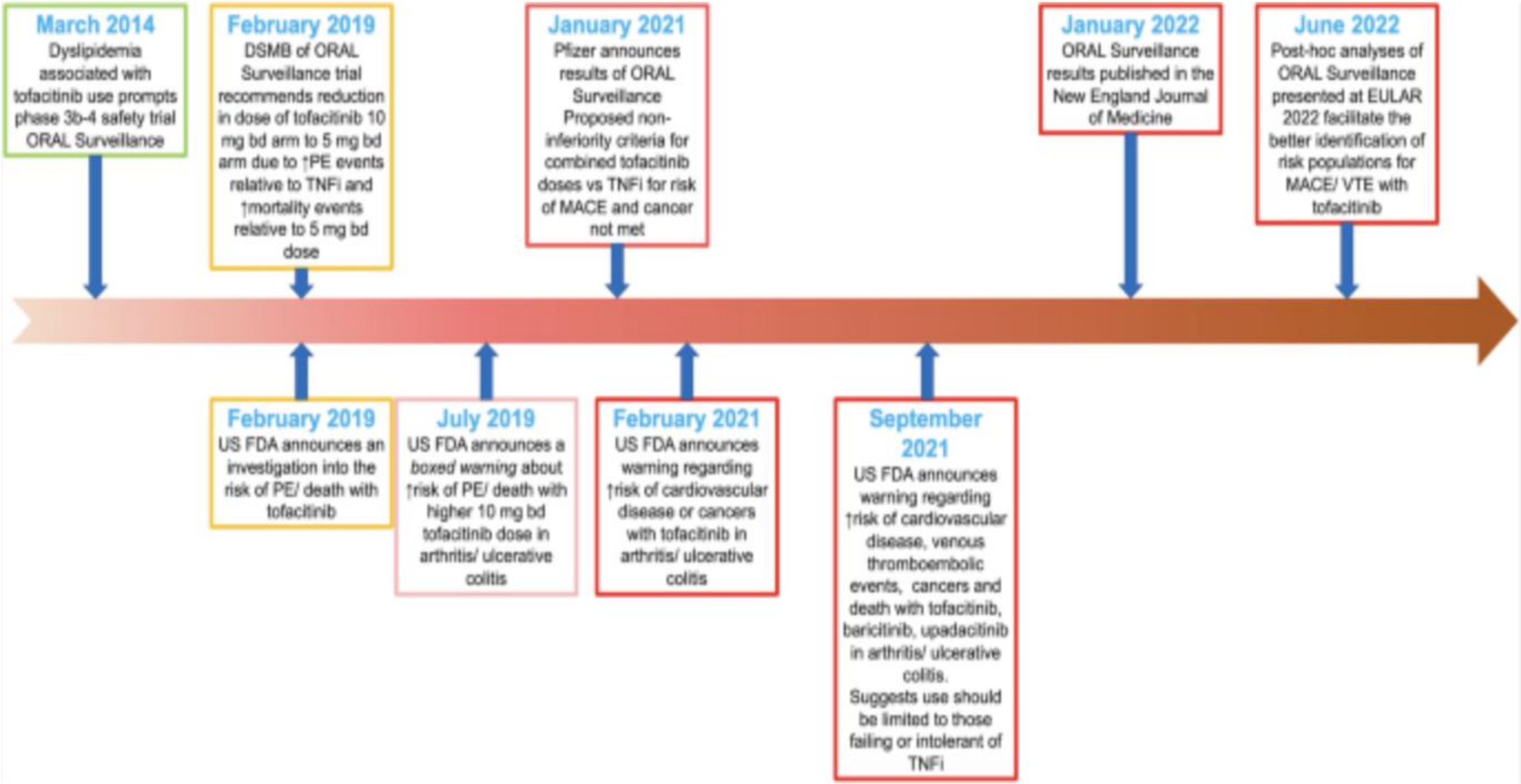
ORAL Surveillance Safety Trial: Tofacitinib vs. TNF Inhibitors

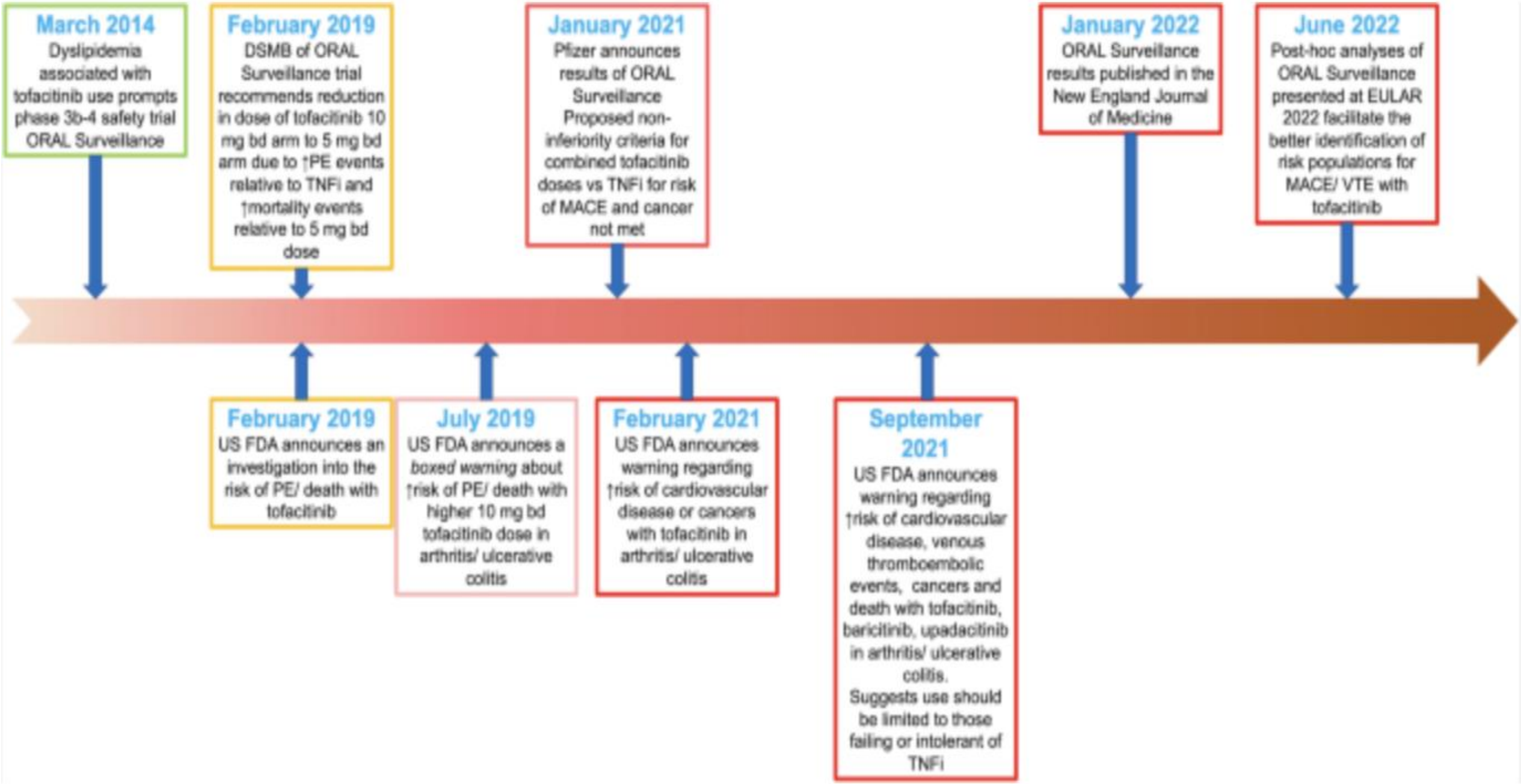
- Randomized, open-label Phase 4 non-inferiority trial
- Inclusion/exclusion
  - Moderate/Severe RA MTX-IR
  - Age>50 years
  - At least one cardiovascular disease risk factor
  - No current/prior malignancy
- Co-primary outcomes
  - Major adverse cardiovascular events and malignancy
  - Non-inferiority margin set at 1.8
- After a signal for venous thromboembolic disease was detected for Tofa 10 mg BID in Feb 2019, patients on this dose were changed to 5 mg BID

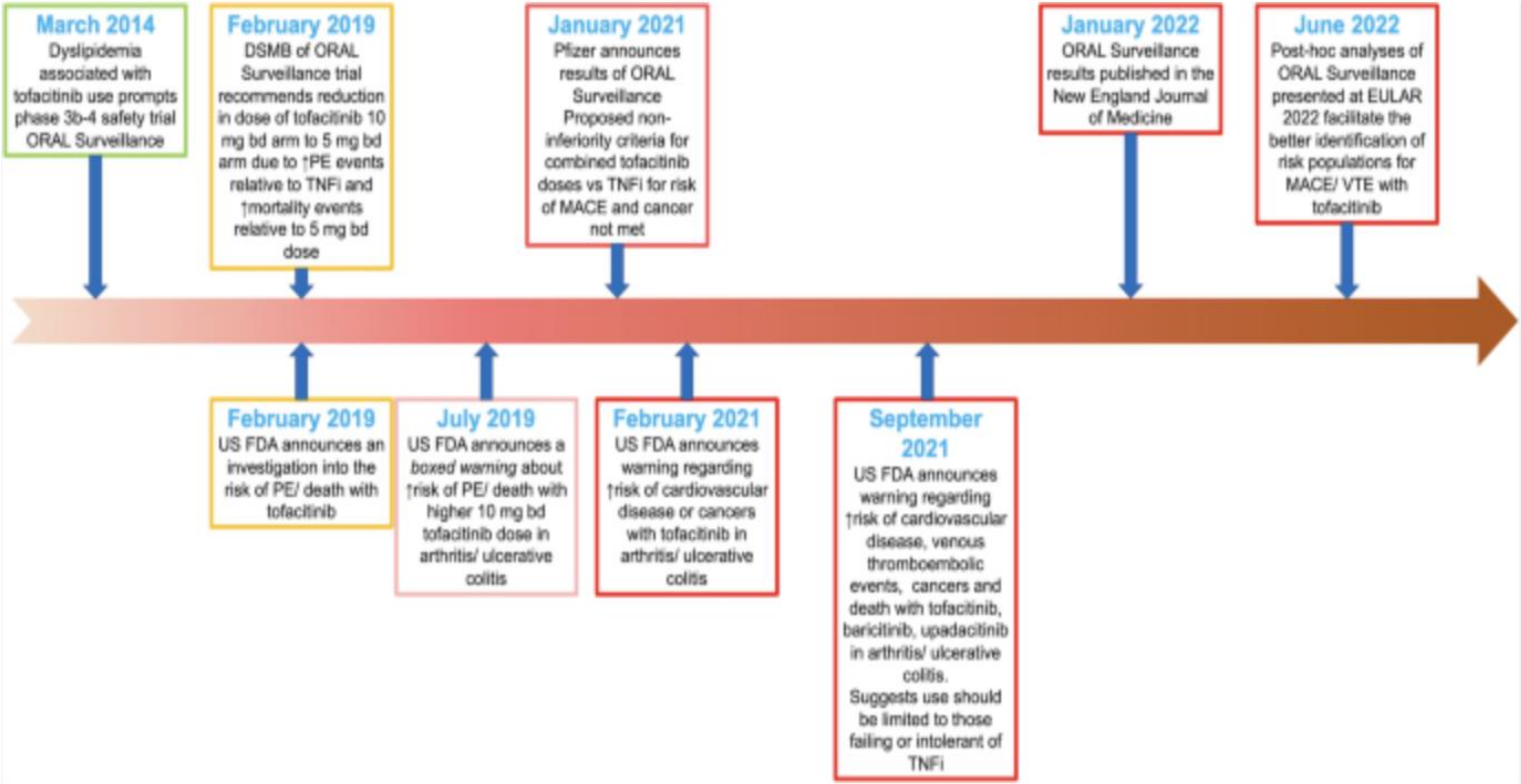


Ytterberg SR et al. N Engl J Med. 2022 Jan 27;386(4):316-326.

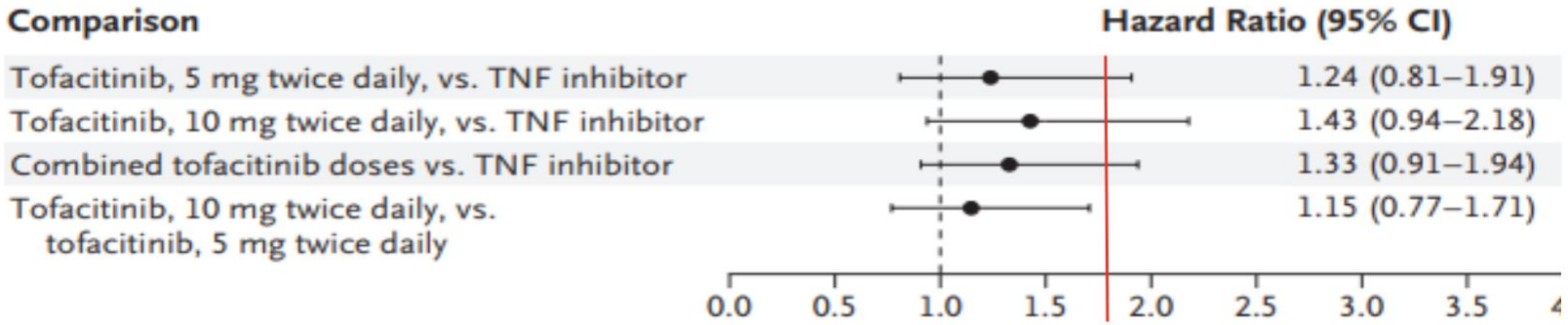

March 2014
Dyslipidemia associated with tofacitinib use prompts phase 3b-4 safety trial ORAL Surveillance
February 2019
DSMB of ORAL Surveillance trial recommends reduction in dose of tofacitinib 10 mg bd arm to 5 mg bd arm due to ↑PE events relative to TNFi and ↑mortality events relative to 5 mg bd dose
January 2021
Pfizer announces results of ORAL Surveillance Proposed non-inferiority criteria for combined tofacitinib doses vs TNFi for risk of MACE and cancer not met
January 2022
ORAL Surveillance results published in the New England Journal of Medicine
June 2022
Post-hoc analyses of ORAL Surveillance presented at EULAR 2022 facilitate the better identification of risk populations for MACE/ VTE with tofacitinib
February 2019
US FDA announces an investigation into the risk of PE/ death with tofacitinib
July 2019
US FDA announces a *boxed warning* about ↑risk of PE/ death with higher 10 mg bd tofacitinib dose in arthritis/ ulcerative colitis
February 2021
US FDA announces warning regarding ↑risk of cardiovascular disease or cancers with tofacitinib in arthritis/ ulcerative colitis
September 2021
US FDA announces warning regarding ↑risk of cardiovascular disease, venous thromboembolic events, cancers and death with tofacitinib, baricitinib, upadacitinib in arthritis/ ulcerative colitis.
Suggests use should be limited to those failing or intolerant of TNFi


March 2014
Dyslipidemia associated with tofacitinib use prompts phase 3b-4 safety trial ORAL Surveillance
February 2019
DSMB of ORAL Surveillance trial recommends reduction in dose of tofacitinib 10 mg bd arm to 5 mg bd arm due to ↑PE events relative to TNFi and ↑mortality events relative to 5 mg bd dose
January 2021
Pfizer announces results of ORAL Surveillance Proposed non-inferiority criteria for combined tofacitinib doses vs TNFi for risk of MACE and cancer not met
January 2022
ORAL Surveillance results published in the New England Journal of Medicine
June 2022
Post-hoc analyses of ORAL Surveillance presented at EULAR 2022 facilitate the better identification of risk populations for MACE/ VTE with tofacitinib
February 2019
US FDA announces an investigation into the risk of PE/ death with tofacitinib
July 2019
US FDA announces a *boxed warning* about ↑risk of PE/ death with higher 10 mg bd tofacitinib dose in arthritis/ ulcerative colitis
February 2021
US FDA announces warning regarding ↑risk of cardiovascular disease or cancers with tofacitinib in arthritis/ ulcerative colitis
September 2021
US FDA announces warning regarding ↑risk of cardiovascular disease, venous thromboembolic events, cancers and death with tofacitinib, baricitinib, upadacitinib in arthritis/ ulcerative colitis.
Suggests use should be limited to those failing or intolerant of TNFi

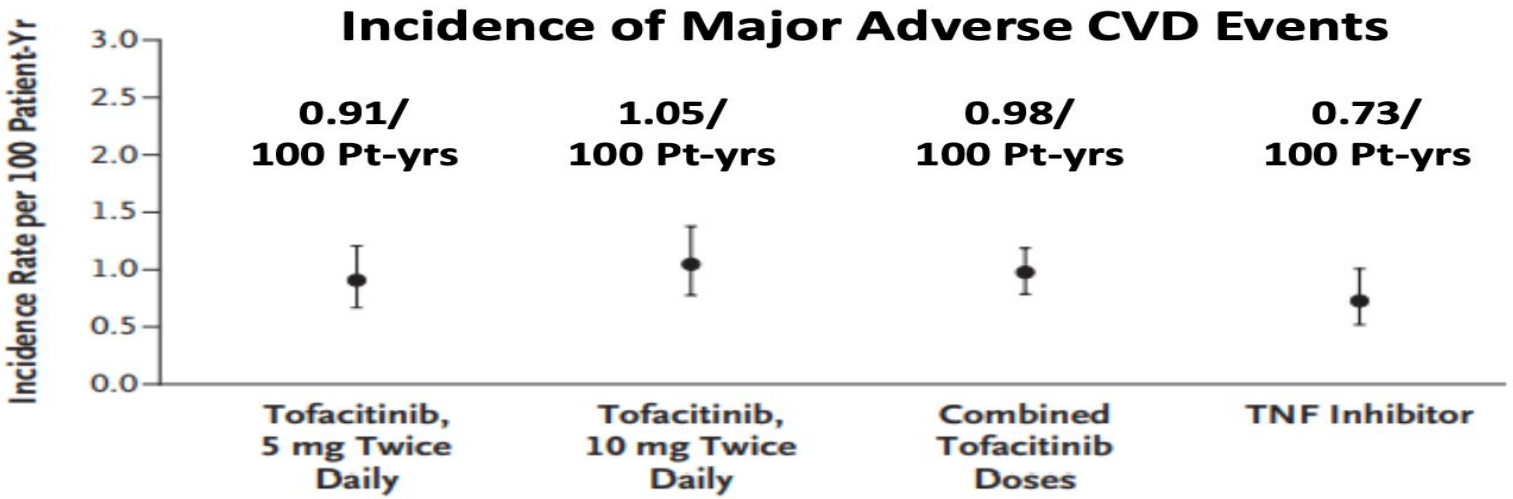

March 2014
Dyslipidemia associated with tofacitinib use prompts phase 3b-4 safety trial ORAL Surveillance
February 2019
DSMB of ORAL Surveillance trial recommends reduction in dose of tofacitinib 10 mg bd arm to 5 mg bd arm due to ↑PE events relative to TNFi and ↑mortality events relative to 5 mg bd dose
January 2021
Pfizer announces results of ORAL Surveillance Proposed non-inferiority criteria for combined tofacitinib doses vs TNFi for risk of MACE and cancer not met
January 2022
ORAL Surveillance results published in the New England Journal of Medicine
June 2022
Post-hoc analyses of ORAL Surveillance presented at EULAR 2022 facilitate the better identification of risk populations for MACE/ VTE with tofacitinib
February 2019
US FDA announces an investigation into the risk of PE/ death with tofacitinib
July 2019
US FDA announces a *boxed warning* about ↑risk of PE/ death with higher 10 mg bd tofacitinib dose in arthritis/ ulcerative colitis
February 2021
US FDA announces warning regarding ↑risk of cardiovascular disease or cancers with tofacitinib in arthritis/ ulcerative colitis
September 2021
US FDA announces warning regarding ↑risk of cardiovascular disease, venous thromboembolic events, cancers and death with tofacitinib, baricitinib, upadacitinib in arthritis/ ulcerative colitis.
Suggests use should be limited to those failing or intolerant of TNFi


March 2014
Dyslipidemia associated with tofacitinib use prompts phase 3b-4 safety trial ORAL Surveillance
February 2019
DSMB of ORAL Surveillance trial recommends reduction in dose of tofacitinib 10 mg bd arm to 5 mg bd arm due to ↑PE events relative to TNFi and ↑mortality events relative to 5 mg bd dose
January 2021
Pfizer announces results of ORAL Surveillance Proposed non-inferiority criteria for combined tofacitinib doses vs TNFi for risk of MACE and cancer not met
January 2022
ORAL Surveillance results published in the New England Journal of Medicine
June 2022
Post-hoc analyses of ORAL Surveillance presented at EULAR 2022 facilitate the better identification of risk populations for MACE/ VTE with tofacitinib
February 2019
US FDA announces an investigation into the risk of PE/ death with tofacitinib
July 2019
US FDA announces a *boxed warning* about ↑risk of PE/ death with higher 10 mg bd tofacitinib dose in arthritis/ ulcerative colitis
February 2021
US FDA announces warning regarding ↑risk of cardiovascular disease or cancers with tofacitinib in arthritis/ ulcerative colitis
September 2021
US FDA announces warning regarding ↑risk of cardiovascular disease, venous thromboembolic events, cancers and death with tofacitinib, baricitinib, upadacitinib in arthritis/ ulcerative colitis.
Suggests use should be limited to those failing or intolerant of TNFi

Tofacitinib was **not non-inferior** to TNF inhibitors for cardiovascular events



The incidence of MACE was higher with the combined tofacitinib doses (3.4%; 98 patients) than with a TNF inhibitor (2.5%; 37 patients).



No. of Patients with First Event/Total No. (%)	47/1455 (3.2)	51/1456 (3.5)	98/2911 (3.4)	37/1451 (2.5)
No. of Patient-Yr	5166.32	4871.96	10,038.28	5045.27
Incidence Rate per 100 Patient-Yr (95% CI)	0.91 (0.67–1.21)	1.05 (0.78–1.38)	0.98 (0.79–1.19)	0.73 (0.52–1.01)
NNH (patient-yr) vs. TNF Inhibitor	567	319	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	113	64	—	—

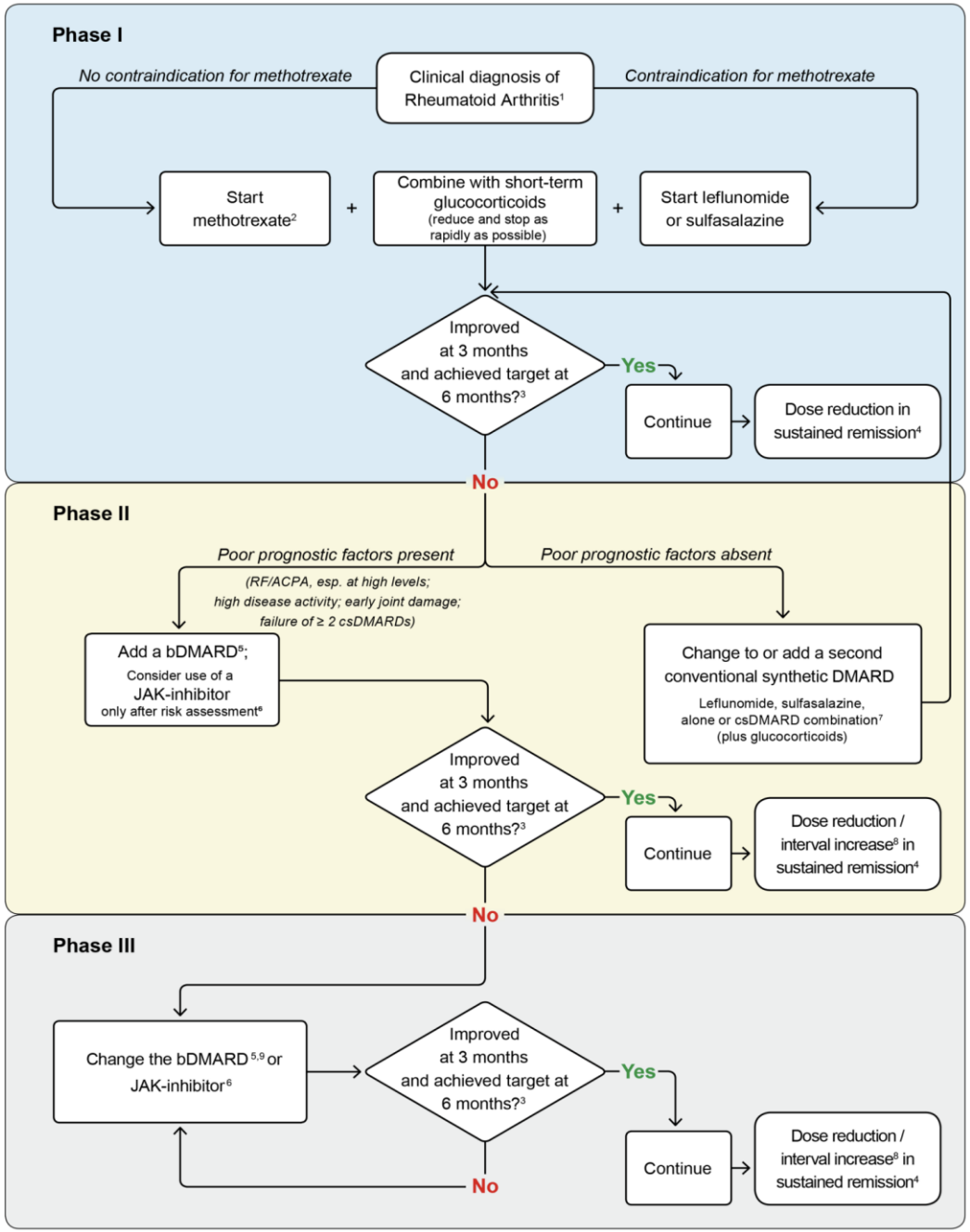
Ytterberg SR et al. N Engl J Med. 2022 Jan 27;386(4):316-326

Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

Risk factors

Age>65
History of CVD/MI/thromboembolic event
History of current or past smoking
CVD risk factors (hypertension, DM, obesity)
Risk factors for clots (blood clotting disorders, hormone replacement therapy, major surgery or immobile)

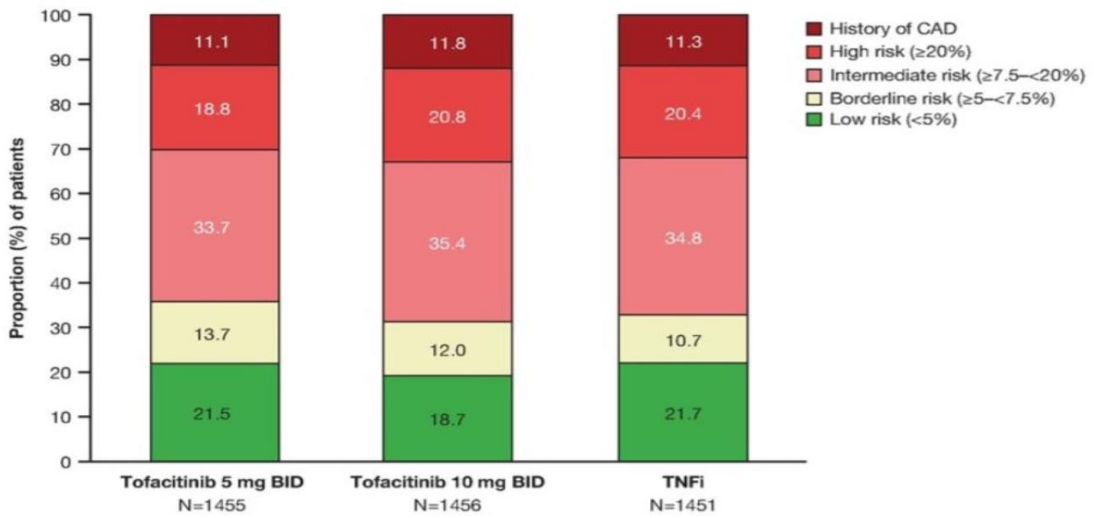


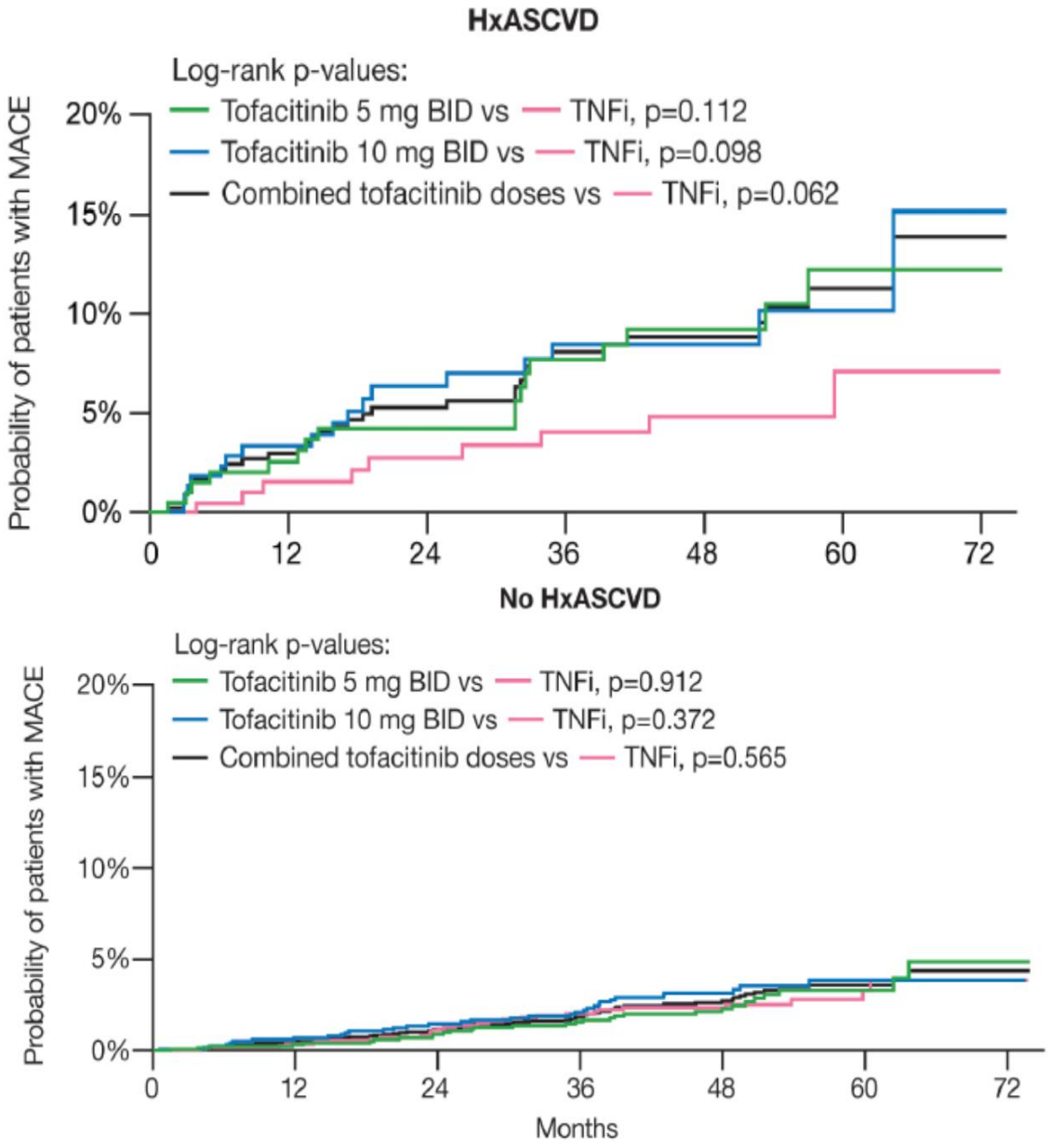
CLINICAL SCIENCE

Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: a post hoc analysis from ORAL Surveillance

Christina Charles-Schoeman ,[1] Maya H Buch ,[2,3] Maxime Dougados ,[4,5] Deepak L Bhatt ,[6] Jon T Giles,[7] Steven R Ytterberg,[8] Gary G Koch,[9] Ivana Vranic,[10] Joseph Wu,[11] Cunshan Wang,[11] Kenneth Kwok,[12] Sujatha Menon,[11] Jose L Rivas,[13] Arne Yndestad,[14] Carol A Connell,[11] Zoltan Szekanecz [15]

- CVD events and differential effect vs. TNFi concentrated in those with a history of coronary disease and those with the highest aggregate CVD risk



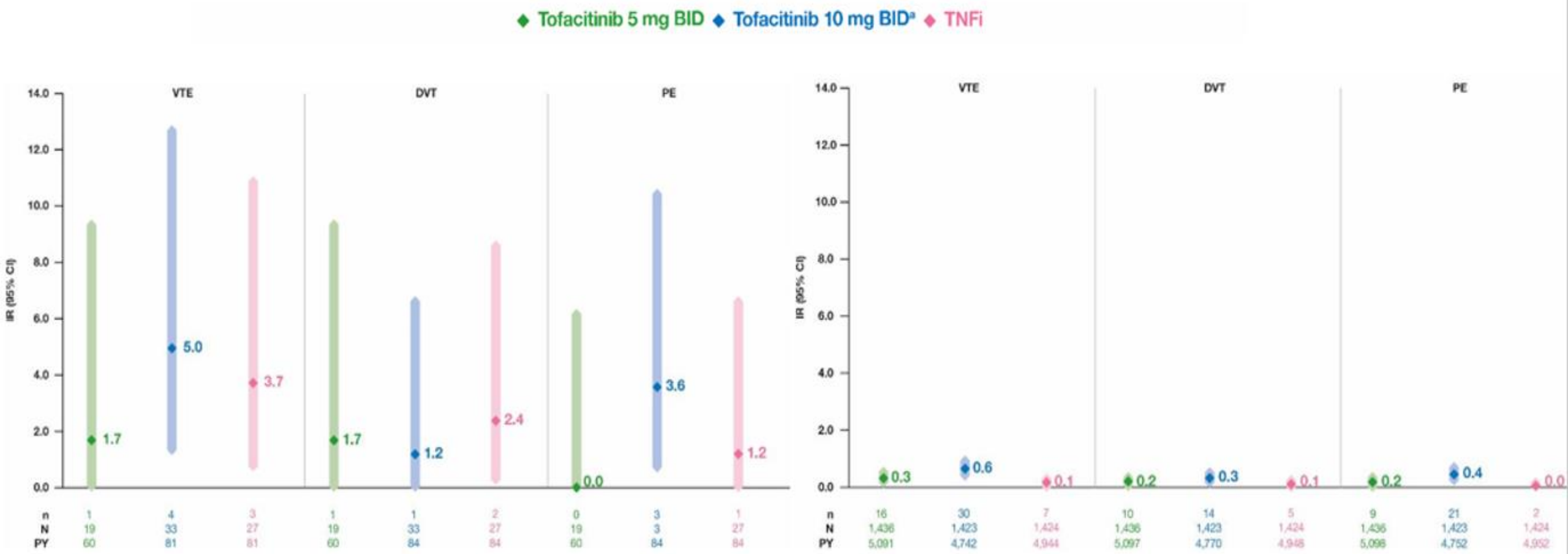


Charles-Schoeman C, et al Ann Rheum Dis 2023 Jan;82(1):119-129.

Incidence Rates for VTE, DVT, and PE in Patients With and Without a History of VTE

Patients with History of VTE

Patients without History of VTE



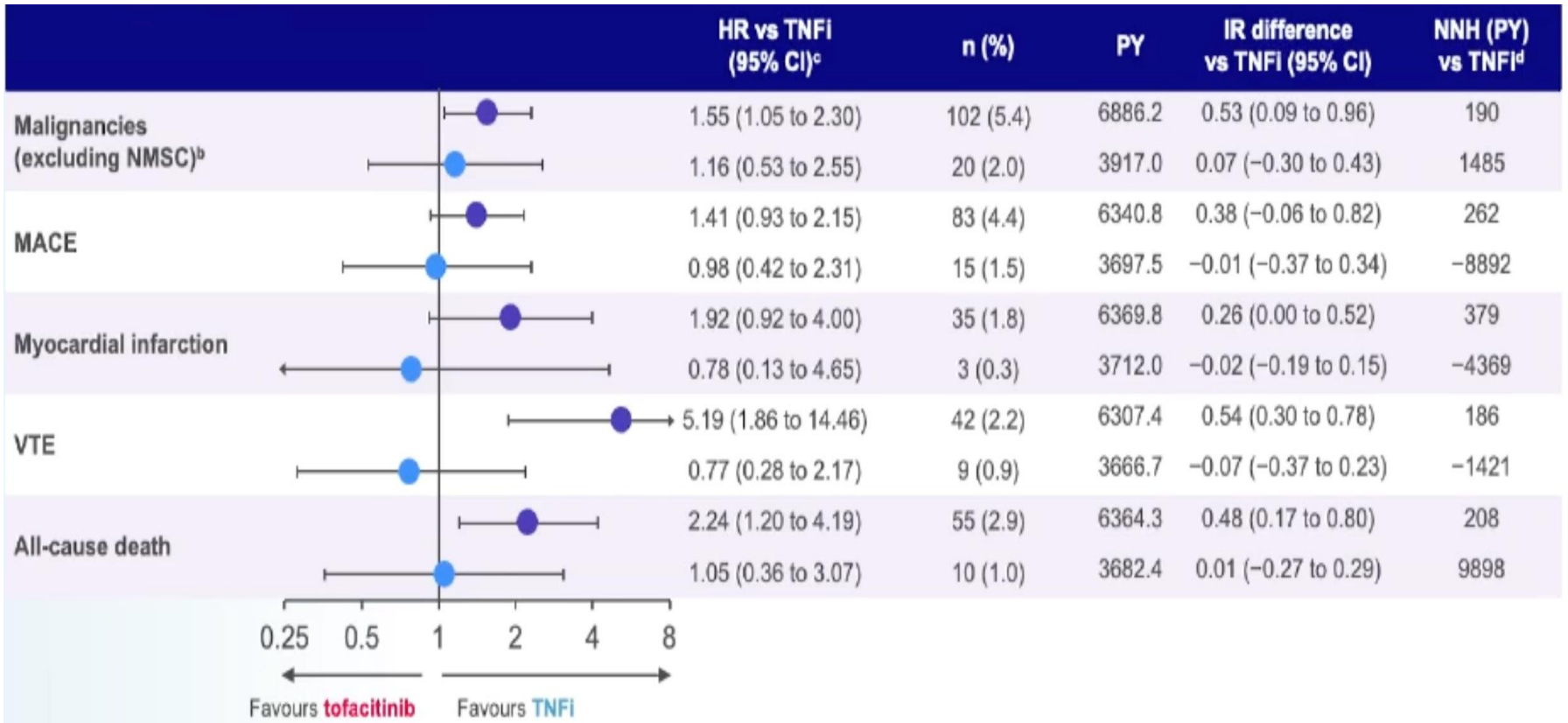
[a]The tofacitinib 10 mg BID treatment group included patients who were switched from tofacitinib 10 to 5 mg BID as a result of a study modification in February 2019. BID, twice daily; CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate; PE, pulmonary embolism; PY, patient-years; TNFi, tumor necrosis factor inhibitor; VTE, venous thromboembolism

Charles-Schoeman C, et al. The Risk of Venous Thromboembolic Events in Patients with RA Aged ≥ 50 Years with ≥ 1 Cardiovascular Risk Factor: Results from a Phase 3b/4 Randomized Safety Study of Tofacitinib vs TNF Inhibitors | *Arthritis Rheumatol.* 2021; 73 (suppl 10).

CLINICAL SCIENCE

Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance

Lars Erik Kristensen,[1] Silvio Danese,[2] Arne Yndestad,[3] Cunshan Wang,[4] Edward Nagy,[5] Irene Modesto,[6] Jose Rivas,[6] Birgitta Benda[7]



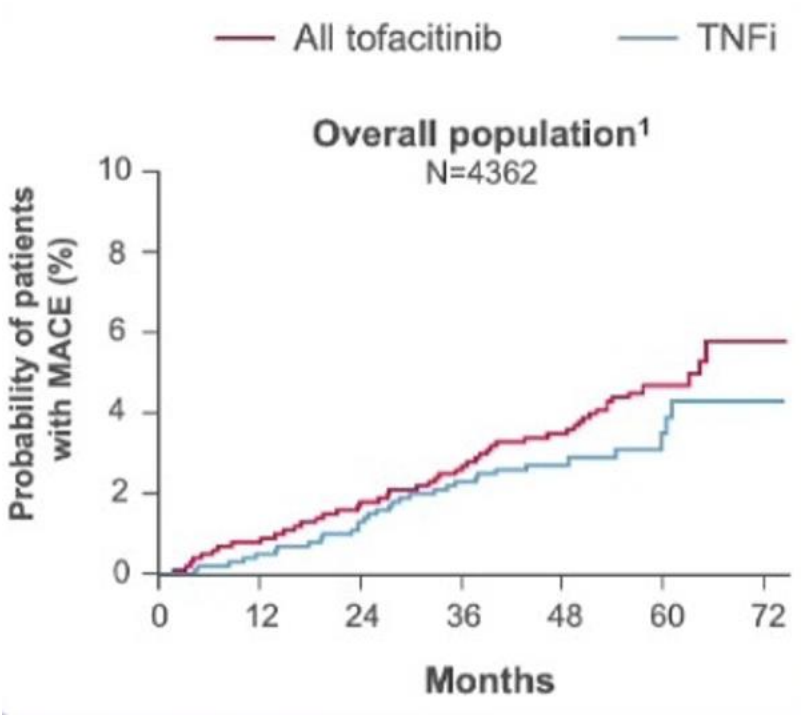
Patients who were aged ≥65 years or ever smoked had an increased risk of adverse events with tofacitinib[a] vs TNFi

Kristensen L, et al Ann Rheum Dis 2023

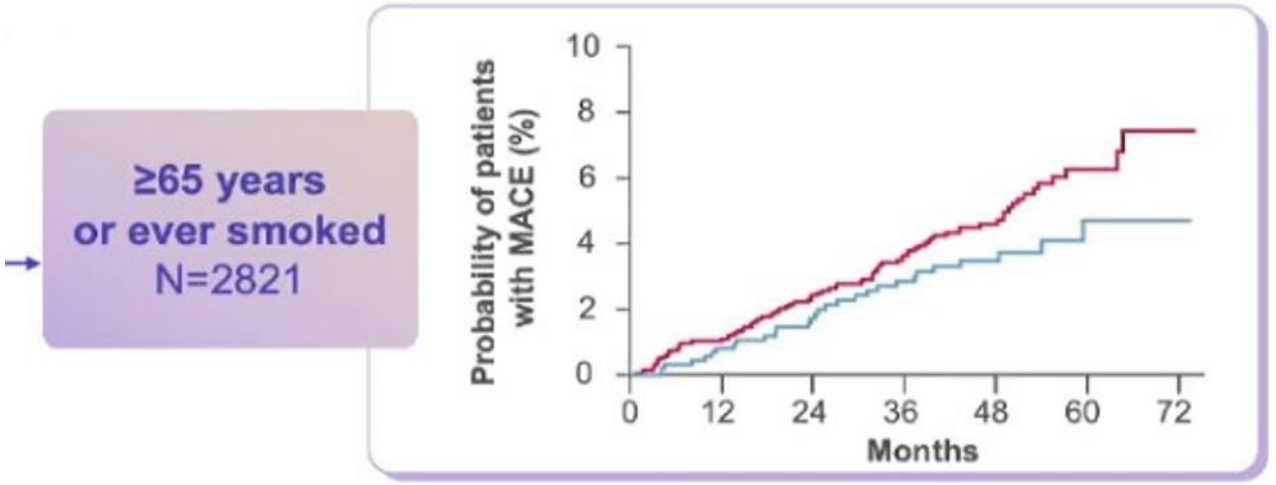
CLINICAL SCIENCE

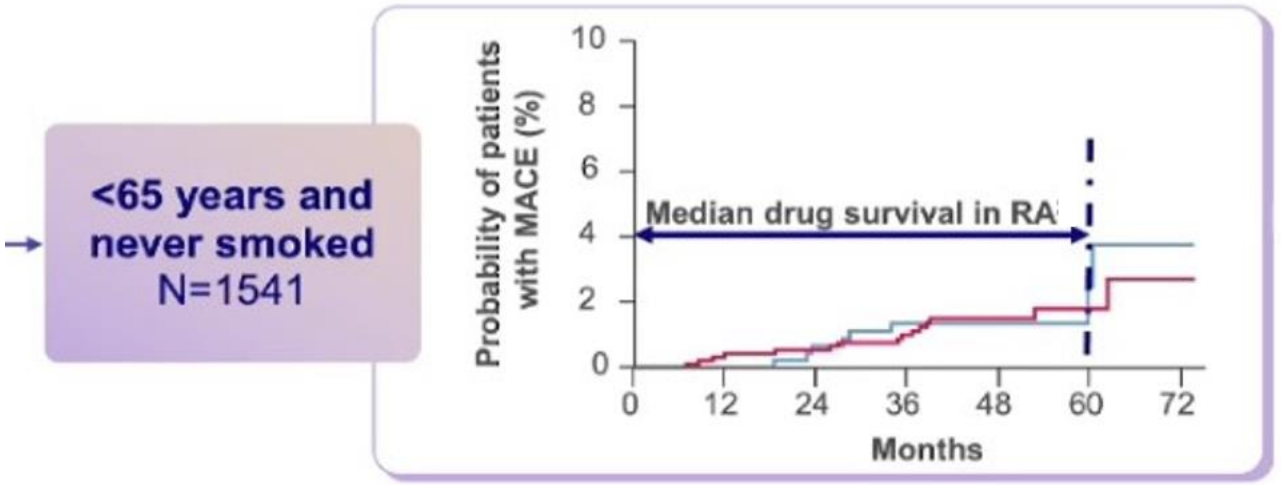
Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance

Lars Erik Kristensen,[1] Silvio Danese,[2] Arne Yndestad,[3] Cunshan Wang,[4] Edward Nagy,[5] Irene Modesto,[6] Jose Rivas,[6] Birgitta Benda[7]



Patients < 65 year old and never smoked (low risk population) showed no detectable increase risk for MACE for TOFA compared to TNFi



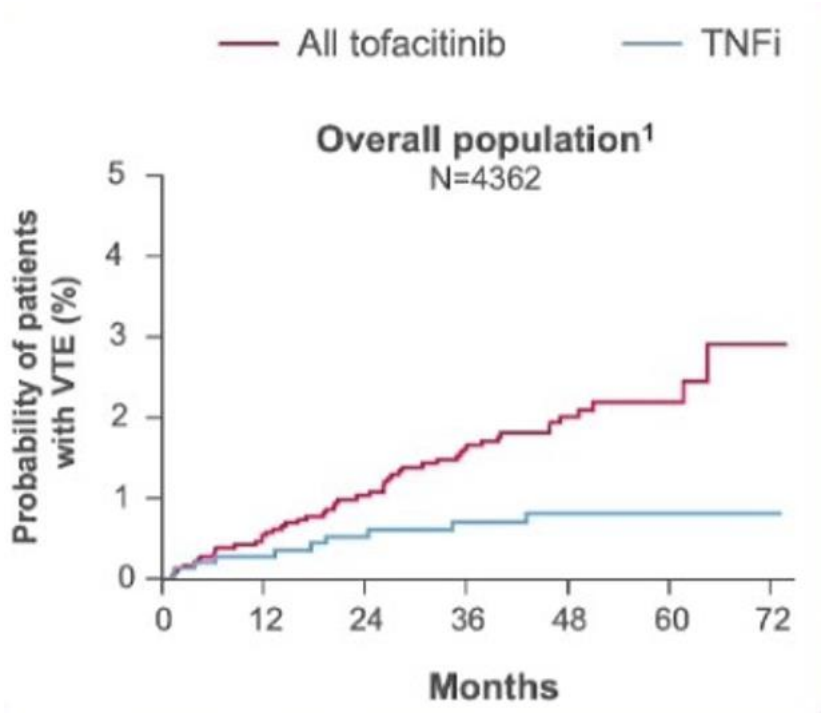


Kristensen L, et al Ann Rheum Dis 2023

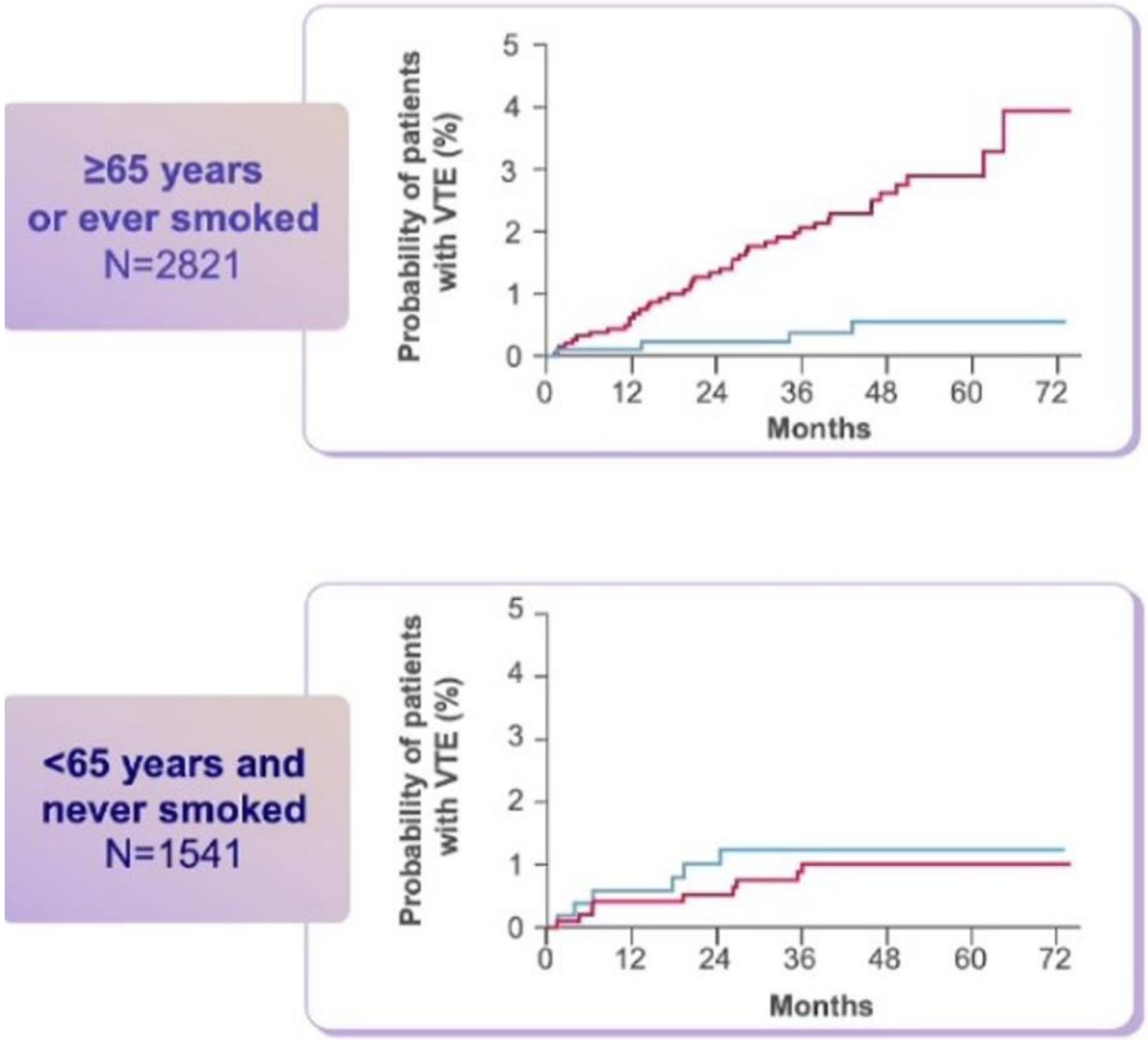
CLINICAL SCIENCE

Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance

Lars Erik Kristensen,[1] Silvio Danese,[2] Arne Yndestad,[3] Cunshan Wang,[4] Edward Nagy,[5] Irene Modesto,[6] Jose Rivas,[6] Birgitta Benda[7]



Patients < 65 year old and never smoked (low risk population) showed no detectable increase risk for VTE for TOFA compared to TNFi



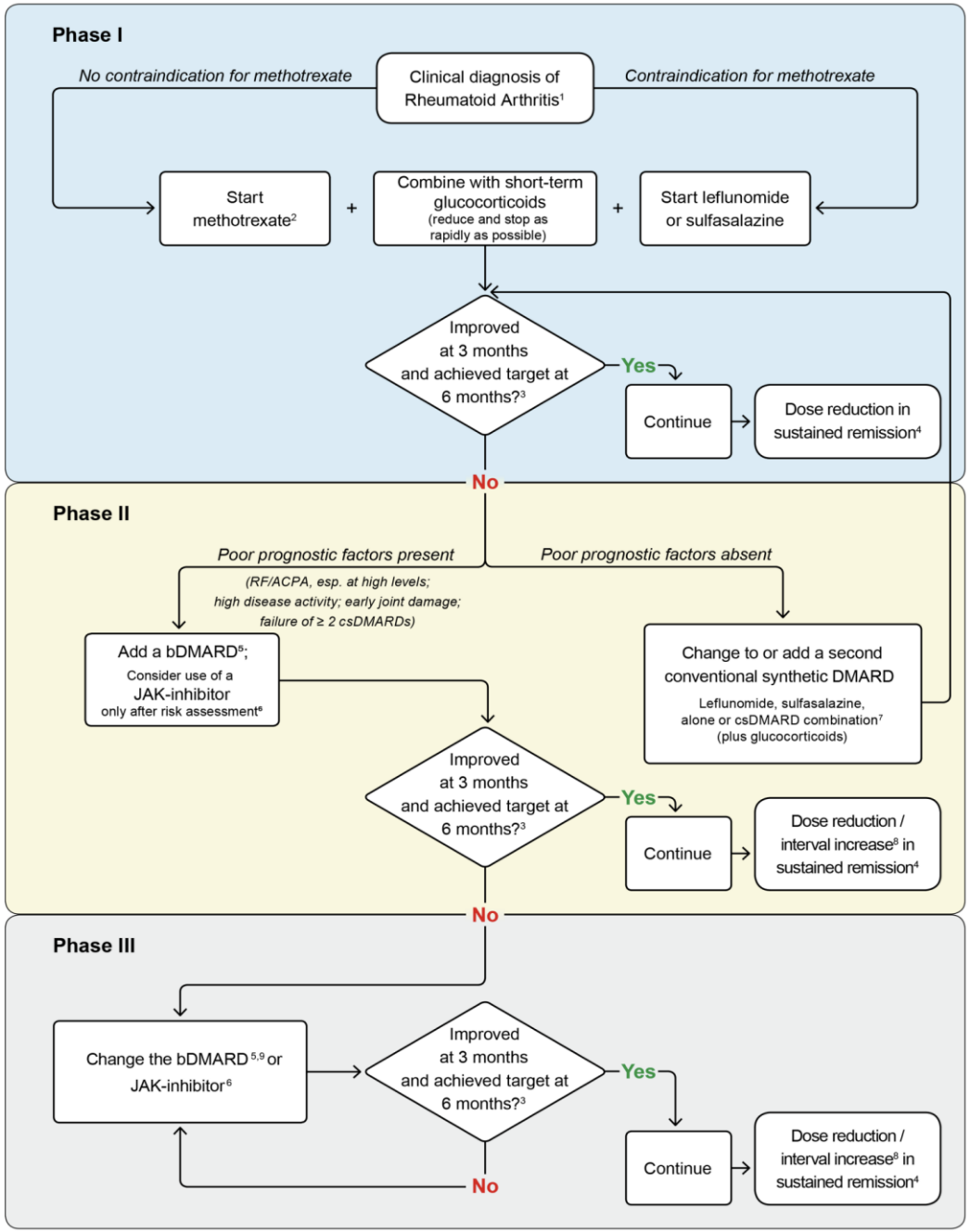
Kristensen L, et al Ann Rheum Dis 2023

Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

Risk factors

Age>65
History of CVD/MI/thromboembolic event
History of current or past smoking
CVD risk factors (hypertension, DM, obesity)
Risk factors for clots (blood clotting disorders, hormone replacement therapy, major surgery or immobile)

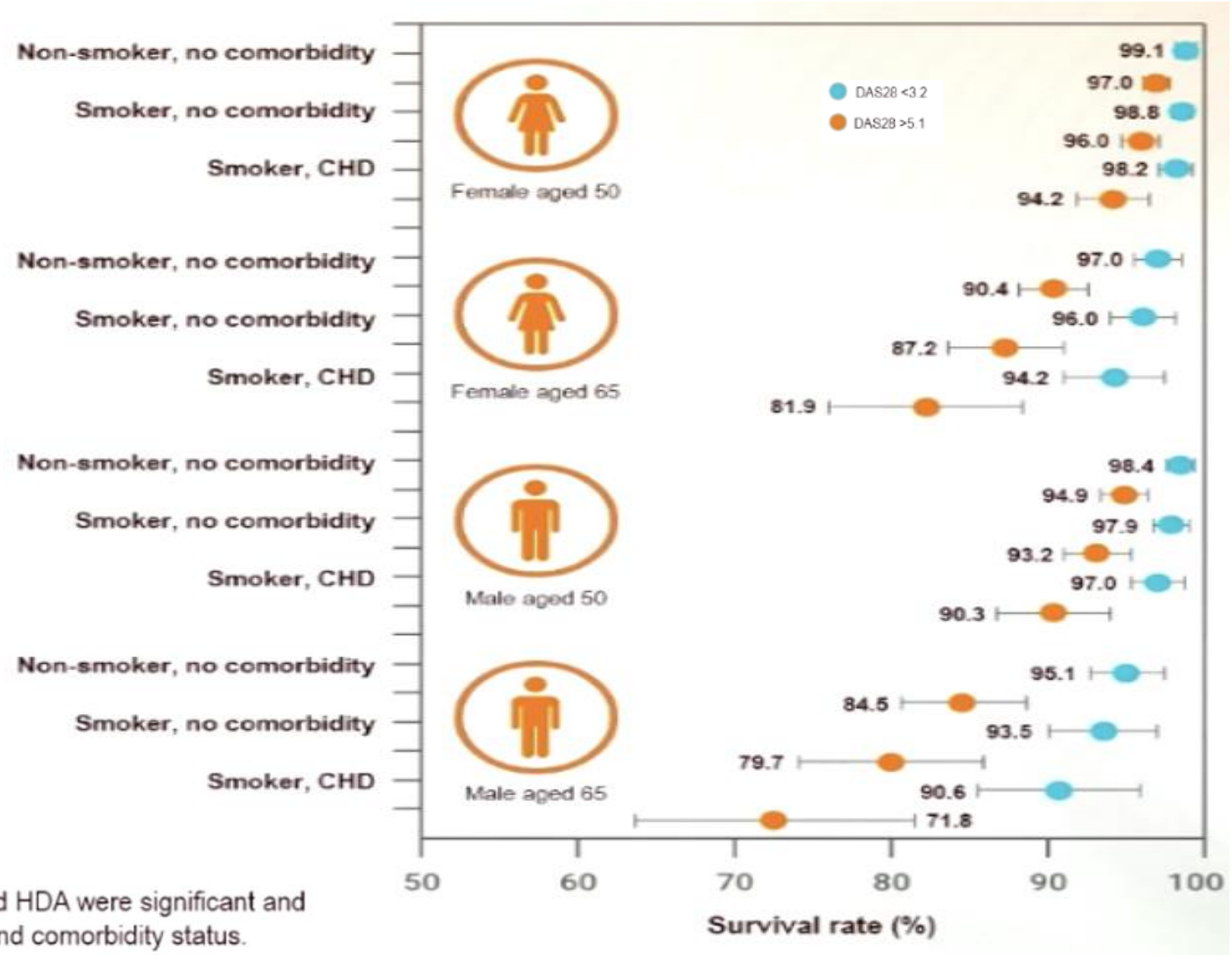


EXTENDED REPORT

Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab

Joachim Listing,[1] Jörn Kekow,[2] Bernhard Manger,[3] Gerd-Rüdiger Burmester,[4] Dagmar Pattloch,[1] Angela Zink,[1,4] Anja Strangfeld[1]

5-year survival rate for patients with high and low disease activity

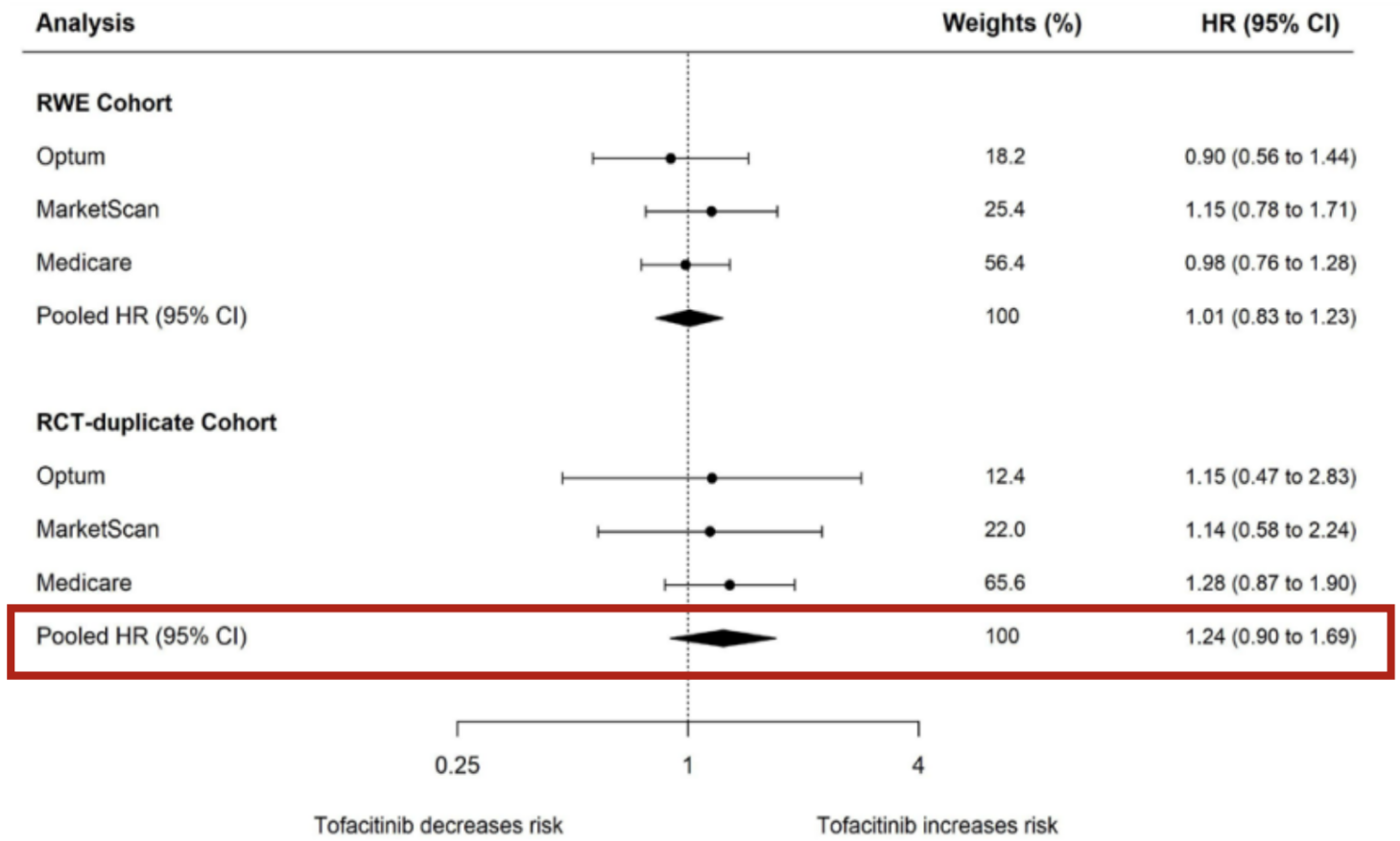


The difference in survival between patients with LDA and HDA were significant and ranged from 3–23%, depending on age, sex, smoking and comorbidity status.

Listing J et al Ann Rheum Dis 2015

Real-World Data: STAR-RA Study

- Claims data from Optum, MarketScan, Medicare
  - 89,411 TNFi initiators
  - 12,852 Tofacitinib initiators
- Analyzed the total cohort and a subgroup that would meet the CVD risk factor inclusions of ORAL Surveillance
- Primary outcome was hospitalization for MI or CVA



Khosrow-Khavar F, et al. Ann Rheum Dis. 2022 .

EPIDEMIOLOGICAL SCIENCE

Venous thromboembolism with JAK inhibitors and other immune-modulatory drugs: a Swedish comparative safety study among patients with rheumatoid arthritis

Viktor Molander ,[1,2] Hannah Bower ,[1] Thomas Frisell ,[1] Benedicte Delcoigne ,[1] Daniela Di Giuseppe,[1] Johan Askling ,[1,2] The ARTIS study group

- The Swedish Rheumatology Quality Register was linked to national health registers

  to identify treatment cohorts (exposure) of initiatorsof a JAKi (TOFA/BARI), a TNFi, or a non-TNFi bDMARD (n=32 737 treatment initiations).
- We also identified a general population cohort matched 1:5, n=92 108), an 'overall RA' comparator cohort (n=85 722)

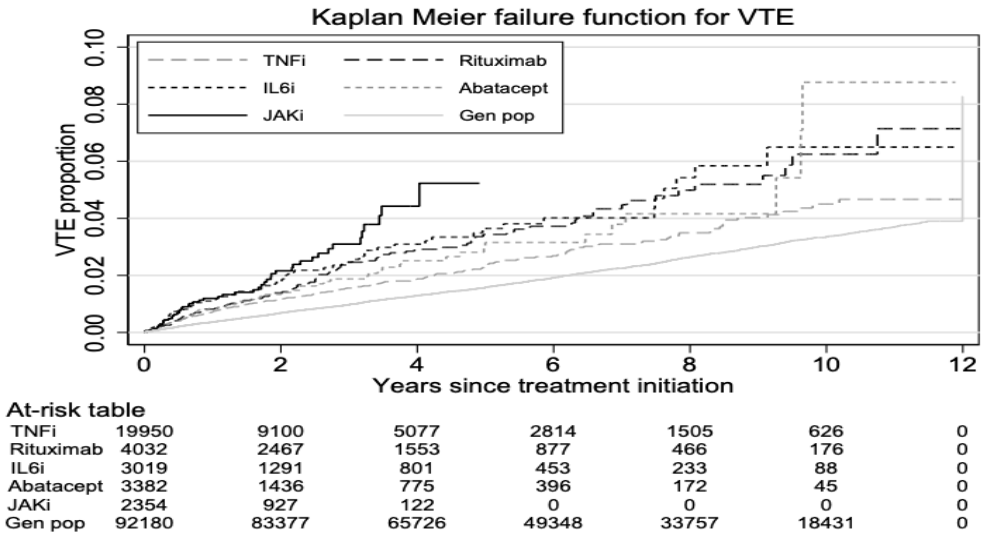
Table 2 Number of treatment initiations, person-years at risk, VTE events, age- and sex-standardised incidence rates, and HRs for VTE in Swedish patients with RA (by treatment b/tsDMARD cohort and overall) and matched individuals from the general population between 2010 and 2020

	Obs.	PYs at risk	VTE events	Standardised IR/1000 PYs (95% CI)	Unadjusted HR (95% CI)	HR (95% CI) Model 1*	HR (95% CI) Model 2†	HR (95% CI) Model 3‡
Cohort								
TNFi	19 950	55 765	287	5.15 (4.58 to 5.78)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Rituximab	4032	14 871	102	6.05 (4.98 to 7.34)	1.35 (1.08 to 1.70)	1.09 (0.86 to 1.38)	0.97 (0.76 to 1.23)	0.94 (0.74 to 1.20)
IL6i	3019	8 354	66	7.54 (5.92 to 9.59)	1.54 (1.18 to 2.01)	1.44 (1.09 to 1.92)	1.30 (0.97 to 1.73)	1.25 (0.94 to 1.67)
Abatacept	3382	8 651	56	5.69 (4.38 to 7.40)	1.25 (0.94 to 1.67)	1.10 (0.81 to 1.49)	0.89 (0.65 to 1.20)	0.89 (0.66 to 1.21)
JAKi	2354	4 184	48	11.33 (8.54 to 15.04)	2.16 (1.59 to 2.93)	1.94 (1.40 to 2.70)	1.63 (1.17 to 2.28)	1.73 (1.24 to 2.42)
Baricitinib§	1825	3 412	41	11.35 (8.35 to 15.41)	2.27 (1.64 to 3.15)	2.00 (1.41 to 2.83)	1.69 (1.19 to 2.40)	1.79 (1.25 to 2.55)
Tofacitinib§	424	667	7	11.30 (5.39 to 23.70)	1.96 (0.92 to 4.15)	1.91 (0.89 to 4.11)	1.56 (0.72 to 3.35)	1.66 (0.77 to 3.59)
Overall RA cohort	85 722	633 871	4476	5.86 (5.69 to 6.04)	n/a	n/a	n/a	n/a
Gen pop	92 180	597 854	2001	3.28 (3.14 to 3.43)	0.67 (0.59 to 0.76)	0.66 (0.57 to 0.76)	n/a	n/a

*Model 1 adjusted for age, sex and line of therapy. Overall RA cohort excluded from model.
†Model 2 additionally adjusted for comorbidities and socioeconomic variables. Overall RA cohort and general population excluded from model.
‡Model 3 additionally adjusted for RA disease variables, civil status and smoking, using an indicator for missing variables. Overall RA cohort and general population excluded from model.
§Estimates obtained from a separate model where JAKi cohort is split into baricitinib and tofacitinib.
b/tsDMARD, biologic/targeted synthetic disease modifying anti-rheumatic drug; Gen pop, general population; IL6i, interleukin 6 inhibitor; IR, incidence rate; JAKi, Janus kinase inhibitor; n/a, not applicable; PY, person years; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

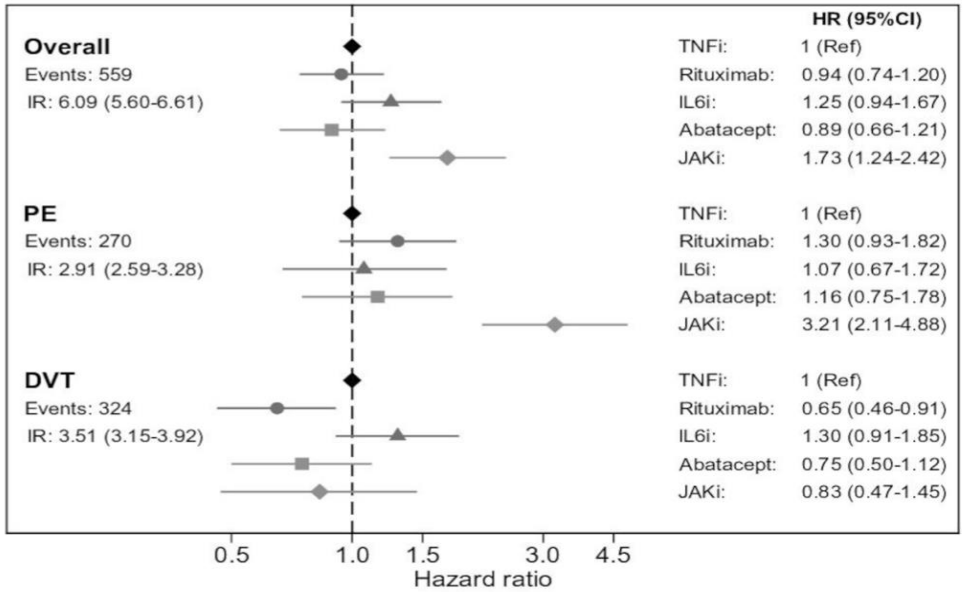
Selection bias – no information on disease activity

Real world data: Swedish registry



At-risk table

TNFi	19950	9100	5077	2814	1505	626	0
Rituximab	4032	2467	1553	877	466	176	0
IL6i	3019	1291	801	453	233	88	0
Abatacept	3382	1436	775	396	172	45	0
JAKi	2354	927	122	0	0	0	0
Gen pop	92180	83377	65726	49348	33757	18431	0



Molander V, et al. Ann Rheum Dis 2022

Clinical science

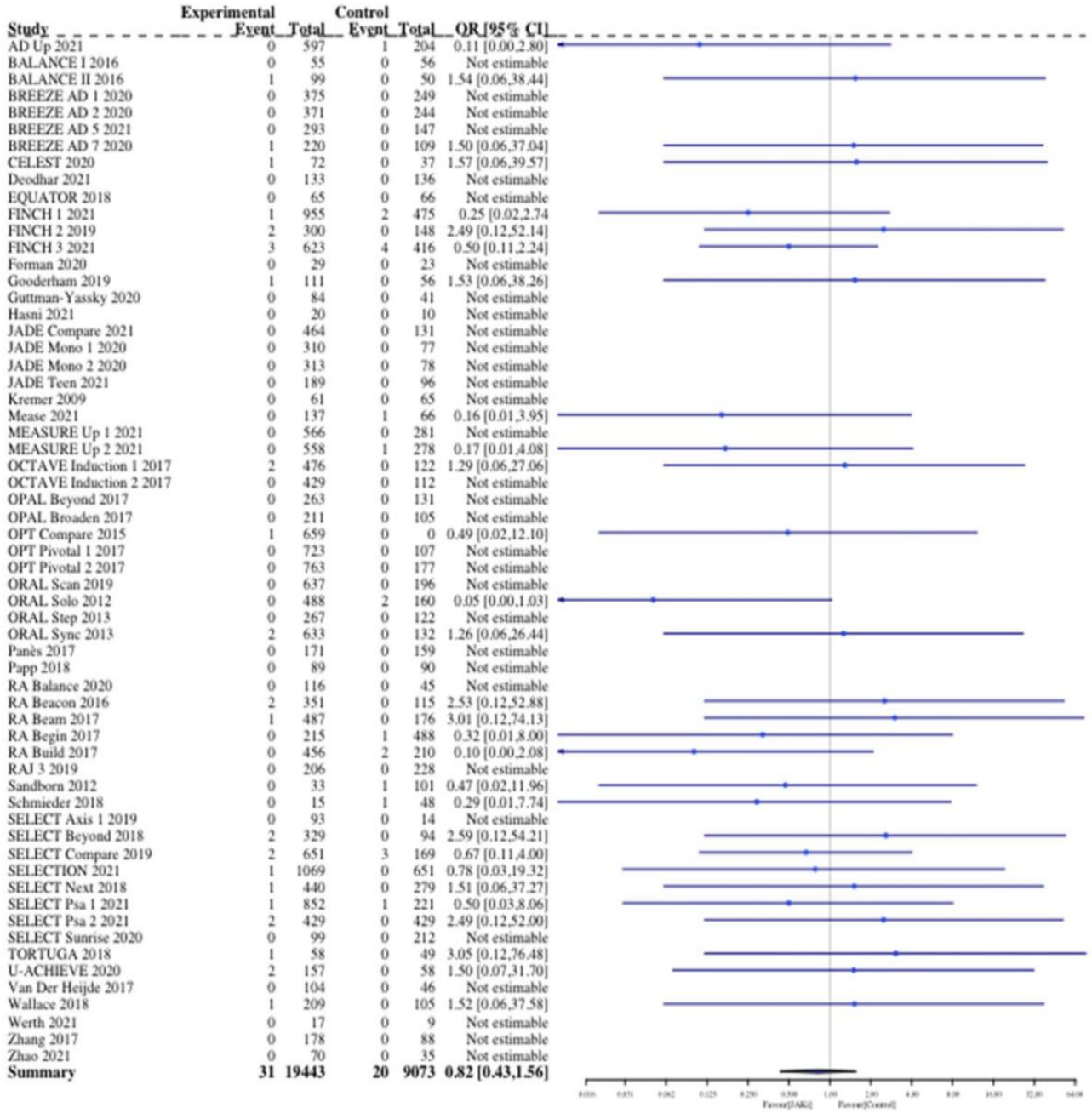
RHEUMATOLOGY

Venous and arterial thromboembolic risk of Janus kinase inhibitors: a systematic review with meta-analysis

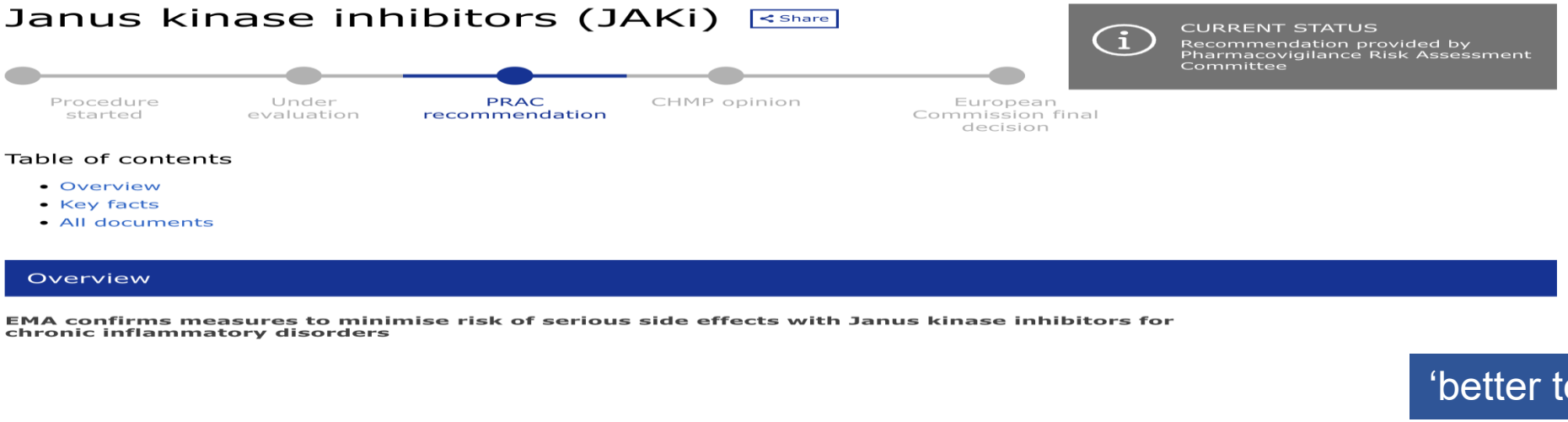
Francesco Campanaro [1,‡], Andrea Zaffaroni[2,‡], Elettra Cacioppo[2], Antonella Cappelli[1], Lorenza Bertù[3], Marco Paolo Donadini[3,4,*], Alessandro Squizzato[3,5], Alberto Batticciotto[1]

57 RCT

Tofacitinib,	Rheumatoid Arthritis
Baricitinib	Psoriatric Arthritis
Upadacitinib	Ankylosing Arthritis
Figlotinib	Atopic dermatitis
Deucravacitinib (TYK 2)	Skin Psoriasis
Ivarmacitinib (JAK1)	Crohns Disease
Brepocitinib (TYK2/JAK1)	Ulcerative colitis
	SLE



Campanaro F et al, Rheumatology 2023



‘better to be safe than sorry’

1.EU-Pharmacovigilance Risk Assessment Committee (October 2022)

• Warning for use in people >65 years, CVD risk factors, smoking, high risk of cancer •

Should be used if no other treatment options are available

• Caution in people with higher VTE risk (avoid or lower dose)

• Approved by Committee for Medicinal Products for Human Use on 11/3/22

EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

Share

News 13/01/2023

EMA's human medicines comm
Pharmacovigilance Risk Assess
kinase (JAK) inhibitors used to
cardiovascular conditions, bloo

These medicines should be use
available: those aged 65 years
heart attack or stroke), those
risk of cancer.

JAK inhibitors should be used
veins (venous thromboembolis
patient groups who are at risk

Information for healthcare professionals

- An EMA review has found that, compared with TNF-alpha inhibitors, Janus kinase (JAK) inhibitors used to treat chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata) are linked to a higher risk of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, serious infections and all-cause mortality.
- The review included the final results from an open-label clinical trial (ORAL Surveillance study)[1] of the JAK inhibitor Xeljanz (tofacitinib) in patients with rheumatoid arthritis and cardiovascular risk factors which found a higher risk of these events with Xeljanz than with TNF-alpha inhibitors.
- Preliminary findings from an observational study (B023) involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of MACE and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.
- EMA concluded that the identified risks apply to all JAK inhibitors approved for the treatment of chronic inflammatory disorders.
- These medicines (Xeljanz, Cibinqo, Olumaint, Rinvoq and Jyseleca) should only be used in the following patients if no suitable treatment alternatives are available: those aged 65 years or above, those who are current or past long-time smokers, those with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, or those with other malignancy risk factors. Cautious use is also recommended in patients with known risk factors for VTE other than those listed above.
- If JAK inhibitors are needed in patients with these risk factors, a lower dose may be recommended, depending on the medicine, the indication and the specific risk factor.
- Healthcare professionals should discuss the risks associated with JAK inhibitors with their patients.
- It is recommended that healthcare professionals carry out periodic examinations of their patients' skin to check for skin cancer, particularly for patients at risk for skin cancer.
- A letter will be sent to all healthcare professionals expected to prescribe these medicines to inform them of the outcome of the review. Full treatment recommendations will be included in the updated summary of product characteristics and the educational material for the respective products.

EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders | European Medicines Agency (europa.eu)s

Baricitinib: Phase 4 Safety Study Underway

- RA-BRIDGE (n=2600) and RA-BRANCH (n=1300)
  - RA-BRIDGE completed enrollment-completion ~2025
  - RA-BRANCH (pragmatic trial) currently enrolling-completion ~2026
- Phase 4 randomized open label non-inferiority trials (NIM 1.8)
  - Bari 2mg, 4mg, TNFi (ADA or ETAN)
- Primary outcome is VTE
  - Secondary: Arterial thrombosis, MACE, malignancy, infection
- Enriched for VTE and MACE risk factors
  - Prior VTE, age, BMI

https://clinicaltrials.gov/ct2/show/study/NCT04086745?term=baricitinib&type=Intr&phase=3&draw=2&rank=3
https://clinicaltrials.gov/ct2/show/study/NCT03915964?term=baricitinib&type=Intr&phase=3&draw=2&rank=4

EULAR recommendations for the management of psoriatic arthritis: 2023 update

Laure Gossec (Paris, France) and Josef Smolen (Vienna, Austria)

On behalf of the EULAR PsA management taskforce

Steering group: Andreas Kerschbaumer, Ricardo Ferreira, Heidi Bertheussen, Xenofon Baraliakos, Daniel Aletaha, Dennis McGonagle, Désirée van der Heijde, Iain McInnes, Bente Appel Esbensen, Kevin Winthrop, Wolf-Henning Boehncke

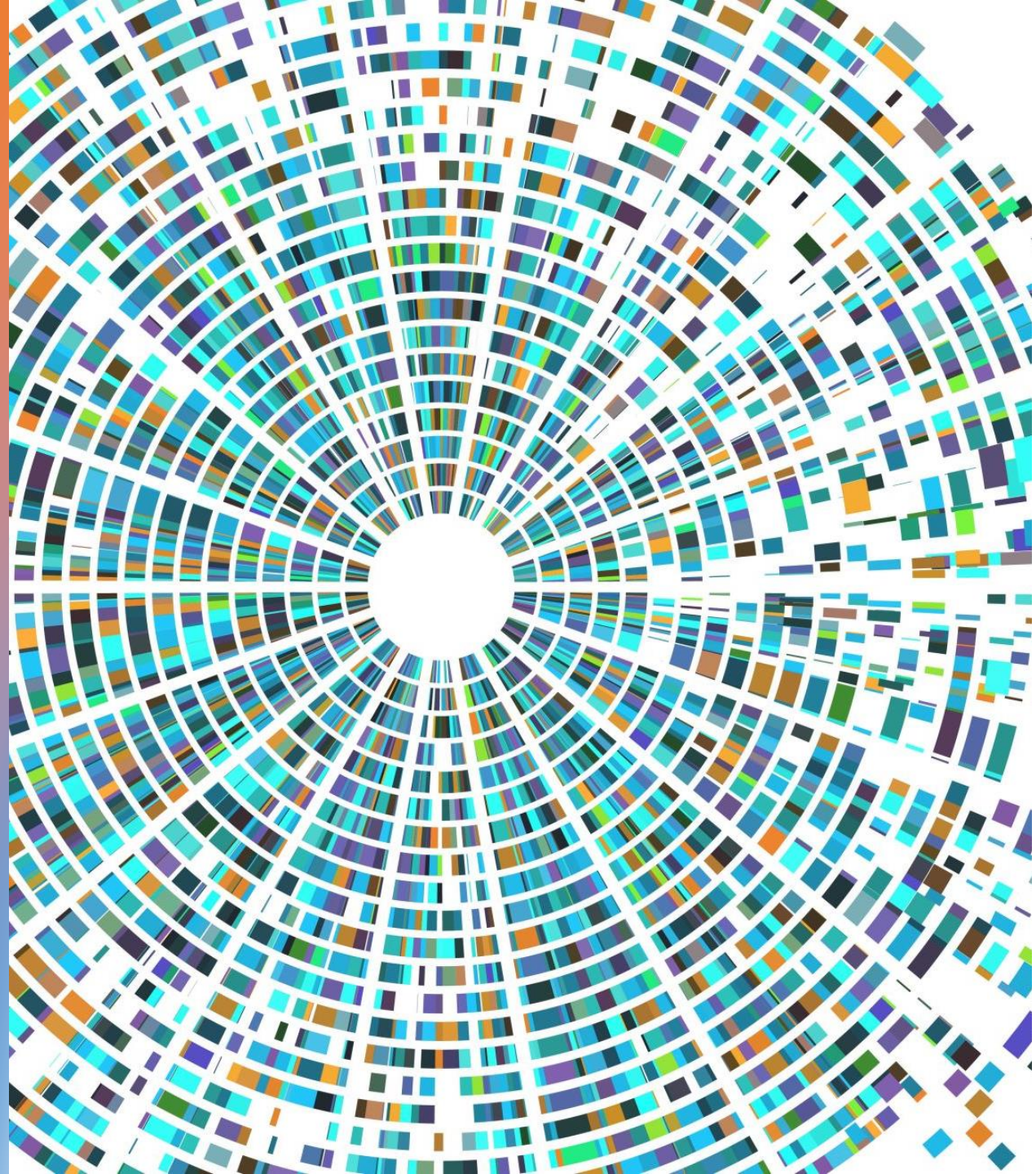
Taskforce members: Peter Nash, Andra Balanescu, Peter Balint, Gerd-Rüdiger Burmester, Juan D Canete, Pascal Claudepierre, Lihi Eder, Merete Hetland, Annamaria Iagnocco, Lars Erik Kristensen, Rik Lories, Ruben Queiro, Daniele Mauro, Helena Marzo-Ortega, Philip Mease, Wendy Olsder, Laura Savage, Georg Schett, Stephanie Shoop-Worall, Yoshiya Tanaka, Filip Van den Bosch, Anette van der Helm-van Mil, Alen Zabotti

4. In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced. 1a A

5. In patients with peripheral arthritis and an inadequate response to at least one bDMARD, or when a bDMARD is not appropriate, a JAKi may be considered, taking safety considerations* into account. 1b/4 B/D

bDMARD Mode of action	TNF inhibitor	IL17A inhibitor	IL12/23 inhibitor	IL23p19 inhibitor	*IL17 A&F inhibitor*
Drugs	Adalimumab Certolizumab Etanercept Infliximab Golimumab	Ixekizumab Secukinumab	Ustekinumab	Guselkumab Risankizumab	*Bimekizumab - Pending approval*

*For JAK-inhibitors, caution is needed for patients aged 65 years or above, current or past long-time smokers, with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors or with other malignancy risk factors; with known risk factors for VTE.



QUESTIONS

- ✓ Do the results of ORAL Surveillance apply to other JAKi's in RA?
- ✓ Do the results of ORAL Surveillance apply to other diseases than RA that are treated with JAKi's?
- ✓ Should I switch patients in high risk groups to other agents?
- ✓ JAKi might be protective against many of the outcomes under study if compared with no therapy, non-biologic DMARDs, or even other bDMARD

What is next - CV risk assessment

JAK inhibitors are here to stay
(great efficacy, novel indications)

RA disease control is protective against CVD outcomes

Screening patients for various risk factors prior to therapy selection "high risk population" (age, smoking, history of ASCVD, VTE, PE)

Continue to weight CVD risk and benefit

Individualize therapy for patients with RA taking into account risk factors, co-morbidities and concomitant medications.

More data for well-design longitudinal studies

Reduce risk
Maximize benefit

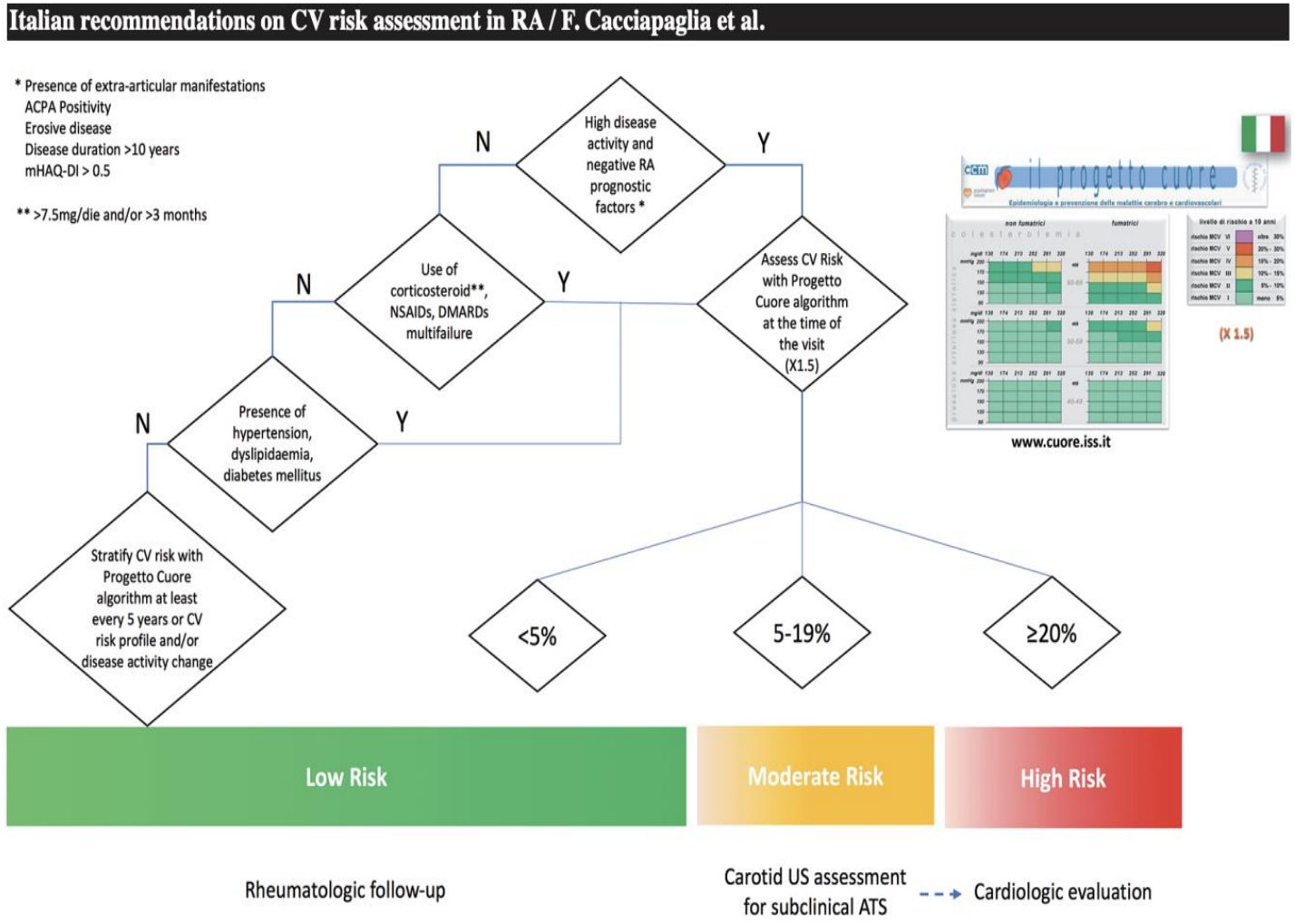


Fig. 1. Recommended algorithm as flowchart for the evaluation of CV risk in RA patients in clinical practice.
ACPA: anti-citrullinated peptides antibodies; CV: cardiovascular; DMARDs: disease-modifying anti-rheumatic drugs; mHAQ-DI: modified Health Assessment Questionnaire Disability Index; NSAIDs: non-steroidal anti-inflammatory drugs; RA: rheumatoid arthritis.

Cacciapaglia et al, Clin Exp Rheumatol. 2023

ΣΥΜΠΕΡΑΣΜΑΤΑ

- ✓ Οι αναστολείς των JAK κινασών συνιστούν μια νέα αποτελεσματική θεραπευτική κατηγορία για την αντιμετώπιση των συστηματικών παθήσεων
- ✓ Η χορήγησή τους σε ασθενείς με παράγοντες κινδύνου θα πρέπει αξιολογείται μεταξύ κινδύνου/αποτελέσματος
- ✓ Η διακοπή της αγωγής θα πρέπει επίσης να σταθμίζεται σε σχέση με τους κινδύνους (υποτροπή της νόσου)
- ✓ Μελλοντικές τυχαιοποιημένες μελέτες και δεδομένα καθημερινής κλινικής πρακτικής θα αποσαφηνίσουν τους πιθανούς μηχανισμούς πρόκλησης καρδιαγγειακών επεισοδίων/νεοπλασιών και το ρόλο που μπορεί να έχει η διαστρωμάτωση του κινδύνου και η επιλογή ασθενών με βάση τους παράγοντες κινδύνου στα μακροχρόνια αποτελέσματα