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Cardiovascular and Venous Thromboembolic Risk With Janus Kinase Inhibitors in Immune-Mediated Inflammatory Diseases: A Systematic Review and Meta-Analysis of Randomized Trials

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Objective. Janus kinase (JAK) inhibition effectively treats immune-mediated inflammatory diseases (IMIDs); however, concern over the risk of major adverse cardiac events (MACE) and venous thromboembolism (VTE) remains. We aimed to evaluate the safety (VTE and MACE outcomes) of JAK inhibitors in the treatment of IMIDs.

Methods. A search in PubMed, Embase, and ClinicalTrials.gov databases was conducted for randomized clinical trials (RCTs) of JAK inhibitors across IMIDs. Primary outcomes were VTE and MACE with JAK inhibitors compared with placebo and active comparator arms stratified by follow-up time.

Results. Sixty-six RCTs enrolled 38,574 patients with a mean age of 48.8 years and a mean follow-up of 10.5 months. JAK inhibitors had a numerically higher rate of VTE when compared with controls (odds ratio [OR] 1.65; 95% confidence interval [CI]: 0.97-2.79), driven by trials with a follow-up duration of 12 or more months (OR 2.17; 95% CI: 1.16-4.05; $P_{interaction}$ = 0.05). When compared with active comparators, JAK inhibitors increased VTE in clinical trials with 12 or more months' versus less than 12 months' follow-up time (OR 2.38 [95% CI: 1.24-4.57] vs 0.30 [95% CI: 0.07-1.26], respectively; $P_{interaction}$ = 0.01). No increased risk of VTE was seen when comparing JAK inhibitors with placebo arms. For the outcome of MACE, the results were largely similar but did not reach statistical significance (OR 1.19; 95% CI: 0.86-1.64).

Conclusion. JAK inhibitors when compared with active comparator arms increased the risk of VTE, which was dependent on duration of exposure. Future clinical trials with extended follow-up are needed to clarify the safety profiles of JAK inhibitors.

INTRODUCTION

Janus kinase (JAK) inhibition via oral small molecule inhibitors is commonly used in treatment across immune-mediated inflammatory diseases (IMIDs), including rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and atopic dermatitis (1). Four JAK inhibitors are currently approved by the US Food and Drug Administration (FDA) in the United States (abrocitinib, baricitinib, upadacitinib, and tofacitinib), whereas filgotinib is approved in Europe for the treatment of certain IMIDs. In prior clinical trials of JAK inhibitors, a concern was raised over a numerically higher rate of venous thromboembolism (VTE), including pulmonary embolism, specifically at higher JAK inhibitor dosing (4 mg of baricitinib) in those with rheumatoid arthritis (2,3). However, expanded meta-analyses of IMIDs

across a variety of JAK inhibitors (4,5) and a prospective registry analysis over 5 years have not shown this (6).

In a clinical trial evaluating tofacitinib in patients with rheumatoid arthritis, tofacitinib displayed a higher incidence of pulmonary embolism when compared with a tumor necrosis factor (TNF) inhibitor (7). This led to a 2019 FDA black box warning for VTE at the higher dose of tofacitinib (10 mg twice daily) as well as a mandate for a postmarketing surveillance study, the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study (8). This study, which enrolled patients with elevated cardiovascular risk rheumatoid arthritis, found after a median follow-up of 4.0 years an increased risk of VTE up to a hazard ratio (HR) of 3.52 with a 95% confidence interval (CI) of 1.74 to 7.12 at 10 mg twice daily of tofacitinib (high dose) and risk of major adverse cardiovascular events

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(MACE) (HR 1.33; 95% CI: 0.91-1.94) (9) across both high and low (5 mg twice daily) doses of tofacitinib (8).

In September 2021, on the basis of preliminary results from ORAL Surveillance, the FDA expanded the black box warning to also include MACE and even malignancy and all-cause mortality (10). Given the high efficacy of JAK inhibitors and the concern for increases in VTE and MACE, our objective was to assess the safety of JAK inhibitors compared with both placebo and active comparator arms used in the treatment of IMIDs.

MATERIALS AND METHODS

Search strategy and selection criteria. This meta-analysis and systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (11). This analysis was not considered for institutional review board review because there was no direct human subject involvement.

A time-limited search from January 1, 1990, to January 28, 2022, was conducted using PubMed and Embase databases. To identify grey literature, www.ClinicalTrials.gov and https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm were searched. We also considered references of the eligible studies to identify further studies. The following Medical Education Subject Headings were used for this search: "Autoimmune disease" or "inflammatory immune-mediated disease" or "rheumatoid arthritis" or "psoriasis" or "psoriatic arthritis" or "inflammatory arthritis" or "ankylosing spondylitis" or "atopic dermatitis" or "systemic lupus erythematosus" or "inflammatory bowel disease" or "ulcerative colitis" or "crohns" and "JAK inhibitors" or "tofacitinib" or "abrocitinib" "baricitinib" or "upadacitinib" or "filgotinib" and "myocardial infarction" or "myocardial ischemia" or "heart failure" or "non-fatal ischemic stroke" or "cardiac mortality" or "deep vein thrombosis" "pulmonary embolism." The search was limited by the following constraints: English language and human study participants.

The prespecified eligibility criteria were randomized clinical trials (RCTs) that met the initial search terms of an IMID involving JAK inhibitors with either a placebo or active comparator arm (eg, an approved biologic or targeted therapy). JAK inhibitors were included if they were approved for the treatment of an IMID either in the United States with the US FDA or in Europe with the European Commission. Studies without a comparison arm and observational studies were not included. Editorials, letters, and review articles were excluded.

The studies were screened by two independent authors (MHM and MSG). Nonrelevant studies were excluded on the basis of the title and abstract. Full-text studies were then screened for final selection on the basis of the abovementioned prespecified inclusion criteria.

Data analysis. Two reviewers independently reviewed the literature and extracted and entered data. We only sought summary estimates data. Data extracted included first author, year of publication, age (years), percentage of male patients, number of patients studied in each arm, IMID type, JAK inhibitor type, follow-up duration (months), and type of comparison arm (placebo or standard of care). We searched the FDA website (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) for JAK inhibitors for unpublished MACE and VTE events. If a discrepancy between data abstracted from FDA dockets and the published literature was found, data from the published literature were used (9). Two authors independently appraised the methodological quality of included trials using the Cochrane Risk of Bias Tool, which assessed selection, allocation, performance, detection, attrition, and reporting bias (Supplementary Table 1) (12).

The prespecified end points were MACE and VTE with JAK inhibitors when compared with 1) both placebo and an active comparator arm (combined, also termed "control arm"), 2) placebo only, and 3) an active comparator arm only (eg, an active treatment such as biologic therapy) as dictated in the clinical trial. MACE was defined as cardiovascular mortality, myocardial ischemia, myocardial infarction, nonfatal ischemic stroke, and heart failure. VTE was defined as a study documented or adjudicated venous thrombolism (e.g. deep vein thrombosis and/or pulmonary embolism).

Continuous variables were reported as mean with standard deviation, categorical variables were expressed as frequency and percentage, and adverse events were reported using odds ratio (OR) and 95% CI. The trials were pooled using the fixed-effect Mantel-Haenszel model (13), and subsequently stratified by duration of follow-up and considered as the primary analysis to allow incorporation of those with large weights (ORAL Surveillance). To statistically allow all clinical trials that met our inclusion criteria, an exploratory analysis was performed using fixed-effect and random-effects models with continuity correction (which accounted for zero events and the incorporation of the maximal number of clinical trials in the analyses) in addition to a person-years analysis (14). Heterogeneity between studies was assessed with the Cochran's Q test and I^2 statistic (15). I^2 values of less than 25%, 25% to 50%, 50% to 75%, and greater than 75% indicated low, moderate, high, and extreme heterogeneity, respectively. A meta-regression analysis was performed to evaluate the relationship of follow-up time on outcomes. A P value less than 0.05 was considered statistically significant. A P value for interaction ($P_{interaction}$) was used to evaluate the difference between subgroups. Risk estimates and effect sizes were calculated using Stata version 17.0 software (StataCorp).

Role of the funding source. There was no funding source for this study.

RESULTS

Literature search. The initial search yielded 2931 reports, of which 133 trials were reviewed in full and 66 met the study eligibility criteria and were included in the final meta-analysis. VTE was

Table 1. Characteristics of studies included for analysis

Author (year)	JAK inhibitor group	Placebo or comparator arm	Total participants	Disease condition	JAK inhibitor	Mean age (years)	Male sex (%)	Follow-up (months)	Placebo, active comparator, or both	Active comparator
Bachelez et al (2015) (16)	659	442	1101	Psoriasis	Tofacitinib	44.3	71.1	3	Both	Etanercept
Bieber et al (2021) (66)	464	373	837	Atopic dermatitis	Abrocitinib	37.9	50.4	4	Both	Dupilumab
Blauvelt et al (2021) (75)	348	344	692	Atopic dermatitis	Upadacitinib	36.7	54.5	4	Active comparator	Dupilumab
Blauvelt et al (2021) (67)	531	267	798	Atopic dermatitis	Abrocitinib	28.7	55	3	Placebo	
Burmester et al (2018) (17)	440	221	661	Rheumatoid arthritis	Upadacitinib	55.7	21.3	3	Placebo	
Burmester et al (2013) (18)	267	132	399	Rheumatoid arthritis	Tofacitinib	54.8	16.8	3	Placebo	
Conaghan et al (2016) (19)	36	37	73	Rheumatoid arthritis	Tofacitinib	49.3	19.2	6	Placebo	
Dougados et al (2017) (22)	456	228	684	Rheumatoid arthritis	Baricitinib	51.7	18.1	3	Placebo	
Fleischmann et al (2012) (23)	272	112	384	Rheumatoid arthritis	Tofacitinib	53.2	13	6	Both	Adalimumab
Fleischmann et al (2019) (24)	650	979	1629	Rheumatoid arthritis	Upadacitinib	54	20.5	3	Both	Adalimumab
Fleischmann et al (2017) (25)	159	210	369	Rheumatoid arthritis	Baricitinib	51	27.1	6	Placebo	
Fleishmann et al (2012) (26)	486	122	608	Rheumatoid arthritis	Tofacitinib	51.8	13.4	3	Placebo	
Fleishmann et al (2017) (27)	760	386	1146	Rheumatoid arthritis	Tofacitinib	49.8	17.1	12	Active comparator	Adalimumab
Genovese et al (2016) (28)	351	176	527	Rheumatoid arthritis	Baricitinib	55.7	18.2	3	Placebo	
Genovese et al (2016) (29)	249	50	299	Rheumatoid arthritis	Upadacitinib	55	20.7	3	Placebo	
Genovese et al (2018) (31)	300	148	448	Rheumatoid arthritis	Filgotinib	55.7	19.6	6	Placebo	
Genovese et al (2018) (30)	329	169	498	Rheumatoid arthritis	Upadacitinib	57.1	16.1	3	Placebo	
Gladman et al (2017) (32)	263	131	394	Psoriatic arthritis	Tofacitinib	49.9	44.7	6	Placebo	
Gooderham et al (2019) (68)	211	56	267	Atopic dermatitis	Abrocitinib	40.8	46.4	3	Placebo	
Guttman-Yassky et al (2020) (69)	126	41	167	Atopic dermatitis	Upadacitinib	40	37.7	4	Placebo	
Guttman-Yassky et al (2021) (70)	566	281	847	Atopic dermatitis	Upadacitinib	34	54	4	Placebo	
Mease et al (2017) (33)	211	211	422	Psoriatic arthritis	Tofacitinib	48	44.6	12	Both	Adalimumab
Hasni et al (2021) (71)	20	10	30	Systemic lupus erythematosus	Tofacitinib	45.9	13.3	3	Placebo	
Silverberg et al (2020) (72)	313	78	391	Atopic dermatitis	Abrocitinib	35.1	58.6	3	Placebo	
Kameda et al (2020) (35)	148	49	197	Rheumatoid arthritis	Upadacitinib	55.2	21.4	3	Placebo	
Kremer et al (2009) (36)	199	65	264	Rheumatoid arthritis	Tofacitinib	50.6	85.6	6	Placebo	
Kremer et al (2012) (37)	438	69	507	Rheumatoid arthritis	Tofacitinib	53.1	19.9	6	Placebo	
Kremer et al (2013) (38)	633	159	792	Rheumatoid arthritis	Tofacitinib	52.2	18.6	12	Placebo	
Kremer et al (2016) (39)	220	56	276	Rheumatoid arthritis	Upadacitinib	57.4	20	3	Placebo	
Lee et al (2014) (40)	770	186	956	Rheumatoid arthritis	Tofacitinib	49.6	20.7	24	Placebo	
McInnes et al (2021) (41)	852	852	1704	Psoriatic arthritis	Upadacitinib	50.6	46.3	3	Both	Adalimumab
Mease et al (2017) (42)	65	66	131	Psoriatic arthritis	Filgotinib	49.5	49.6	4	Placebo	
Mease et al (2021) (73)	429	212	641	Psoriatic arthritis	Upadacitinib	53.4	54.3	6	Placebo	
Ytterberg et al (2022) (9)	2911	1451	4362	Rheumatoid arthritis	Tofacitinib	61	22	48	Active comparator	Adalimumab and etanercept
Panés et al (2017) (43)	188	91	279	Crohn disease	Tofacitinib	39	47.7	2	Placebo	

(Continued)

Table 1. *(Cont'd)*

Author (year)	JAK inhibitor group	Placebo or comparator arm	Total participants	Disease condition	JAK inhibitor	Mean age (years)	Male sex (%)	Follow-up (months)	Placebo, active comparator, or both	Active comparator
Papp et al (2012) (44)	147	50	197	Psoriasis	Tofacitinib	44.3	63.5	3	Placebo	
Papp et al (2015) (45)	723	177	900	Psoriasis	Tofacitinib	45.8	71.4	4	Placebo	
	763	196	959	Psoriasis	Tofacitinib	45.4	67.6	4	Placebo	
Reich et al (2020) (46)	220	108	328	Atopic dermatitis	Baricitinib	33.8	66	4	Placebo	
Rubbert-Roth et al (2020) (47)	303	309	612	Rheumatoid arthritis	Upadacitinib	55.6	18	3	Abatacept	Abatacept
Sandborn et al (2012) (48)	146	48	194	Ulcerative colitis	Tofacitinib	32.3	54.6	2	Placebo	
Sandborn et al (2014) (49)	105	34	139	Crohn disease	Tofacitinib	37.3	50.4	1	Placebo	
Sandborn et al (2017) (50)	476	122	598	Ulcerative colitis	Tofacitinib	41.4	59.2	2	Placebo	
	429	112	541	Ulcerative colitis	Tofacitinib	41	58	2	Placebo	
	394	198	592	Ulcerative colitis	Tofacitinib	42.7	55.5	13	Placebo	
Sandborn et al (2020) (51)	183	37	220	Crohn disease	Upadacitinib	40.3	43.2	4	Placebo	
Sandborn et al (2020) (52)	204	46	250	Ulcerative colitis	Upadacitinib	41	60	2	Placebo	
Sands et al (2020) (53)	57	56	113	Ulcerative colitis	Tofacitinib	42.9	45.5	12	Placebo	
Simpson et al (2020) (54)	375	249	624	Atopic dermatitis	Baricitinib	35.8	62.7	4	Placebo	
	370	244	614	Atopic dermatitis	Baricitinib	34.5	62	4	Placebo	
Simpson et al (2020) (74)	310	77	387	Atopic dermatitis	Abrocitinib	54.8	32.5	3	Placebo	
Smolen et al (2019) (55)	432	216	648	Rheumatoid arthritis	Upadacitinib	54.3	19	3.5	Placebo	
Tanaka et al (2011) (56)	108	28	136	Rheumatoid arthritis	Tofacitinib	51.3	14	3	Placebo	
Tanaka et al (2015) (57)	265	52	317	Rheumatoid arthritis	Tofacitinib	53.4	16.7	3	Placebo	
Tanaka et al (2016) (58)	96	49	145	Rheumatoid arthritis	Baricitinib	53.6	81.4	3	Placebo	
Taylor et al (2017) (59)	487	818	1305	Rheumatoid arthritis	Baricitinib	53.5	22.4	3	Both	Adalimumab
van der Heijde et al (2017) (20)	156	51	207	Ankylosing spondylitis	Tofacitinib	41.6	69	4	Placebo	
van der Heijde et al (2018) (34)	58	58	116	Ankylosing spondylitis	Filgotinib	41.5	74.5	3	Placebo	
van der Heijde et al (2019) (21)	637	158	795	Rheumatoid arthritis	Tofacitinib	NA	NA	12	Placebo	
van der Heijde et al (2019) (60)	93	94	187	Ankylosing spondylitis	Upadacitinib	45.4	70.6	3.5	Placebo	
van Vollenhoven et al (2020) (61)	631	314	945	Rheumatoid arthritis	Upadacitinib	53.4	23.8	6	Placebo	
van Vollenhoven et al (2012) (62)	403	312	715	Rheumatoid arthritis	Tofacitinib	53.2	17.3	6	Both	Adalimumab
Wallace et al (2018) (63)	209	105	314	Systemic lupus erythematosus	Baricitinib	44.4	NA	6	Placebo	
Westhovens et al (2017) (64)	508	86	594	Rheumatoid arthritis	Filgotinib	53.3	19	6	Placebo	
Zhang et al (2017) (65)	178	88	266	Psoriasis	Tofacitinib	41.1	72.9	12	Placebo	

Abbreviation: JAK, Janus kinase.

reported in 66 clinical trials, whereas MACE was reported in in 63 (Table 1, Supplementary Figure 1) (9,16–75).

Baseline characteristics. The included studies encompassed rheumatoid arthritis (n = 30), ankylosing spondylitis (n = 3), psoriasis (n = 5), psoriatic arthritis (n = 5), atopic dermatitis (n = 12), ulcerative colitis (n = 6), Crohn disease (n = 3), and systemic lupus erythematosus (n = 2). A total of 38,574 patients with IMIDs were enrolled between 2005 and 2021 (25,344 randomized to JAK inhibitors and 13,230 randomized to placebo or active comparator arms), with a mean follow-up of 10.5 months. Overall, 54 studies compared JAK inhibitors with only a placebo, eight studies compared JAK inhibitors with both a placebo and an active comparator arm, and four studies compared JAK inhibitors with only an active comparator group abatacept [n = 1], adalimumab [n = 7], dupilimab [n = 2], etanercept or adalimumab [n = 1], and etanercept [n = 1]). The JAK inhibitors evaluated were abrocitinib (n = 5), tofacitinib (n = 30), filgotinib (n = 4), upadacitinib (n = 18), and baricitinib (n = 9). The mean age across all clinical trials was 48.8 years, and 62.8% of patients were women. The baseline characteristics of each study are provided in Table 1.

Outcomes. *Relationship between JAK inhibitors and VTE.* JAK inhibitors displayed a numerically higher risk of VTE when compared with control groups (OR 1.65; 95% CI: 0.97-2.79), which was more pronounced in trials with longer follow-up (≥12 months), resulting in a 117% increased risk of VTE, when

compared with controls ($P_{interaction}$ = 0.05) (Figure 1A). These results on the time-dependent association between follow-up time and risk of VTE were confirmed by meta-regression (P < 0.01). In a subgroup analysis, this increased risk was mainly observed when comparing JAK inhibitors with active comparators with long-term (≥12 months) as opposed to short-term follow-up (<12 months) (OR 2.38 [95% CI: 1.24-4.57] vs 0.30 [95% CI: 0.07-1.26], respectively; $P_{interaction}$ = 0.01) (Figure 1B). No relationship was seen between VTE and JAK inhibitors when compared with placebo arms (Figure 1C). A sensitivity analysis incorporating all 66 clinical trials with VTE outcomes using a variety of different models (and after stratification by follow-up time and a person-years anlaysis) yielded largely similar results and point estimates (Tables 2 and 3, Supplementary Figures 2-5).

Relationship between JAK inhibitors and MACE. There was a numerically higher incidence of MACE in those randomized to JAK inhibitors compared with control groups (OR 1.18; 95% CI: 0.83-1.68), which did not reach statistical significance even when stratified by duration of follow-up (Figure 2A). In a subgroup analysis comparing JAK inhibitors with comparator arms, a numerically higher point estimate was seen in the relationship between JAK inhibitors and MACE in those with long-term follow-up (OR 1.19; 95% CI: 0.83-1.70), but it did not achieve statistical significance (Figure 2B). Finally, no relationship was observed between MACE and JAK inhibitors when compared with the placebo group. A sensitivity analysis incorporating all 63 clinical trials with MACE outcomes using a variety of different models (and after stratification
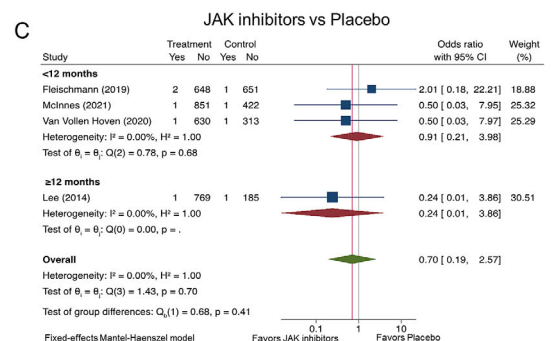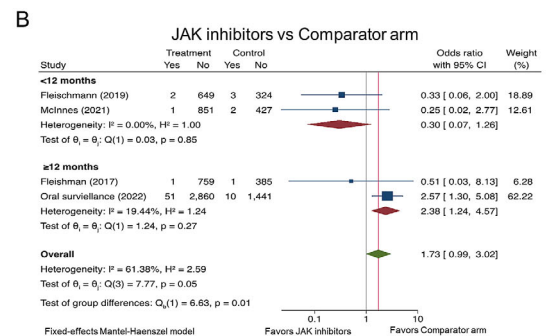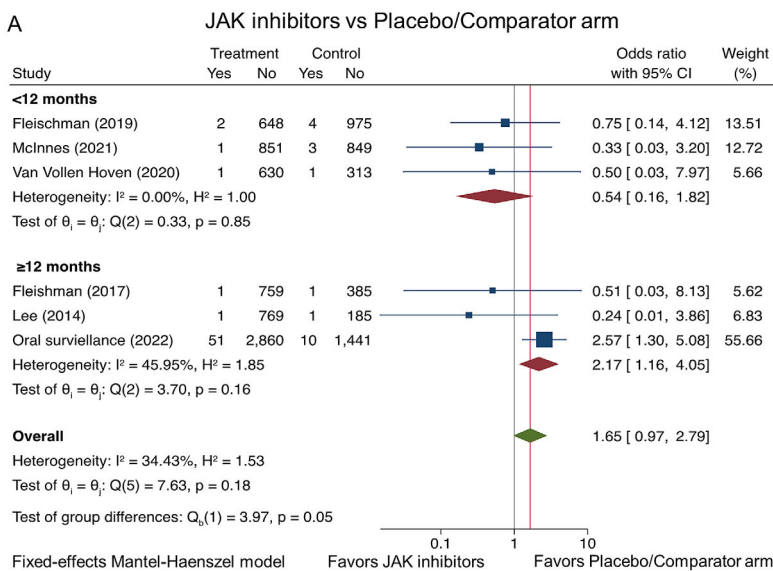

Figure 1. Venous thromboembolism (VTE) risk based on follow-up time in patients randomized to Janus kinase (JAK) inhibitors, placebo, or a comparator arm. **A**, JAK inhibitors versus placebo and comparator arm (termed "controls"). **B**, JAK inhibitors versus comparator arm. **C**, JAK inhibitors versus placebo. Analysis by fixed-effects Mantel-Haenszel model. CI, confidence interval.

Table 2. Summary of outcomes

Outcome (n = study number included)	Overall differences, odds ratio (95% CI)	Long-term follow-up, odds ratio (95% CI)	Short-term follow-up, odds ratio (95% CI)	$P_{interaction}$
VTE with JAK inhibitors vs placebo and active comparator arm by follow-up time				
VTE with MH (no cc) n = 6	1.65 (0.97-2.79)	2.17 (1.16-4.05)	0.54 (0.16-1.82)	0.05
VTE with DL (no cc) n = 6	0.93 (0.36-2.36)	1.12 (0.24-5.17)	0.55 (0.16-1.86)	0.47
VTE with MH (and cc) n = 66	0.95 (0.69-1.32)	1.73 (0.99-3.01)	0.64 (0.42-0.98)	0.01
VTE with DL (and cc) n = 66	0.85 (0.59-1.22)	1.32 (0.64-2.72)	0.58 (0.37-0.92)	0.06
VTE with JAK inhibitors vs placebo arm by follow-up time				
VTE with MH (no cc) n = 4	0.70 (0.19-2.57)	0.24 (0.01-3.86)	0.91 (0.21-3.98)	0.41
VTE with DL (no cc) n = 4	0.65 (0.17-2.45)	0.24 (0.01-3.86)	0.87 (0.19-3.97)	0.43
VTE with MH (and cc) n = 62	0.55 (0.36-0.83)	0.37 (0.11-1.25)	0.57 (0.37-0.89)	0.51
VTE with DL (and cc) n = 62	0.50 (0.32-0.79)	0.37 (0.11-1.27)	0.53 (0.33-0.85)	0.59
VTE with JAK inhibitors vs active comparator arm by follow-up time				
VTE with MH (no cc) n = 4	1.73 (0.99-3.02)	2.38 (1.24-4.57)	0.30 (0.07-1.26)	0.01
VTE with DL (no cc) n = 4	0.75 (0.18-3.08)	2.04 (0.67-6.20)	0.30 (0.07-1.27)	0.04
VTE with MH (and cc) n = 12	1.67 (1.01-2.76)	2.31 (1.25-4.27)	0.60 (0.22-1.61)	0.04
VTE with DL (and cc) n = 12	1.54 (0.90-2.65)	2.25 (1.21-4.21)	0.50 (0.17-1.47)	0.02
MACE with JAK inhibitors vs placebo and active comparator arm by follow-up time				
MACE with MH (no cc) n = 11	1.19 (0.86-1.64)	1.32 (0.93-1.89)	0.67 (0.30-1.49)	0.12
MACE with DL (no cc) n = 11	1.17 (0.84-1.6)	1.30 (0.91-1.86)	0.66 (0.30-1.48)	0.13
MACE with MH (and cc) n = 63	1.03 (0.80-1.32)	1.26 (0.90-1.76)	0.77 (0.53-1.14)	0.06
MACE with DL (and cc) n = 63	1.00 (0.77-1.31)	1.26 (0.89-1.78)	0.71 (0.46-1.09)	0.04
MACE with JAK inhibitors vs placebo arm by follow-up time				
MACE with MH (no cc) n = 8	0.97 (0.49-1.91)	1.20 (0.50-2.91)	0.68 (0.23-2.02)	0.43
MACE with DL (no cc) n = 8	0.87 (0.43-1.77)	1.07 (0.43-2.66)	0.64 (0.21-1.96)	0.48
MACE with MH (and cc) n = 59	0.88 (0.61-1.25)	1.11 (0.53-2.30)	0.81 (0.53-1.22)	0.83
MACE with DL (and cc) n = 59	0.77 (0.52-1.15)	1.02 (0.47-2.21)	0.70 (0.44-1.11)	0.42
MACE with JAK inhibitors vs active comparator arm by follow-up time				
MACE with MH (no cc) n = 5	1.18 (0.83-1.68)	1.19 (0.83-1.70)	0.51 (0.03-8.14)	0.55
MACE with DL (no cc) n = 5	0.98 (0.55-1.77)	0.89 (0.41-1.95)	0.51 (0.03-8.14)	0.70
MACE with MH (and cc) n = 12	1.02 (0.74-1.42)	1.13 (0.80-1.61)	0.40 (0.14-1.16)	0.07
MACE with DL (and cc) n = 12	0.74 (0.41-1.33)	0.68 (0.27-1.72)	0.43 (0.13-1.45)	0.55

Note: Long-term follow-up was defined as ≥12 months, whereas short-term follow-up was defined as <12 months. $P_{interaction}$ = assess within treatment group heterogeneity.

Abbreviations: cc, continuity correction; CI, confidence interval; DL, Dersimonian-Laird; JAK, Janus kinase; MACE, major adverse cardiac events; MH, Mantel-Haenszel; VTE, venous thromboembolism.

Table 3. Summary of outcomes by person-years follow-up

Outcome		JAK inhibitors vs placebo and comparator arm, odds ratio (95% CI)	JAK inhibitors vs comparator arm, odds ratio (95% CI)	JAK inhibitors vs placebo arm, odds ratio (95% CI)
VTE and MACE by person-years of follow-up	VTE with MH	1.64 (0.97-2.78)	1.71 (0.98-3.01)	0.70 (0.19-2.57)
	MACE with MH	1.18 (0.86-1.63)	1.17 (0.83-1.67)	0.99 (0.49-1.91)

Note: Long-term follow-up was defined as ≥12 months, whereas short-term follow-up was defined as <12 months. Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular event; MH, Mantel-Haenszel; VTE, venous thromboembolism.

by follow-up time and a person-years anlaysis) yielded similar results (Tables 2 and 3, Supplementary Figures 6-9).

DISCUSSION

In this meta-analysis of 66 RCTs, JAK inhibitors, when compared with controls, displayed a numerically higher rate of VTE, which was dependent on the duration of exposure (greater than 12 months). The OR for VTE in those randomized to JAK inhibitors versus an active comparator, as opposed to JAK inhibitors versus a placebo, was significantly higher. These findings contrasted with our observed associations with MACE, in which a numerically higher rate of MACE in those randomized to JAK inhibitors was observed, but no statistically significant association was seen.

To our knowledge, this is the largest and most up to date meta-analysis to evaluate the safety (MACE and VTE) of JAK inhibitors, particularly after the publication of the ORAL Surveillance study (9). Prior trials and meta-analyses have shown
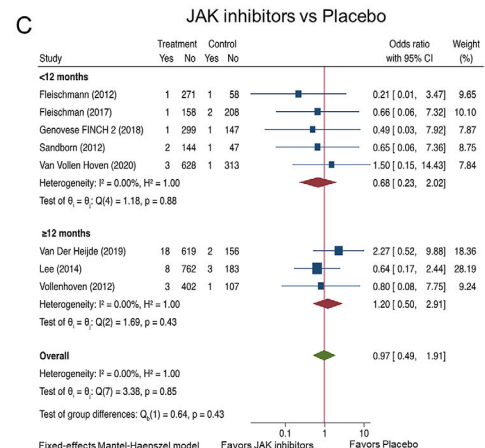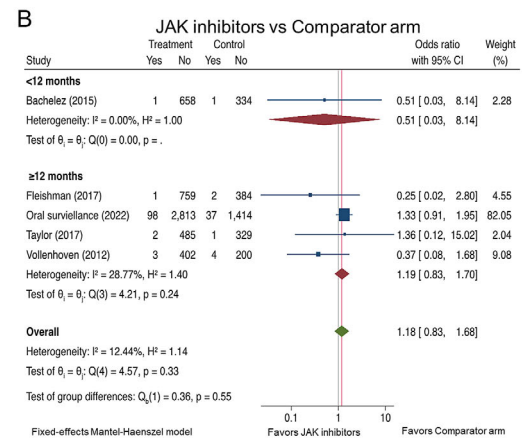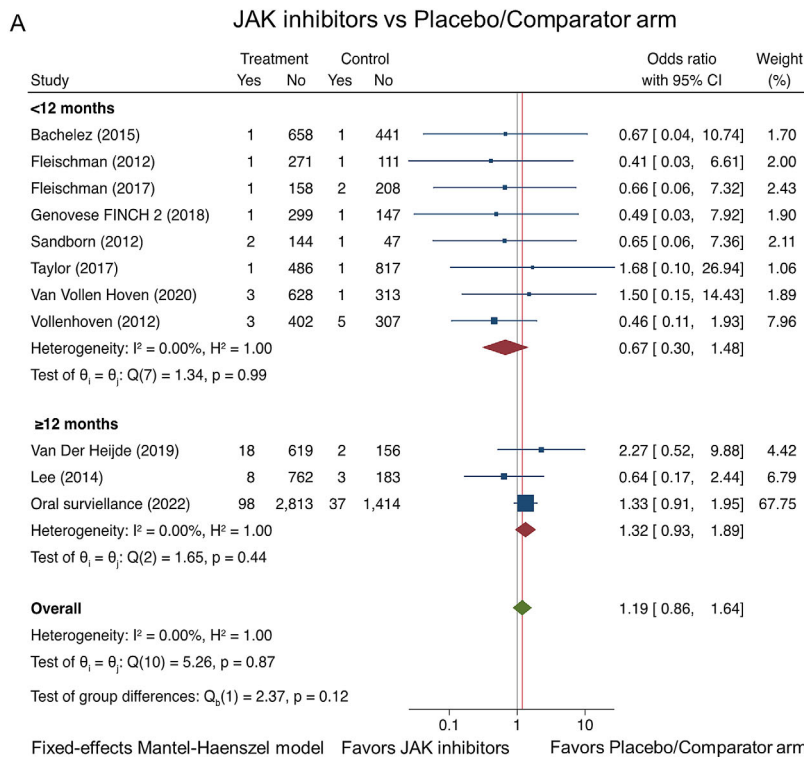

Figure 2. Major adverse cardiovascular events (MACE) risk based on follow-up time in patients randomized to Janus kinase (JAK) inhibitors, placebo, or a comparator arm. **A**, JAK inhibitors versus placebo and comparator arm (termed "controls"). **B**, JAK inhibitors versus comparator arm. **C**, JAK inhibitors versus placebo. Analysis by fixed-effects Mantel-Haenszel model. CI, confidence interval.

heterogeneous outcomes. A meta-analysis by Yates and colleagues (4) evaluated 42 trials and found a nonsignificant difference of VTE with JAK inhibitors compared with placebo and active comparators. Similarly, another meta-analysis of 26 trials with JAK inhibitors found a nonsignificant increased risk of cardiovascular events with JAK inhibitors (5). These results suggest that with the addition of the newly published studies, an association between JAK inhibitors and VTE may be more significant in those with extended (≥12 months) follow-up.

JAK inhibitors inhibit various JAK receptors (depending on the specific drug) and have differential effects on downstream inflammatory activation, including cytokine activation and immunomodulatory capabilities, and thus could cause a variety of potential off-target effects. Overall, although the mechanisms surrounding the association between JAK inhibitors and VTE events are under investigation, earlier clinical trials proposed that a higher risk of VTE with JAK inhibitors was attributed to an elevation in platelet counts; however, this elevation returned to baseline with long-term follow-up (76). Similarly regarding potential MACE, JAK inhibitors, especially baricitinib and tofacitinib, are associated with an increase in circulating total cholesterol levels, including an approximately 11% increase in low-density lipoprotein cholesterol levels (as observed in ORAL Surveillance) (9,77,78). It would be interesting to understand whether in those on JAK inhibitors, the observed increases in platelet count (although temporary), or low-density lipoprotein choleserol correlate with subsequent VTE and/or MACE.

In general, IMIDs are strongly associated with enhanced risk of VTE and MACE (79–81), which may be mitigated with immunomodulatory therapies, including TNF inhibitors (82–86). Thus, a potential protective effect may explain our finding of a higher risk of VTE with JAK inhibitors (and numerically with MACE) versus an active comparator (generally TNF inhibitors) as opposed to JAK inhibitors versus a placebo arm. Whether our hypothesis on a potential beneficial effect of other disease-modifying antirheumatic drugs, as opposed to a harmful impact of JAK inhibitors, in IMIDs is true is not yet clear. Further exploration will require additional clinical trials with an active comparator group in populations with higher cardiovascular (CV) risk to investigate both clinical outcomes and mechanisms of VTE, MACE, and JAK inhibitors.

Conversely, although our study suggested a time-dependent nature association with JAK inhibitors and thrombosis, other studies have not shown this. A recent analysis of the FDA's Adverse Event Reporting System database between 2010 and 2019 found no association (eg, random) between duration of exposure to JAK inhibitors and thrombosis and found that the outcome primarily occurred in older individuals. Although real-world data, these data may be confounded by lack of an active control and comparator group but do strongly highlight the importance in investigating this topic, specifically that JAK inhibitors may actually be associated with thrombosis, and the need for further studies to clarify these discrepancies (87).

Finally, although we did not observe a statistically significant association, the point estimates in the association between

MACE and JAK inhibitors were increased; however, this was predominantly due to the influence of findings from ORAL Surveillance, which had extended follow-up and enrolled those with a higher-risk cardiovascular profile. Therefore, future RCTs will also require enrolling those considered at higher cardiovascular risk, with extended follow-up to expand on these analyses.

These study findings should be interpreted in light of some important limitations. Individual patient-level data were not available, and we could not stratify by populations such as those with pre-existing cardiovascular conditions, those with pre-existing thromboembolic risk factors, and those with advanced age. Importantly, the duration of follow-up time varied significantly across studies, and a large portion of our results are driven by recent findings from ORAL Surveillance, which primarily assessed an older rheumatoid arthritis population with CV risk factors, thus potentially biasing the analyses toward a signal-to-harm across JAK inhibitors. Nevertheless, this trial is important to include because it significantly impacted FDA decisions to implement a black box warning across all JAK inhibitors and inflammatory subtypes, and other trials made up approximately half of the weighted analysis. Additionally, our findings of an adverse effect of JAK inhibitors on VTE in the comparator arm, but not the placebo arm, may also be due to the short duration of contemporary placebo-controlled clinical trials and thus not allowing enough exposure time to observe an adverse impact of JAK inhibitors. Finally, different JAK inhibitors target different cytokines depending on the specific IMIDs (which also have different inherent VTE and CV risks), and this analysis did not parse out these important nuances. All of these factors account for some level of heterogeneity within the meta-analysis and deserve confirmation in larger populations with higher CV risk, in which the signal-to-harm is more substantial.

JAK inhibitors have a higher risk of VTE with long-term follow-up when compared with an active treatment arm, with a numerically higher but nonsignificant association found between JAK inhibitors and MACE. The results of future large-scale RCTs with long-term follow-up and in those patients with pre-existing cardiovascular and thromboembolic conditions will give a clear picture on the safety of JAK inhibitors and are sorely needed.

AUTHOR CONTRIBUTIONS

REFERENCES

1. Lin CM, Cooles FA, Isaacs JD. Basic mechanisms of JAK inhibition. Mediterr J Rheumatol 2020;31 Suppl 1:100–4.

2. Smolen JS, Genovese MC, Takeuchi T, Hyslop DL, Macias WL, Rooney T, et al. Safety profile of baricitinib in patients with active

rheumatoid arthritis with over 2 years median time in treatment. J Rheumatol 2019;46:7–18.

3. Cohen SB. JAK inhibitors and VTE risk: how concerned should we be? [Commentary]. Nat Rev Rheumatol 2021;17:133–4.

4. Yates M, Mootoo A, Adas M, Bechman K, Rampes S, Patel V, et al. Venous thromboembolism risk with JAK inhibitors: a meta-analysis. Arthritis Rheumatol 2021;73:779–88.

5. Xie W, Huang Y, Xiao S, Sun X, Fan Y, Zhang Z. Impact of Janus kinase inhibitors on risk of cardiovascular events in patients with rheumatoid arthritis: systematic review and meta-analysis of randomised controlled trials. Ann Rheum Dis 2019;78:1048–54.

6. Kremer JM, Bingham CO III, Cappelli LC, Greenberg JD, Madsen AM, Geier J, et al. Postapproval comparative safety study of tofacitinib and biological disease-modifying antirheumatic drugs: 5-year results from a United States-based rheumatoid arthritis registry. ACR Open Rheumatol 2021;3:173–84.

7. Mease P, Charles-Schoeman C, Cohen S, Fallon L, Woolcott J, Yun H, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis 2020;79:1400–13.

8. US Food and Drug Administration. FDA approves boxed warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR). 2021. URL: https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and.

9. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med 2022;386:316–26.

10. US Food and Drug Administration. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. 2021. URL: https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death.

11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

12. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

13. Cai T, Parast L, Ryan L. Meta-analysis for rare events. Stat Med 2010; 29:2078–89.

14. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods 2016;7: 55–79.

15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

16. Bachelez H, van de Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet 2015;386:552–61.

17. Burmester GR, Kremer JM, van den Bosch F, Kivitz A, Bessette L, Li Y, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018; 391:2503–12.

18. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013;381:451–60.

19. Conaghan PG, Østergaard M, Bowes MA, Wu C, Fuerst T, van der Heijde D, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. Ann Rheum Dis 2016;75:1024–33.

20. Van der Heijde D, Deodhar A, Wei JC, Drescher E, Fleishaker D, Hendrikx T, et al. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. Ann Rheum Dis 2017;76:1340–7.

21. Van der Heijde D, Strand V, Tanaka Y, Keystone E, Kremer J, Zerbini CA, et al. Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: clinical efficacy, radiographic, and safety outcomes from a twenty-four-month, phase III study. Arthritis Rheumatol 2019;71:878–91.

22. Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study [published erratum appears in Ann Rheum Dis 2017;76:1634]. Ann Rheum Dis 2017;76:88–95.

23. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum 2012;64: 617–29.

24. Fleischmann R, Pangan AL, Song IH, Mysler E, Bessette L, Peterfy C, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. Arthritis Rheumatol 2019;71:1788–800.

25. Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Rheumatol 2017;69:506–17.

26. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367:495–507.

27. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017;390:457–68.

28. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 2016;374:1243–52.

29. Genovese MC, Smolen JS, Weinblatt ME, Burmester GR, Meerwein S, Camp HS, et al. Efficacy and safety of ABT-494, a selective JAK-1 inhibitor, in a phase IIb study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Rheumatol 2016;68:2857–66.

30. Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet 2018;391:2513–24.

31. Genovese MC, Kalunian K, Gottenberg JE, Mozaffarian N, Bartok B, Matzkies F, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. JAMA 2019;322:315–25.

32. Gladman D, Rigby W, Azevedo VF, Behrens F, Blanco R, Kaszuba A, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. N Engl J Med 2017;377:1525–36.

33. Mease P, Hall S, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med 2017;377:1537–50.

34. Van der Heijde D, Baraliakos X, Gensler LS, Maksymowych WP, Tseluyko V, Nadashkevich O, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. Lancet 2018;392:2378–87.

35. Kameda H, Takeuchi T, Yamaoka K, Oribe M, Kawano M, Zhou Y, et al. Efficacy and safety of upadacitinib in Japanese patients with rheumatoid arthritis (SELECT-SUNRISE): a placebo-controlled phase IIb/III study. Rheumatology (Oxford) 2020;59:3303–13.

36. Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum 2009;60:1895–905.

37. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum 2012;64:970–81.

38. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 2013;159:253–61.

39. Kremer JM, Emery P, Camp HS, Friedman A, Wang L, Othman AA, et al. A phase IIb study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an inadequate response to anti-tumor necrosis factor therapy. Arthritis Rheumatol 2016;68:2867–77.

40. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014;370:2377–86.

41. McInnes IB, Anderson JK, Magrey M, Merola JF, Liu Y, Kishimoto M, et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. N Engl J Med 2021;384:1227–39.

42. Mease P, Coates LC, Helliwell PS, Stanislavchuk M, Rychlewska-Hanczewska A, Dudek A, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. Lancet 2018;392:2367–77.

43. Panés J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D'Haens G, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut 2017;66:1049–59.

44. Papp KA, Menter A, Strober B, Langley RG, Buonanno M, Wolk R, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a phase 2b randomized placebo-controlled dose-ranging study. Br J Dermatol 2012;167:668–77.

45. Papp KA, Menter MA, Abe M, Elewski B, Feldman SR, Gottlieb AB, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. Br J Dermatol 2015;173:949–61.

46. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T, et al. Efficacy and safety of baricitinib combined with topical corticosteroids for treatment of moderate to severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol 2020;156:1333–43.

47. Rubbert-Roth A, Enejosa J, Pangan AL, Haraoui B, Rischmueller M, Khan N, et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. N Engl J Med 2020;383:1511–21.

48. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012;367:616–24.

49. Sandborn WJ, Ghosh S, Panes J, Vranic I, Wang W, Niezychowski W. A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn's disease. Clin Gastroenterol Hepatol 2014;12:1485–93.

50. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2017;376:1723–36.

51. Sandborn WJ, Feagan BG, Loftus EV Jr, Peyrin-Biroulet L, van Assche G, D'Haens G, et al. Efficacy and safety of upadacitinib in a randomized trial of patients with Crohn's disease. Gastroenterology 2020;158:2123–38.

52. Sandborn WJ, Ghosh S, Panes J, Schreiber S, D'Haens G, Tanida S, et al. Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis. Gastroenterology 2020;158:2139–49.

53. Sands BE, Armuzzi A, Marshall JK, Lindsay JO, Sandborn WJ, Danese S, et al. Efficacy and safety of tofacitinib dose de-escalation and dose escalation for patients with ulcerative colitis: results from OCTAVE Open. Aliment Pharmacol Ther 2020;51:271–80.

54. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol 2020;183:242–55.

55. Smolen JS, Pangan AL, Emery P, Rigby W, Tanaka Y, Vargas JI, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONO-THERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet 2019;393:2303–11.

56. Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH, Tofacitinib Study Investigators. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken) 2011;63:1150–8.

57. Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyoizumi S, Zwillich S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. Mod Rheumatol 2015;25:514–21.

58. Tanaka Y, Emoto K, Cai Z, Aoki T, Schlichting D, Rooney T, et al. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis receiving background methotrexate therapy: a 12-week, double-blind, randomized placebo-controlled study. J Rheumatol 2016;43:504–11.

59. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 2017;376:652–62.

60. Van der Heijde D, Song IH, Pangan AL, Deodhar A, van den Bosch F, Maksymowych WP, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet 2019;394:2108–17.

61. Van Vollenhoven R, Takeuchi T, Pangan AL, Friedman A, Mohamed MF, Chen S, et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active comparator-controlled trial. Arthritis Rheumatol 2020;72:1607–20.

62. Van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–19.

63. Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, Petri MA, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet 2018;392: 222–31.

64. Westhovens R, Taylor PC, Alten R, Pavlova D, Enríquez-Sosa F, Mazur M, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). Ann Rheum Dis 2017;76:998–1008.

65. Zhang J, Tsai TF, Lee MG, Zheng M, Wang G, Jin H, et al. The efficacy and safety of tofacitinib in Asian patients with moderate to severe chronic plaque psoriasis: a phase 3, randomized, double-blind, placebo-controlled study. J Dermatol Sci 2017;88:36–45.

66. Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. N Engl J Med 2021;384:1101–12.

67. Blauvelt A, Silverberg JI, Lynde CW, Bieber T, Eisman S, Zdybski J, et al. Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial. J Am Acad Dermatol 2022;86:104–12.

68. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C, et al. Efficacy and safety of oral Janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis: a phase 2 randomized clinical trial. JAMA Dermatol 2019;155:1371–9.

69. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol 2020;145:877–84.

70. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet 2021; 397:2151–68.

71. Hasni SA, Gupta S, Davis M, Poncio E, Temesgen-Oyelakin Y, Carlucci PM, et al. Phase 1 double-blind randomized safety trial of the Janus kinase inhibitor tofacitinib in systemic lupus erythematosus. Nat Commun 2021;12:3391.

72. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol 2020;156:863–73.

73. Mease PJ, Lertratanakul A, Anderson JK, Papp K, van den Bosch F, Tsuji S, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis 2020;80:312–20.

74. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396:255–66.

75. Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, de Bruin-Weller M, Barbarot S, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol 2021;157:1047–55.

76. Rajasimhan S, Pamuk O, Katz JD. Safety of Janus kinase inhibitors in older patients: a focus on the thromboembolic risk. Drugs Aging 2020;37:551–8.

77. Wolk R, Armstrong EJ, Hansen PR, Thiers B, Lan S, Tallman AM, et al. Effect of tofacitinib on lipid levels and lipid-related parameters in patients with moderate to severe psoriasis. J Clin Lipidol 2017;11: 1243–56.

78. Kremer JM, Genovese MC, Keystone E, Taylor PC, Zuckerman SH, Ruotolo G, et al. Effects of baricitinib on lipid, apolipoprotein, and lipoprotein particle profiles in a phase IIb study of patients with active rheumatoid arthritis. Arthritis Rheumatol 2017;69: 943–52.

79. Chung WS, Peng CL, Lin CL, Chang YJ, Chen YF, Chiang JY, et al. Rheumatoid arthritis increases the risk of deep vein thrombosis and pulmonary thromboembolism: a nationwide cohort study. Ann Rheum Dis 2014;73:1774–80.

80. Lee JJ, Pope JE. A meta-analysis of the risk of venous thromboembolism in inflammatory rheumatic diseases. Arthritis Res Ther 2014; 16:435.

81. Durante A, Bronzato S. The increased cardiovascular risk in patients affected by autoimmune diseases: review of the various manifestations. J Clin Med Res 2015;7:379–84.

82. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31.

83. Yuan S, Carter P, Bruzelius M, Vithayathil M, Kar S, Mason AM, et al. Effects of tumour necrosis factor on cardiovascular disease and cancer: a two-sample Mendelian randomization study. EBioMedicine 2020;59:102956.

84. Mäki-Petäjä KM, Hall FC, Booth AD, Wallace SM, Yasmin, Bearcroft PW, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-α therapy. Circulation 2006;114:1185–92.

85. Sattin M, Towheed T. The Effect of TNFα-inhibitors on cardiovascular events in patients with rheumatoid arthritis: an updated systematic review of the literature. Curr Rheumatol Rev 2016;12(3): 208–22.

86. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:576–82.

87. Setyawan J, Azimi N, Strand V, Yarur A, Fridman M. Reporting of thromboembolic events with JAK inhibitors: analysis of the FAERS Database 2010-2019. Drug Saf 2021;44:889–97.