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.
(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 “immunemediated disease” or “rheumatoid arthritis” or “psoriasis” or “psoriatic arthritis” or “inflammatory arthritis” or “ankylosing spondylitis” or “psoriatic arthritis” or “systemic lupus erythematosus” or “inflammatory bowel disease” or “ulcerative colitis” or “Crohn’s” and “JAK inhibitors” or “toleratubin” or “abrocitinib” or “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 thrombosis (eg, 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 I² statistic (15). I² 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 (Pinteraction) 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) | 659 | 442 | 1101 | Psoriasis | Tofacitinib | 44.3 | 71.1 | 3 | Both | Etanercept |
| Bieber et al (2021) | 464 | 373 | 837 | Atopic dermatitis | Abrocitinib | 37.9 | 50.4 | 4 | Both | Dupilumab |
| Blauvelt et al (2021) | 348 | 344 | 692 | Atopic dermatitis | Upadacitinib | 36.7 | 54.5 | 4 | Both | Dupilumab |
| Blauvelt et al (2021) | 531 | 267 | 798 | Atopic dermatitis | Abrocitinib | 28.7 | 55 | 3 | Placebo |
| Burmester et al (2018) | 440 | 221 | 661 | Rheumatoid arthritis | Upadacitinib | 55.7 | 21.3 | 3 | Placebo |
| Burmester et al (2013) | 267 | 132 | 399 | Rheumatoid arthritis | Tofacitinib | 54.8 | 16.8 | 3 | Placebo |
| Conaghan et al (2016) | 36 | 37 | 73 | Rheumatoid arthritis | Baricitinib | 51.7 | 18.1 | 3 | Placebo |
| Fleischmann et al (2012) | 272 | 112 | 384 | Rheumatoid arthritis | Tofacitinib | 53.2 | 13 | 6 | Both | Adalimumab |
| Fleischmann et al (2019) | 650 | 979 | 1629 | Rheumatoid arthritis | Upadacitinib | 54 | 20.5 | 3 | Both | Adalimumab |
| Fleischmann et al (2017) | 159 | 210 | 369 | Rheumatoid arthritis | Baricitinib | 51 | 27.1 | 6 | Placebo |
| Fleishmann et al (2012) | 486 | 122 | 608 | Rheumatoid arthritis | Abrocitinib | 51.8 | 13.4 | 3 | Placebo |
| Fleishmann et al (2017) | 760 | 386 | 1146 | Rheumatoid arthritis | Tofacitinib | 49.8 | 17.1 | 12 | Active | Adalimumab |
| Genovese et al (2016) | 351 | 176 | 527 | Rheumatoid arthritis | Baricitinib | 55.7 | 18.2 | 3 | Placebo |
| Genovese et al (2016) | 249 | 50 | 299 | Rheumatoid arthritis | Upadacitinib | 55 | 20.7 | 3 | Placebo |
| Genovese et al (2018) | 300 | 148 | 448 | Rheumatoid arthritis | Filgotinib | 55.7 | 19.6 | 6 | Placebo |
| Genovese et al (2018) | 329 | 169 | 498 | Rheumatoid arthritis | Tofacitinib | 57.1 | 16.1 | 3 | Placebo |
| Gladman et al (2017) | 263 | 131 | 394 | Psoriatic arthritis | Tofacitinib | 49.9 | 44.7 | 6 | Placebo |
| Gooderham et al (2019) | 211 | 56 | 267 | Atopic dermatitis | Abrocitinib | 40.8 | 46.4 | 3 | Placebo |
| Guttman-Yassky et al (2020) | 126 | 41 | 167 | Atopic dermatitis | Abrocitinib | 40 | 37.7 | 4 | Placebo |
| Guttman-Yassky et al (2021) | 566 | 281 | 847 | Atopic dermatitis | Upadacitinib | 34 | 54 | 4 | Placebo |
| Hasni et al (2021) | 20 | 10 | 30 | Systemic lupus erythematosus | Tofacitinib | 45.9 | 13.3 | 3 | Placebo |
| Silverberg et al (2020) | 313 | 78 | 391 | Atopic dermatitis | Abrocitinib | 35.1 | 58.6 | 3 | Placebo |
| Kameda et al (2020) | 148 | 49 | 197 | Rheumatoid arthritis | Tofacitinib | 55.2 | 21.4 | 3 | Placebo |
| Kremer et al (2009) | 199 | 65 | 264 | Rheumatoid arthritis | Tofacitinib | 50.6 | 85.6 | 6 | Placebo |
| Kremer et al (2012) | 438 | 69 | 507 | Rheumatoid arthritis | Tofacitinib | 53.1 | 19.9 | 6 | Placebo |
| Kremer et al (2013) | 633 | 159 | 792 | Rheumatoid arthritis | Tofacitinib | 52.2 | 18.6 | 12 | Placebo |
| Kremer et al (2016) | 220 | 56 | 276 | Rheumatoid arthritis | Upadacitinib | 57.4 | 20 | 3 | Placebo |
| Lee et al (2014) | 770 | 186 | 956 | Rheumatoid arthritis | Tofacitinib | 49.6 | 20.7 | 24 | Placebo |
| McNee et al (2021) | 852 | 852 | 1704 | Psoriatic arthritis | Tofacitinib | 50.6 | 46.3 | 3 | Both | Adalimumab |
| Mease et al (2017) | 65 | 66 | 131 | Psoriatic arthritis | Filgotinib | 49.5 | 49.6 | 4 | Placebo |
| Mease et al (2021) | 429 | 212 | 641 | Psoriatic arthritis | Tofacitinib | 53.4 | 54.3 | 6 | Placebo |
| Ytterberg et al (2022) | 2911 | 1451 | 4362 | Rheumatoid arthritis | Tofacitinib | 61 | 22 | 48 | Active comparator | Adalimumab and etanercept |
| Panés et al (2017) | 188 | 91 | 279 | Crohn disease | Tofacitinib | 39 | 47.7 | 2 | Placebo |

(Continued)
| 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 | Tofacitinib | 147 | Psoriasis | 44.3 | 63.5 | 3 | Placebo |
| Papp et al (2015) | 45 | Tofacitinib | 723 | Psoriasis | 45.8 | 71.4 | 4 | Placebo |
| Reich et al (2020) | 46 | Tofacitinib | 696 | Atopic dermatitis | 33.8 | 66 | 4 | Placebo |
| Rubbert-Roth et al (2020) | 47 | Upadacitinib | 303 | Rheumatoid arthritis | 55.6 | 18 | 3 | Abatacept |
| Sandborn et al (2012) | 48 | Tofacitinib | 146 | Ulcerative colitis | 42.7 | 55.5 | 13 | Placebo |
| Sandborn et al (2014) | 49 | Tofacitinib | 105 | Crohn disease | 42.9 | 45.5 | 12 | Placebo |
| Sandborn et al (2017) | 50 | Tofacitinib | 476 | Ulcerative colitis | 41 | 58 | 2 | Placebo |
| Simpson et al (2020) | 51 | Tofacitinib | 375 | Atopic dermatitis | 35.8 | 62.7 | 3 | Placebo |
| Simpson et al (2020) | 52 | Tofacitinib | 57 | Ulcerative colitis | 34.5 | 62 | 4 | Placebo |
| Simpson et al (2020) | 53 | Tofacitinib | 370 | Atopic dermatitis | 34.5 | 62 | 4 | Placebo |
| Simonsen et al (2019) | 54 | Upadacitinib | 432 | Rheumatoid arthritis | 54.3 | 19 | 3.5 | Placebo |
| Tanaka et al (2011) | 55 | Tofacitinib | 108 | Rheumatoid arthritis | 51.3 | 14 | 3 | Placebo |
| Tanaka et al (2015) | 56 | Tofacitinib | 265 | Rheumatoid arthritis | 53.4 | 16.7 | 3 | Placebo |
| Tanaka et al (2016) | 57 | Tofacitinib | 96 | Rheumatoid arthritis | 53.6 | 81.4 | 3 | Placebo |
| Taylor et al (2017) | 58 | Tofacitinib | 487 | Rheumatoid arthritis | 53.5 | 22.4 | 3 | Both |
| van der Heijde et al (2017) | 59 | Tofacitinib | 156 | Ankylosing spondylitis | 41.6 | 69 | 4 | Placebo |
| van der Heijde et al (2018) | 60 | Tofacitinib | 58 | Ankylosing spondylitis | 41.5 | 74.5 | 3 | Placebo |
| van der Heijde et al (2019) | 61 | Tofacitinib | 637 | Rheumatoid arthritis | NA | NA | 12 | Placebo |
| van der Heijde et al (2019) | 62 | Tofacitinib | 93 | Ankylosing spondylitis | 45.4 | 70.6 | 3.5 | Placebo |
| van Vollenhoven et al (2020) | 63 | Tofacitinib | 631 | Rheumatoid arthritis | 53.4 | 23.8 | 6 | Placebo |
| van Vollenhoven et al (2020) | 64 | Tofacitinib | 403 | Rheumatoid arthritis | 53.2 | 17.3 | 6 | Both |
| Wallace et al (2018) | 65 | Tofacitinib | 209 | Systemic lupus erythematosus | 44.4 | NA | 6 | Placebo |
| Westhovens et al (2017) | 66 | Tofacitinib | 508 | Rheumatoid arthritis | 53.3 | 19 | 6 | Placebo |
| Zhang et al (2017) | 67 | Tofacitinib | 178 | Psoriasis | 41.1 | 72.9 | 12 | Placebo |

Abbreviation: JAK, Janus kinase.
Baseline characteristics. The included studies encompassed rheumatoid arthritis (n = 30), ankylosing spondylitis (n = 9), 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], dupilumab [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 analysis) 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.
| 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) | $P_{\text{interaction}}$ |
|-----------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|-----------------|
| 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 (0.17-2.46) | 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 = 62 | 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 = 62 | 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. $P_{\text{interaction}}$ = 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.
by follow-up time and a person-years analysis) 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

| Outcome | Major adverse cardiovascular events |
|---------|-----------------------------------|
| **A**   | JAK inhibitors vs Placebo/Comparator arm |
| Study   | Treatment | Control | Odds ratio with 95% CI | Weight (%) |
| <12 months |          |         |                        |           |
| Bachier (2015) | 1       | 658     | 1                     | 1.64 [0.97-2.78] | 0.67 [0.04, 10.74] | 1.70 |
| Fleischman (2012) | 1       | 271     | 1                     | 1.41 [0.03, 6.61] | 0.01 [0.002, 0.01] | 2.00 |
| Fleischman (2017) | 1       | 178     | 2                     | 1.66 [0.06, 7.32] | 0.07 [0.05, 2.24] | 2.43 |
| Genovese FINCH 2 (2018) | 1       | 299     | 1                     | 0.49 [0.03, 7.92] | 0.03 [0.02, 0.05] | 1.90 |
| Sandborn (2012) | 2       | 144     | 1                     | 0.60 [0.06, 7.36] | 0.04 [0.03, 0.06] | 2.11 |
| Taylor (2017) | 1       | 285     | 1                     | 1.68 [0.10, 26.84] | 0.02 [0.005, 0.03] | 1.06 |
| Van Vollenhoven (2000) | 3       | 628     | 2                     | 1.50 [0.15, 14.43] | 0.03 [0.02, 0.04] | 1.89 |
| Vollenhoven (2012) | 3       | 402     | 5                     | 0.48 [0.11, 1.93] | 0.07 [0.06, 1.00] | 7.96 |
| Heterogeneity: F = 0.00%, H² = 1.00 | 0.07 [0.00, 0.00] | 1.00 |
| Test of H = 0; Q(7) = 1.34, p = 0.99 |

| <12 months |          |         |                        |           |
| Van Der Heijde (2019) | 18      | 619     | 2                     | 2.27 [0.52, 9.88] | 4.42 |
| Lee (2014) | 8        | 762     | 3                     | 0.64 [0.17, 2.47] | 6.79 |
| Oral surveillance (2002) | 98      | 2,813   | 37                    | 1.33 [0.19, 1.96] | 67.75 |
| Heterogeneity: F = 0.00%, H² = 1.00 | 1.32 [0.93, 1.89] |
| Test of H = 0; Q(10) = 5.26, p = 0.67 |
| Test of group differences: Q(1) = 2.37, p = 0.12 |

| Overall |          |         |                        |           |
| Heterogeneity: F = 0.00%, H² = 1.00 | 1.19 [0.86, 1.64] |
| Test of H = 0; Q(10) = 5.26, p = 0.67 |
| Test of group differences: Q(1) = 2.37, p = 0.12 |

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 cholesterol 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

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Garshick had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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