Arthritis & Rheumatology
Vol. 76, No. 8, August 2024, pp 1218–1229
DOI 10.1002/art.42846

American College of Rheumatology
Empowering Rheumatology Professionals

Risk of Venous Thromboembolism With Tofacitinib Versus Tumor Necrosis Factor Inhibitors in Cardiovascular Risk-Enriched Rheumatoid Arthritis Patients

Christina Charles-Schoeman,[1] Roy Fleischmann,[2] Eduardo Mysler,[3] Maria Greenwald,[4] Steven R. Ytterberg,[5] Gary G. Koch,[6] Deepak L. Bhatt,[7] Cunshan Wang,[8] Ted R. Mikuls,[9] All-shine Chen,[8] Carol A. Connell,[8] John C. Woolcott,[10] Sujatha Menon,[8] Yan Chen,[10] Kristen Lee,[10] and Zoltán Szekanecz[11]

Objective. The ORAL Surveillance trial found a dose-dependent increase in venous thromboembolism (VTE) and pulmonary embolism (PE) events with tofacitinib versus tumor necrosis factor inhibitors (TNFi). We aimed to assess VTE incidence over time and explore risk factors of VTE, including disease activity, in ORAL Surveillance.

Methods. Patients with rheumatoid arthritis (RA) aged 50 years or older with at least one additional cardiovascular risk factor received tofacitinib 5 or 10 mg twice daily (BID) or TNFi. Post hoc, cumulative probabilities and incidence rates (patients with first events/100 patient-years) by 6-month intervals were estimated for adjudicated VTE, deep vein thrombosis, and PE. Cox regression models identified risk factors. Clinical Disease Activity Index leading up to the event was explored in patients with VTE.

Results. Cumulative probabilities for VTE and PE were higher with tofacitinib 10 mg BID, but not 5 mg BID, versus TNFi. Incidence rates were consistent across 6-month intervals within treatments. Across treatments, risk factors for VTE included prior VTE, body mass index greater than or equal to 35 kg/m^2, older age, and history of chronic lung disease. At the time of the event, most patients with VTE had active disease as defined by Clinical Disease Activity Index.

Conclusion. Incidences of VTE and PE were higher with tofacitinib (10 > 5 mg BID) versus TNFi and were generally consistent over time. Across treatments, VTE risk factors were aligned with previous studies in the general RA population. These data highlight the importance of assessing VTE risk factors, including age, body mass index, and VTE history, when considering initiation of tofacitinib or TNFi in patients with active RA.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by systemic inflammation with frequent joint destruction.[1] Compared with the general population, patients with RA have a greater risk of venous thromboembolism (VTE) events, including deep vein thrombosis (DVT) and pulmonary embolism (PE),[2–7] which may result from a combination of hypercoagulation, stasis, and endothelial dysfunction associated with RA-induced systemic inflammation.[8–10] In addition to active RA, multiple predisposing factors can trigger VTE through additive or synergistic interactions.[10,11] These include genetic factors (family history of VTE, inherited thrombophilia), older age, active cancer, Black race, smoking, obesity, major surgical procedures,

ClinicalTrials.gov identifier: NCT02092467.

Selected data in this manuscript were previously presented at ACR Convergence 2021. These data were also presented at EULAR 2022 and PANLAR 2022.

Sponsored by Pfizer.

[1]Christina Charles-Schoeman, MD, MS: University of California Los Angeles, Los Angeles, California; [2]Roy Fleischmann, MD: Metroplex Clinical Research Center and University of Texas Southwestern Medical Center, Dallas, Texas; [3]Eduardo Mysler, MD: Organización Médica de Investigación, Buenos Aires, Argentina; [4]Maria Greenwald, MD: Desert Medical Advances, Palm Desert, California; [5]Steven R. Ytterberg, MD: Mayo Clinic, Rochester, Minnesota; [6]Gary G. Koch, PhD: The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [7]Deepak L. Bhatt, MD, MPH: Mount Sinai Health System, New York, New York; [8]Cunshan Wang, PhD, All-shine Chen, PhD, Carol A. Connell, RN, PhD, Sujatha Menon, PhD: Pfizer Inc, Groton, Connecticut; [9]Ted R. Mikuls, MD, MSPH: University of Nebraska Medical Center and Veterans Affairs Nebraska Western Iowa Health Care System, Omaha, Nebraska; [10]John C. Woolcott, PhD, Yan Chen, MD, PhD, Kristen Lee, MD: Pfizer Inc, Collegeville, Pennsylvania; [11]Zoltán Szekanecz, MD, PhD, DSc: University of Debrecen, Debrecen, Hungary.

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Additional supplementary information cited in this article can be found online in the Supporting Information section (http://onlinelibrary.wiley.com/doi/10.1002/art.42846).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/art.42846.

Address correspondence via email to Christina Charles-Schoeman, MD, MS, at ccharles@mednet.ucla.edu.

Submitted for publication November 15, 2022; accepted in revised form March 12, 2024.

immobilization, and use of corticosteroids, oral contraception, and hormone replacement therapy (HRT).[11–20] Furthermore, patients with RA have increased risk of cardiovascular diseases,[21] and associations between cardiovascular risk factors and VTE risk have been reported.[22]

ORAL Surveillance (NCT02092467), a postauthorization safety study of patients with RA aged 50 years or older with at least one additional cardiovascular risk factor, could not demonstrate the noninferiority of tofacitinib versus tumor necrosis factor inhibitors (TNFi) for the coprimary endpoints of adjudicated major adverse cardiovascular events and malignancies excluding nonmelanoma skin cancer. For these outcomes, incidence was increased with tofacitinib 5 and 10 mg twice daily (BID) versus TNFi.[23]

Primary analyses of ORAL Surveillance found that adjudicated VTE and PE events occurred more frequently and in a dose-dependent manner (10 > 5 mg BID) with tofacitinib compared with TNFi.[23] An exploratory analysis could not identify any biomarkers mechanistically associated with the increased risk of VTE for tofacitinib versus TNFi.[24] Across treatments, VTE appeared to be associated with disease activity; risk of VTE trended higher in patients with Clinical Disease Activity Index (CDAI)–defined active disease versus those in remission.[25] Notably, a recent subgroup analysis of ORAL Surveillance indicated that increased risk of major safety outcomes, including VTE, with tofacitinib versus TNFi was driven by age and smoking history.[26]

Here, we aimed to further our understanding of VTE events in ORAL Surveillance by evaluating cumulative probabilities and incidence over time and by examining the relationship between VTE events and risk factors of VTE at group level and in individual patients with RA.

PATIENTS AND METHODS

Study design and patients. ORAL Surveillance (NCT02092467) was a randomized, open-label, noninferiority, Phase 3b/4, safety endpoint study conducted from March 2014 to July 2020 in patients with active RA despite methotrexate treatment who were aged 50 years or older and had at least one additional cardiovascular risk factor (current smoker, hypertension, high-density lipoprotein-cholesterol <40 mg/dL, diabetes mellitus, family history of premature coronary heart disease, extra-articular disease associated with RA, or history of coronary artery disease). Full study design details were reported previously.[23] Patients were randomized 1:1:1 to receive oral tofacitinib 5 or 10 mg BID, or a subcutaneous TNFi (adalimumab 40 mg every 2 weeks [North America: United States, Puerto Rico, and Canada] or etanercept 50 mg once weekly [rest of the world]), with their prestudy methotrexate dose, unless modification was clinically indicated.

ORAL Surveillance was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Guidelines for Good Clinical Practice, and local country regulations, and was approved by each center's institutional review board or Independent Ethics Committee. Patients provided written informed consent.

Outcomes and statistical analyses. Adjudicated VTE events were assessed by an external, independent committee. All randomized patients receiving at least one dose of the study drug were included in the analysis (safety analysis population). An ad hoc safety analysis conducted by the Data and Safety Monitoring Board identified an increased PE frequency with tofacitinib 10 mg BID versus TNFi and an increase in overall mortality with tofacitinib 10 mg BID versus 5 mg BID or TNFi, resulting in a 2019 protocol amendment and dose reduction from tofacitinib 10 to 5 mg BID.[27] All patients, including those who had their dose reduced from tofacitinib 10 to 5 mg BID, were analyzed in their originally randomized group; data collected after the dose switch were included in the tofacitinib 10 mg BID group. Demographics/baseline disease characteristics were reported descriptively for patients with VTE events within the total time risk period, defined as the time from first study dose to the last contact date (ie, the maximum of adverse event start date, adverse event stop date, last visit date, withdrawal date, or last telephone contact date; if a patient died, the last contact date was date of death).

For calculation of the incidence and risk of adjudicated VTE, DVT, and PE, events were counted within a predefined risk period. Because these events are considered to have a short latency period, the risk period was based on the 28-day on-treatment time, defined as the time from first study dose to last study dose plus 28 days or to the last contact date, whichever was earliest. Events that occurred outside the predefined risk period were excluded from the analysis. Patients without events were censored at the end of the risk period.

Cumulative probabilities of patients with VTE events over time across treatments were estimated using Kaplan-Meier analyses and compared using log-rank tests.

Exposure-adjusted incidence rates (IRs) were defined as the number of patients with a first event per 100 patient-years, along with two-sided 95% confidence intervals (CIs) using the exact Poisson method.[28] Hazard ratios (HRs) and 95% CIs were estimated, based on Cox proportional hazard models for pairwise comparisons among treatments (tofacitinib 5 or 10 mg BID versus TNFi; tofacitinib 10 versus 5 mg BID), with treatment as the only covariate.[29] Sensitivity analyses were performed (IRs and HRs for VTE, DVT, and PE) in which data were censored after patients randomized to the tofacitinib 10 mg BID group had their dose reduced to 5 mg BID following the 2019 protocol amendment. For comparability, this dataset contained only data collected on or before April 22, 2019, for all patients across treatments. IRs and HRs for VTE, DVT, and PE were also calculated by age or by baseline cardiovascular risk profile (history of

atherosclerotic cardiovascular disease [ASCVD] and baseline cardiovascular risk scores), as previously described.[30]

The number needed to harm (NNH) was calculated post hoc based on the IR difference of tofacitinib 5 or 10 mg BID versus TNFi. A positive NNH indicated the number of patient-years of tofacitinib exposure needed for one more patient to report an additional event versus TNFi; a negative NNH indicated the number of patient-years of TNFi exposure needed for one more patient to report an additional event versus tofacitinib. The number of patients exposed for 5 years needed to harm was calculated by dividing the number of patient-years NNH by 5. NNH by age was also reported.

Potential baseline risk factors for VTE events were identified post hoc using simple (including treatment and one baseline risk factor at a time) and multivariable (including treatment and >1 baseline risk factor) models. First, potential risk factors, selected based on previous reports in the literature, were screened using the simple Cox analyses, which included treatment and a single candidate baseline risk factor in each model. Potential baseline risk factors with *P* less than 0.10 in the simple Cox analyses were subjected to further selection via a backward selection algorithm in a multivariable Cox model, which included the effects of treatment (not subject to backward selection) and all potential baseline risk factors identified in the simple Cox analyses. The predefined cutoff for a risk factor to stay in the multivariable model was *P* less than 0.10. HRs with 95% CIs, nominal *P* values of treatment, and baseline risk factors were reported. Baseline risk factors with *P* less than 0.05 from the multivariable Cox models were considered as predictive. Post hoc multivariable Cox models were used to identify time-dependent risk factors for VTE events, including DVT and PE (see Supplementary Materials). As sensitivity analyses to the multivariable Cox model via backward selection described in this article, a multivariable Cox analysis via forward selection and a multivariable Poisson regression analysis via forward selection were performed.

For patients with an adjudicated VTE event, disease activity was evaluated throughout the study (up to the last visit preceding the VTE event) using CDAI and categorized as remission (≤2.8) or low (>2.8–≤10), moderate (>10–≤22), or high (>22) disease activity.[31] The number of patients with VTE in each CDAI category was reported descriptively. Characteristics of individual patients with VTE, including demographic characteristics, CDAI score prior to the event, and persistent and transient risk factors associated with provoked VTE, were reported descriptively.

It should be noted that ORAL Surveillance was not powered to assess comparisons for VTE events across treatments. No multiplicity adjustments were applied across analyses.

RESULTS

Patients. Of 4,362 patients who were randomized and treated, 1,455 received tofacitinib 5 mg BID, 1,456 received tofacitinib 10 mg BID, and 1,451 received TNFi. Median follow-up duration was 4.0 years. Demographics/baseline disease characteristics were previously reported[23]; selected demographics/baseline disease characteristics for the study population are in Supplementary Table 1.

Cumulative probabilities and incidence of VTE events over time with tofacitinib and TNFi. As previously reported,[23] VTE events occurred during the 28-day on-treatment period in 17 (1.2%), 34 (2.3%), and 10 (0.7%) patients receiving tofacitinib 5 mg BID, tofacitinib 10 mg BID, and TNFi, respectively. IRs and HRs (tofacitinib 5 and 10 mg BID versus TNFi) for VTE, DVT, and PE, as previously reported,[23] are shown in Supplementary Figure 1, along with NNH for tofacitinib 5 and 10 mg BID relative to TNFi. Details regarding patients with VTE are in the Supplementary Results.

Kaplan-Meier analyses for VTE, DVT, and PE events (Figure 1) showed that separation was evident between tofacitinib 10 mg BID and TNFi for VTE and PE, and less evident for DVT (log-rank *P* values 0.0001, <0.0001, and 0.0730, respectively), and also indicated a dose-dependency; there was separation between tofacitinib 10 mg BID and 5 mg BID for VTE and PE. Kaplan-Meier estimates for VTE, DVT, and PE events with tofacitinib 5 mg BID and TNFi were similar (log-rank *P* values >0.05) (Figure 1). Over 72 months, the estimated cumulative probability of an event with tofacitinib 5 mg BID, tofacitinib 10 mg BID, and TNFi, respectively, was 1.4%, 4.5%, and 0.8% for VTE, 0.9%, 1.5%, and 0.6% for DVT, and 0.7%, 3.4%, and 0.3% for PE.

Across 6-month time intervals (up to 54 months onwards), IRs for VTE, DVT, and PE were generally higher with both tofacitinib doses versus TNFi and with tofacitinib 10 versus 5 mg BID. Importantly, visual inspection over the 6-month intervals indicated that the IRs of VTE were consistent over time within each treatment group (ie, not restricted to the acute phase after treatment initiation) and they generally aligned with the overall IRs (Figure 2). Sensitivity analyses conducted for adjudicated VTE, DVT, and PE, wherein data were censored after patients receiving tofacitinib 10 mg BID had been switched to 5 mg BID, were consistent with primary results from the main analyses (Supplementary Figure 2).

Baseline risk factors for VTE events across treatments. Within the total time risk period, 66 patients had VTE events (tofacitinib 5 mg BID: n = 18; tofacitinib 10 mg BID: n = 36; and TNFi: n = 12). Patients with versus without VTE events (Table 1) had a slightly higher mean age and mean body mass index (BMI) and were more likely to have a history of VTE, hypertension, coronary heart disease, and be receiving corticosteroids at baseline. Other baseline disease characteristics were generally similar between patients with and without VTE events (Table 1). Few patients received oral contraceptives or HRT or anticoagulant treatment, with no consistent trends between patients with versus without VTE events (Table 1).

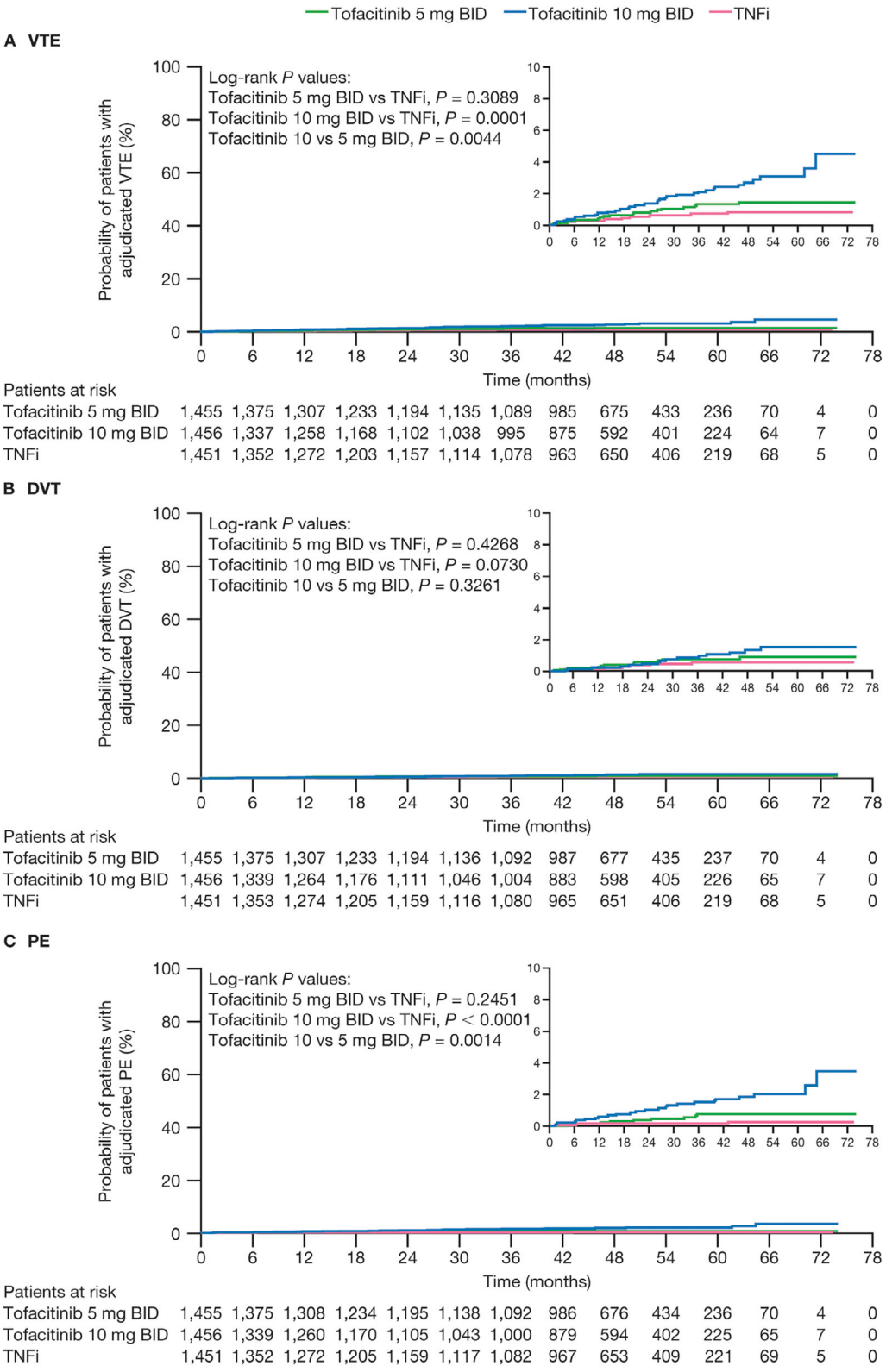


Figure 1. Kaplan-Meier plots of the probability of patients with adjudicated (A) VTE, (B) DVT, and (C) PE events (28-day on-treatment time). For patients randomized to the tofacitinib 10 mg BID group who had their dose reduced to 5 mg BID, data collected after the dose switch were included in the tofacitinib 10 mg BID group. The three pairwise comparisons (tofacitinib 5 mg BID, tofacitinib 10 mg BID, and TNFi) were based on a log-rank test, which followed chi-square distribution with degrees of freedom equal to 1 for each pairwise comparison. BID, twice daily; DVT, deep vein thrombosis; PE, pulmonary embolism; TNFi, tumor necrosis factor inhibitor; VTE, venous thromboembolism.

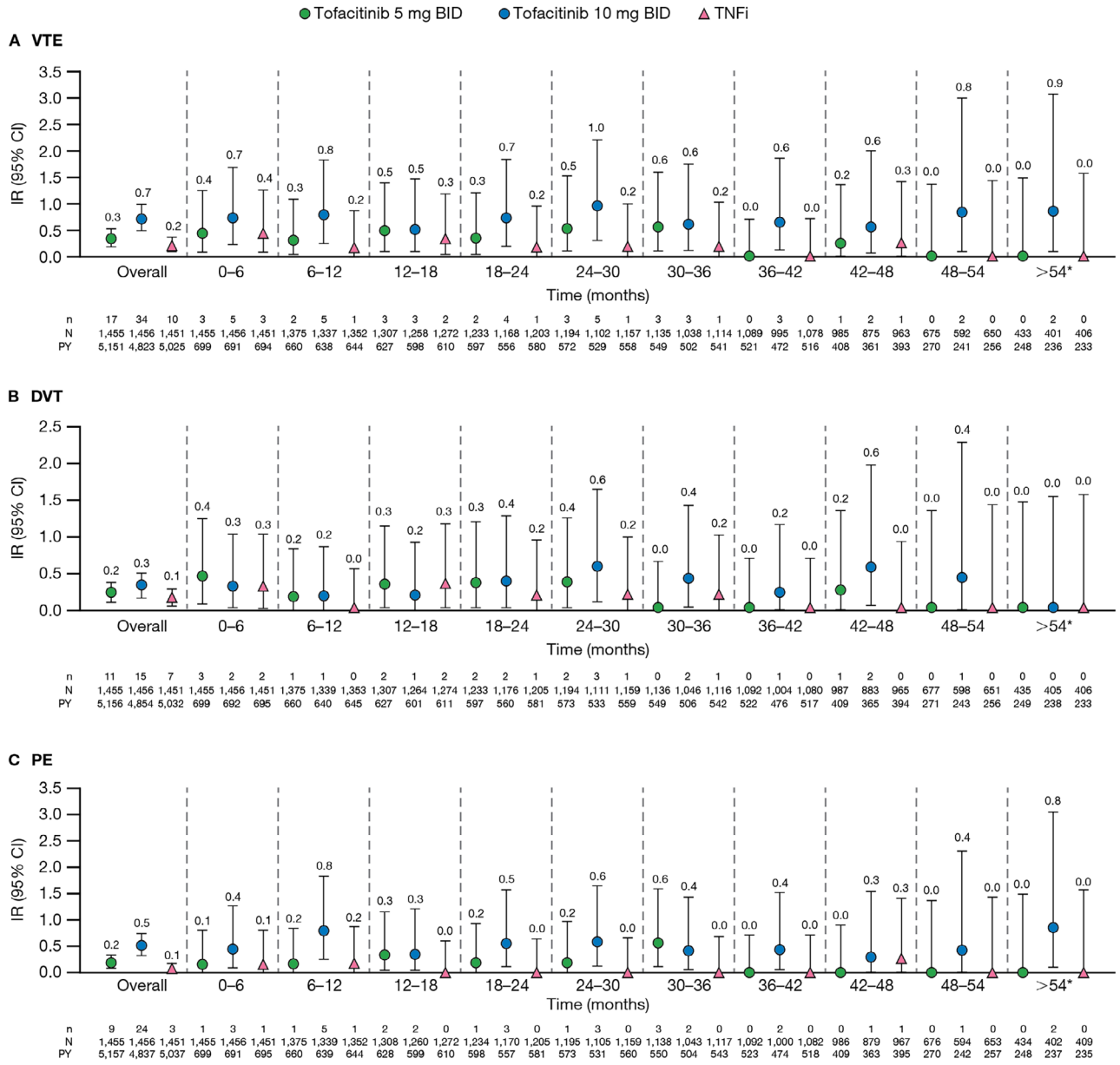


Figure 2. IRs (patients with first events/100 PY; 95% CIs) for adjudicated (A) VTE, (B) DVT, and (C) PE events, by 6-month intervals (28-day on-treatment time). For patients randomized to the tofacitinib 10 mg BID group who had their dose reduced to 5 mg BID, data collected after the dose switch were included in the tofacitinib 10 mg BID group. Overall IRs (95% CIs) were previously reported[23] and are included as reference. *Includes data after 54 months up to approximately 72 months. BID, twice daily; CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate; n, number of patients with a first event within the time interval; N, number of patients at risk within each time interval; PE, pulmonary embolism; PY, patient-years; TNFi, tumor necrosis factor inhibitor; VTE, venous thromboembolism.

Multivariable Cox analyses identified a history of VTE, BMI greater than or equal to 35 kg/m^2, older age, and a history of chronic lung disease as baseline risk factors for VTE across all treatments ($P < 0.05$; Supplementary Figure 3A; multivariable Cox models for DVT and PE are shown in Supplementary Figure 3B and 3C). Results from the simple Cox analyses screening for potential baseline risk factors are in Supplementary Table 2 (risk factors with $P < 0.10$ were subjected to further selection via backward selection with $P < 0.10$ to retain a risk factor in the multivariable model). Time-dependent risk factor analyses results are in Supplementary Figure 4. Additional sensitivity/exploratory analyses with forward selection for Cox regression and Poisson regression identified the same, or nearly the same, explanatory variables for inclusion in the final model (data not shown).

Association of age with risk of VTE with tofacitinib versus TNFi. Older age was a risk factor in the multivariable model for VTE, and analysis by age (younger than 65 and 65

Table 1. Patient demographics and baseline disease characteristics for patients with vs without VTE events (total time analysis)

	Patients with VTE events (N1 = 66)			Patients without VTE events (N1 = 4,296)		
	Tofacitinib 5 mg BID (N = 18)	Tofacitinib 10 mg BID[a] (N = 36)	TNFi (N = 12)	Tofacitinib 5 mg BID (N = 1,437)	Tofacitinib 10 mg BID[a] (N = 1,420)	TNFi (N = 1,439)
Age, years, mean (SD)	66.5 (7.3)	63.1 (6.4)	62.9 (5.4)	60.7 (6.8)	61.4 (7.1)	61.3 (7.5)
≥65 years, n (%)	11 (61.1)	15 (41.7)	4 (33.3)	402 (28.0)	463 (32.6)	458 (31.8)
Female sex, n (%)	14 (77.8)	24 (66.7)	11 (91.7)	1,155 (80.4)	1,100 (77.5)	1,106 (76.9)
Race, n (%)						
White	18 (100)	30 (83.3)	10 (83.3)	1,110 (77.2)	1,096 (77.2)	1,089 (75.7)
Black	0 (0)	3 (8.3)	2 (16.7)	63 (4.4)	62 (4.4)	81 (5.6)
Asian	0 (0)	0 (0)	0 (0)	65 (4.5)	56 (3.9)	55 (3.8)
Other	0 (0)	3 (8.3)	0 (0)	199 (13.8)	206 (14.5)	214 (14.9)
BMI, kg/m^2, mean (SD) [N2]	32.3 (8.6) [17]	34.2 (6.7) [36]	36.0 (10.0) [12]	29.7 (6.5) [1,431]	29.6 (6.3) [1,417]	29.7 (6.6) [1,432]
BMI ≥30 kg/m^2, n (%)	8 (44.4)	25 (69.4)	8 (66.7)	598 (41.6)	569 (40.1)	609 (42.3)
Smoking status, n (%)						
Never smoked	8 (44.4)	12 (33.3)	8 (66.7)	727 (50.6)	740 (52.1)	764 (53.1)
Current smoker	6 (33.3)	7 (19.4)	1 (8.3)	405 (28.2)	395 (27.8)	352 (24.5)
Past smoker	4 (22.2)	17 (47.2)	3 (25.0)	305 (21.2)	285 (20.1)	323 (22.4)
Baseline HDL-c <40 mg/dL, n (%)	0 (0)	6 (16.7)	1 (8.3)	172 (12.0)	189 (13.3)	172 (12.0)
Baseline CRP >2.87 mg/L, n (%)	16 (88.9)	30 (83.3)	9 (75.0)	1,263 (87.9)	1,240 (87.3)	1,257 (87.4)
History of VTE (DVT or PE), n (%)	1 (5.6)	4 (11.1)	3 (25.0)	18 (1.3)	29 (2.0)	24 (1.7)
History of hypertension, n (%)	14 (77.8)	28 (77.8)	11 (91.7)	941 (65.5)	926 (65.2)	958 (66.6)
History of diabetes mellitus, n (%)	1 (5.6)	9 (25.0)	3 (25.0)	242 (16.8)	252 (17.7)	252 (17.5)
History of coronary heart disease, n (%)	1 (5.6)	7 (19.4)	4 (33.3)	160 (11.1)	165 (11.6)	160 (11.1)
History of extraarticular disease, n (%)	5 (27.8)	15 (41.7)	4 (33.3)	527 (36.7)	506 (35.6)	548 (38.1)
Oral contraceptives or HRT use at baseline, n (%)	2 (11.1)	1 (2.8)	0 (0)	49 (3.4)	40 (2.8)	45 (3.1)
Corticosteroid use at baseline, n (%)	12 (66.7)	24 (66.7)	11 (91.7)	824 (57.3)	805 (56.7)	819 (56.9)
Aspirin use at baseline, n (%)	3 (16.7)	13 (36.1)	3 (25.0)	209 (14.5)	218 (15.4)	221 (15.4)
Anticoagulant[b] use at baseline, n (%)	1 (5.6)	1 (2.8)	1 (8.3)	46 (3.2)	65 (4.6)	61 (4.2)
Hydroxychloroquine[c] use at baseline, n (%)	3 (16.7)	4 (11.1)	1 (8.3)	124 (8.6)	136 (9.6)	140 (9.7)
Baseline CDAI, mean (SD) [N2]	38.7 (12.6) [17]	41.7 (12.9) [36]	41.6 (11.9) [12]	39.8 (11.9) [1,393]	39.8 (12.1) [1,368]	39.7 (11.9) [1,375]
Baseline SDAI, mean (SD) [N2]	40.3 (12.9) [17]	43.4 (13.6) [36]	42.8 (12.9) [12]	41.5 (12.5) [1,393]	41.5 (12.6) [1,368]	41.4 (12.5) [1,374]
Baseline HAQ-DI, mean (SD) [N2]	1.5 (0.7) [18]	1.6 (0.7) [36]	1.5 (0.4) [12]	1.6 (0.6) [1,426]	1.6 (0.6) [1,402]	1.6 (0.6) [1,414]

[a] For patients randomized to the tofacitinib 10 mg BID group who had their dose reduced to 5 mg BID, data collected after the dose switch were included in the tofacitinib 10 mg BID group.
[b] Aspirin was not considered an anticoagulant.
[c] Included hydroxychloroquine, chloroquine, and quinine.
BID, twice daily; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DVT, deep vein thrombosis; HAQ-DI, Health Assessment Questionnaire-Disability Index; HDL-c, high-density lipoprotein-cholesterol; HRT, hormone replacement therapy; n, number of patients meeting baseline criteria; N, number of patients in each treatment group; N1, number of patients with or without VTE events; N2, number of patients with observations; PE, pulmonary embolism; SD, standard deviation; SDAI, Simplified Disease Activity Index; TNFi, tumor necrosis factor inhibitor; VTE, venous thromboembolism.

years or older) was prespecified in ORAL Surveillance.[23] As previously reported,[23] IRs and HRs of VTE (Figure 3) and PE (Supplementary Figure 5) in the overall population were dose-dependently increased with tofacitinib versus TNFi. NNH indicated that 198 and 763 patients would need to be treated with tofacitinib 10 mg BID or 5 mg BID, respectively, for one year to have one additional event of VTE versus TNFi. Across treatments, rates of DVT were similar (Supplementary Figure 6).

IRs of VTE, PE, and DVT with tofacitinib were numerically higher in patients who were aged 65 years or older versus younger than 65 years (Figure 3A, Supplementary Figure 5A, and Supplementary Figure 6A). In patients younger than 65 years of age, risk of VTE was higher with tofacitinib 10 mg BID versus TNFi (HR [95% CI] 2.90 [1.23–6.87]; NNH versus TNFi: 259 patient-years), but a risk difference was not suggested with tofacitinib 5 mg BID versus TNFi (HR [95% CI] 0.93 [0.32–2.64]; NNH versus TNFi: –6,465 patient-years) (Figure 3B). In patients who were 65 years or older, risk of VTE was higher versus TNFi for both tofacitinib 5 mg BID (HR [95% CI] 3.73 [1.03–13.54]; NNH versus TNFi: 188 patient-years) and tofacitinib 10 mg BID (HR [95% CI] 5.02 [1.44–17.47]; NNH versus TNFi: 126 patient-years) (Figure 3B). Data on risk for PE with tofacitinib versus TNFi in patients aged younger than 65 years or 65 years or older (generally similar to those for VTE) and DVT are in Supplementary Figures 5B and 6B, respectively.

Association of baseline cardiovascular risk profile with risk of VTE with tofacitinib versus TNFi. IRs for VTE, DVT, and PE were higher in patients with versus without history of ASCVD with tofacitinib 10 mg BID and TNFi but not with tofacitinib 5 mg BID (Supplementary Figure 7). Patients with history of ASCVD had a higher risk of VTE, DVT, and PE with tofacitinib 10 mg BID versus TNFi, whereas among patients without history of ASCVD, risk of VTE, DVT, and PE was higher with both tofacitinib doses versus TNFi (Supplementary Figure 8). Further

assessment of patients without history of ASCVD showed that IRs for VTE, DVT, and PE generally increased with increasing baseline cardiovascular risk scores in the tofacitinib 5 and 10 mg BID groups (Supplementary Figure 7).

Disease activity and other VTE risk factors in individual patients with VTE. Across treatments, most patients with VTE had residual disease activity preceding the event. Few VTE events occurred in patients who were in

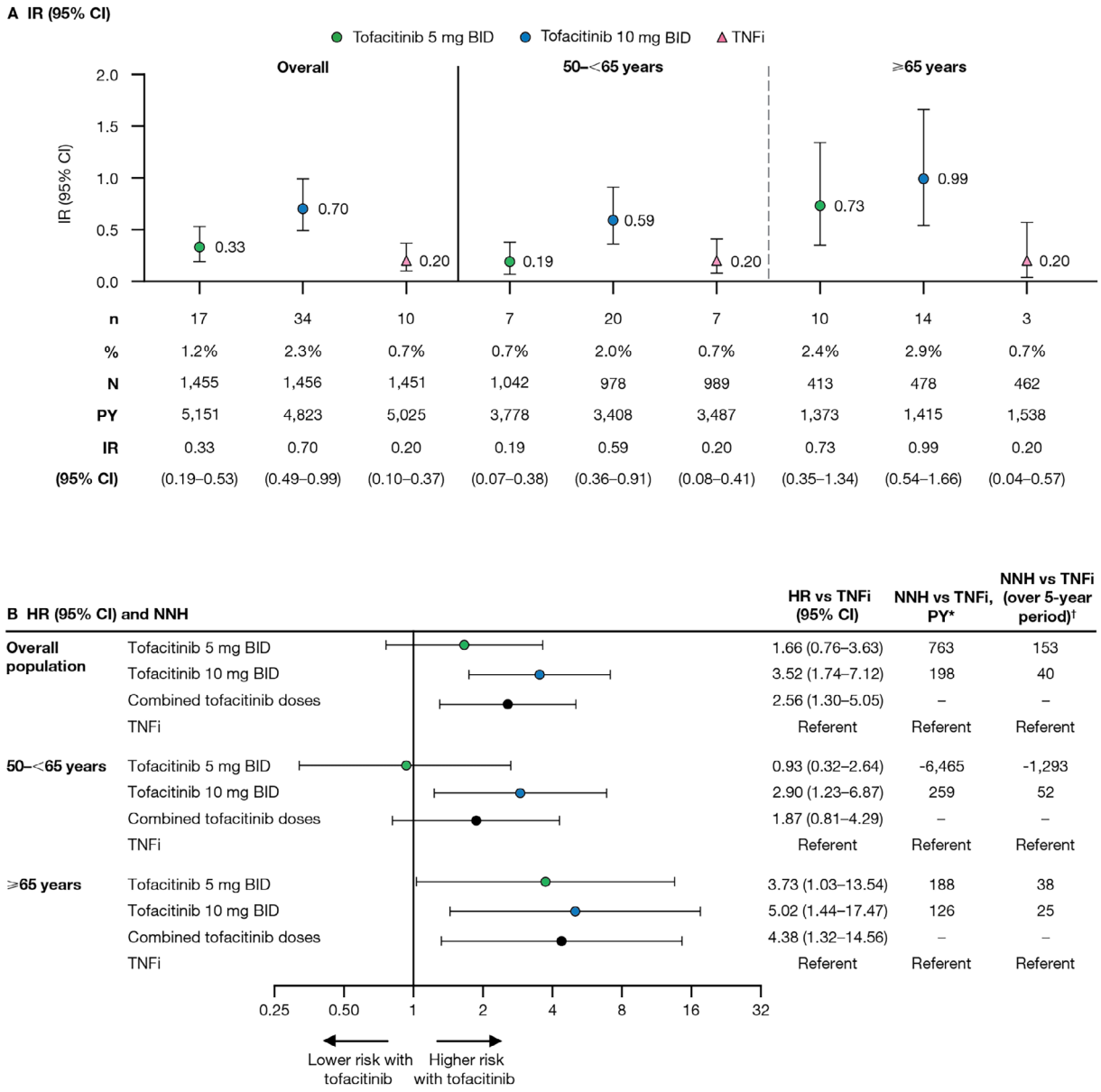


Figure 3. Risk of VTE with tofacitinib versus TNFi, overall and by age (28-day on-treatment time): (A) IRs (patients with first events/100 PY; 95% CIs) and (B) HRs (95% CIs) with tofacitinib versus TNFi. For patients randomized to the tofacitinib 10 mg BID group who had their dose reduced to 5 mg BID, data collected after the dose switch were included in the tofacitinib 10 mg BID group. Overall IRs (95% CIs) and HRs (95% CIs) (except HRs for combined tofacitinib doses) were previously reported[23] and are included as reference. HRs (95% CIs), shown on a logarithmic scale, were based on two simple Cox proportional hazard models with treatment as a covariate; one was for comparing combined tofacitinib doses versus TNFi and the other was for pairwise comparisons among the treatments. *A positive NNH indicated the number of PY of tofacitinib exposure needed for one more patient to report an additional event versus TNFi; a negative NNH indicated the number of PY of TNFi exposure needed for one more patient to report an additional event versus tofacitinib. †A positive NNH (over 5 years) indicated the number of patients who would need to be treated with tofacitinib for 5 years to have one additional event compared with TNFi; a negative NNH (over 5 years) indicated the number of patients who would need to be treated with TNFi for 5 years to have one additional event compared with tofacitinib. BID, twice daily; CI, confidence interval; HR, hazard ratio; IR, incidence rate; n, number of patients with a first event within the risk period; N, number of patients in each treatment group in the safety population; NNH, number needed to harm; PY, patient-years; TNFi, tumor necrosis factor inhibitor; VTE, venous thromboembolism.

CDAI-defined remission (1/17 [5.9%], 6/33 [18.2%], and 0/10 [0.0%] events with tofacitinib 5 mg BID, tofacitinib 10 mg BID, and TNFi, respectively); 88.3% (53/60) of events occurred in patients with CDAI-defined high, moderate, or low disease activity (Figure 4).

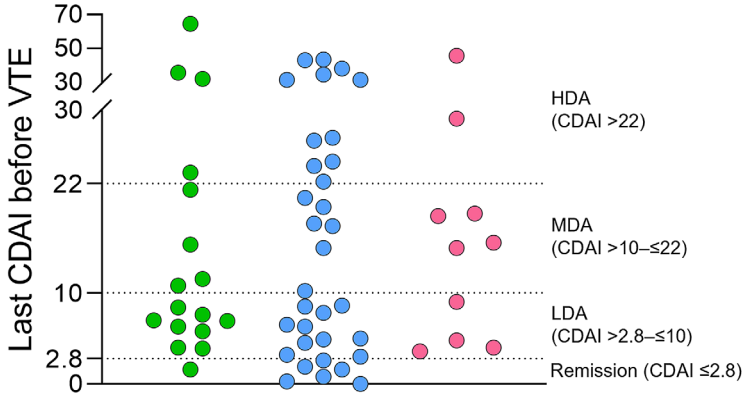
CDAI disease activity category leading up to the event and other risk factors or triggers for patients with VTE are shown in Figure 5 (further patient details provided in Supplementary Table 3). Early events (ie, occurring up to 6 months) largely occurred in patients with high or moderate disease activity. These data also show that several of the patients with VTE remained in the trial for a relatively long time with uncontrolled disease activity.

Most patients with events had at least one risk factor for VTE that was present at baseline (eg, BMI ≥35 kg/m^2, age ≥65 years, or history of smoking) (Figure 5 and Supplementary Table 3). Moreover, across treatments, patients with VTE events frequently acquired important transient risk factors during the trial; 41.2% (7/17), 17.6% (6/34), and 50.0% (5/10) of patients with VTE treated with tofacitinib 5 mg BID, tofacitinib 10 mg BID, or TNFi, respectively, had surgery or were hospitalized because of acute illness within 3 months before the VTE. Infections occurred within 3 months of VTE in 52.9% (9/17), 44.1% (15/34), and 40.0% (4/10) of patients treated with tofacitinib 5 mg BID, tofacitinib 10 mg BID, or TNFi, respectively (urinary tract and respiratory infections were the most common) (Supplementary Table 3).

Three patients died because of adjudicated VTE; one received tofacitinib 5 mg BID (75-year-old female past smoker, with adjudicated DVT, PE, and concomitant influenza and pneumonia; patient #8 in Figure 5) and two received tofacitinib 10 mg BID (67-year-old male past smoker and a 55-year-old female past smoker with previous VTE; both with adjudicated PE; patients #33 and #50, respectively, in Figure 5).

DISCUSSION

The ORAL Surveillance trial found a dose-dependent increase in events of VTE and PE with tofacitinib versus TNFi in patients with RA aged 50 years or older with at least one additional cardiovascular risk factor.[23] These post hoc analyses found that over 72 months, the cumulative probabilities of VTE and PE events were higher with tofacitinib 10 mg BID versus TNFi and higher with tofacitinib 10 versus 5 mg BID. VTE events were observed throughout the trial, and IRs were similar over longitudinal follow-up (measured in 6-month intervals), suggesting that incidence of events was not restricted to the acute phase after treatment initiation and did not increase with longer treatment duration. Exploration of the relationship between VTE events and



	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	TNFi
Patients with VTE (N)	17	33*	10
CDAI status at last visit before event, % (n)			
Remission	5.9% (1)	18.2% (6)	0.0% (0)
LDA	47.1% (8)	30.3% (10)	40.0% (4)
MDA	23.5% (4)	18.2% (6)	40.0% (4)
HDA	23.5% (4)	33.3% (11)	20.0% (2)

Figure 4. CDAI scores at last visit before VTE event. Each dot represents an individual patient with VTE during the 28-day on-treatment time. Data represent the most recent CDAI measurement available preceding the VTE event (visits were scheduled at day 1, months 2 and 3, and approximately every 3 months thereafter). For patients randomized to the tofacitinib 10 mg BID group who had their dose reduced to 5 mg BID, data collected after the dose switch were included in the tofacitinib 10 mg BID group. *One patient in the tofacitinib 10 mg BID group had a missing CDAI score and is not included here. BID, twice daily; CDAI, Clinical Disease Activity Index; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; n, number of patients in each CDAI category; N, number of patients with a first VTE event within the risk period; TNFi, tumor necrosis factor inhibitor; VTE, venous thromboembolism.

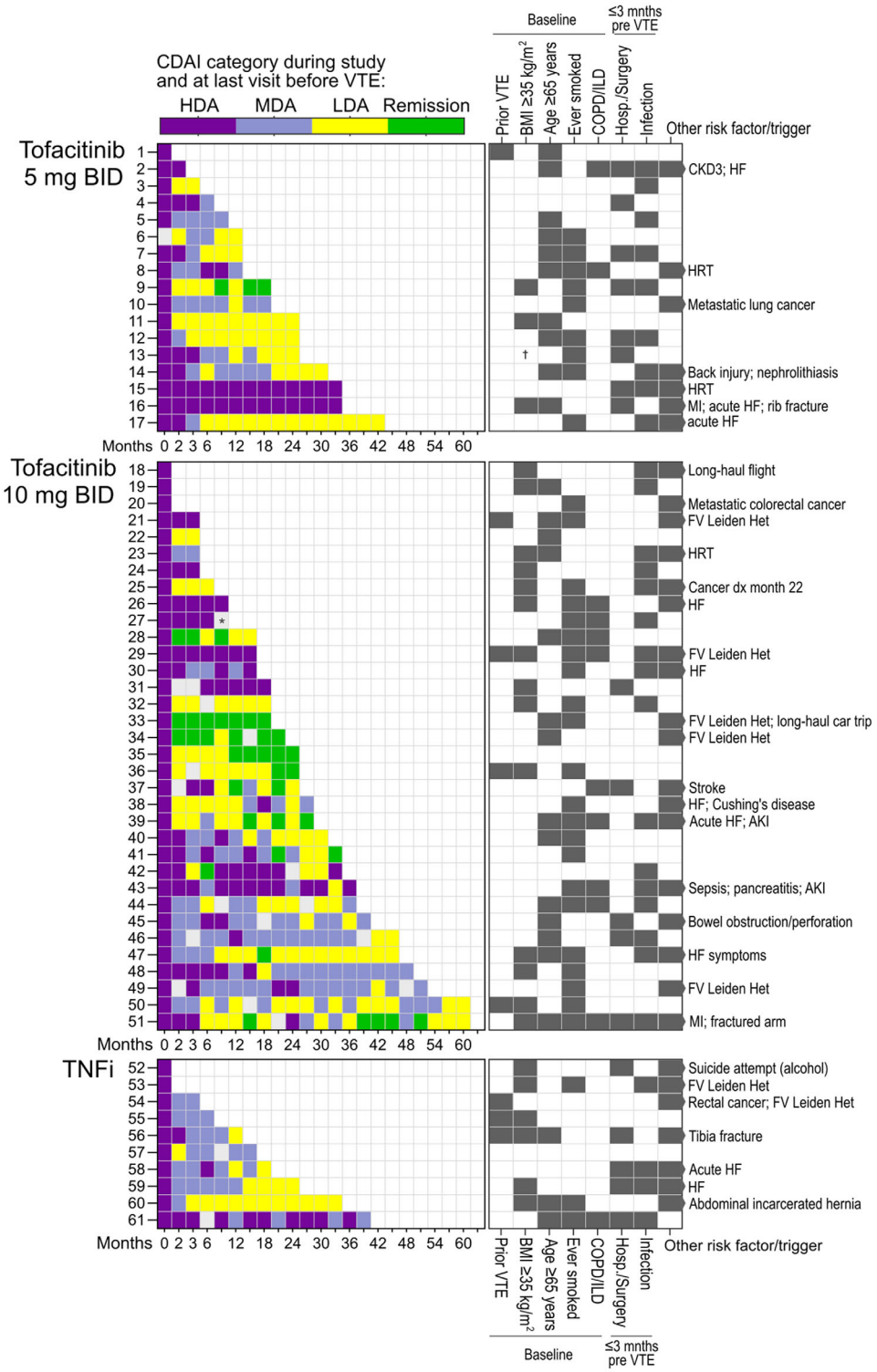


Figure 5. Disease activity and risk factors of individual patients with VTE. Rows represent individual patients with VTE during the 28-day on-treatment time, ordered by time to event per treatment arm. CDAI disease activity categories (remission, ≤2.8; LDA, >2.8–≤10; MDA, >10–≤22; HDA, >22) are shown up to the most recent CDAI measurement available preceding the VTE event. Light gray boxes represent missing CDAI values. Events of surgery, hospitalization, and infection were only included if occurring within 3 months before VTE. For patients randomized to the tofacitinib 10 mg BID group who had their dose reduced to 5 mg BID, data collected after the dose switch were included in the tofacitinib 10 mg BID group.*CDAI value missing at month 9. †BMI missing at baseline; weight was 116 kg. AKI, acute kidney injury; BID, twice daily; BMI, body mass index; CDAI, Clinical Disease Activity Index; CKD3, chronic kidney disease stage 3; COPD, chronic obstructive pulmonary disease; dx, diagnosis; FV Leiden Het, Factor V Leiden heterozygous mutation; HDA, high disease activity; HF, heart failure; Hosp., hospitalization; HRT, hormone replacement therapy; ILD, interstitial lung disease; LDA, low disease activity; MDA, moderate disease activity; MI, myocardial infarction; TNFi, tumor necrosis factor inhibitor; VTE, venous thromboembolism.

risk factors for VTE indicated that most events, across treatments, occurred in patients with more than one VTE risk factor, including residual disease activity.

Absolute risk (IRs [95% CIs]) for VTE, DVT, and PE with tofacitinib and TNFi in ORAL Surveillance was broadly comparable with ranges previously reported for tofacitinib and biologic disease-modifying antirheumatic drugs among patients with RA with cardiovascular risk factors.[32] Furthermore, IRs (95% CIs) for VTE, DVT, and PE events with tofacitinib 5 mg BID in ORAL Surveillance were also similar to data reported in integrated safety analyses of the baricitinib and upadacitinib RA trial programs.[33,34] However, with tofacitinib 10 mg BID in ORAL Surveillance, IRs for VTE and PE events (0.70 and 0.50, respectively) were higher than those reported in tofacitinib clinical trial and registry data (VTE 0.37–0.51 and 0.22, respectively; PE 0.24–0.25 and 0.11, respectively) or biologic disease-modifying antirheumatic drug clinical trial and registry data (VTE [registry data only]: 0.51; PE 0.06–0.2 and 0.27, respectively).[32] Notably, IRs (95% CI) for VTE with tofacitinib 5 and 10 mg BID were also similar to those reported from post hoc analyses applying risk-enrichment criteria (similar to those of ORAL Surveillance) to the upadacitinib[35] and baricitinib[33] RA clinical trial programs.

Events of VTE are considered a consequence of interactions between multiple persistent or transient provoking factors.[10,11] We identified previous VTE, morbid obesity (BMI ≥35 kg/m^2), and older age (≥65 years) as baseline and persistent risk factors for VTE across treatments in ORAL Surveillance. Our results align with reports of risk factors for VTE in patients with RA,[36] including those treated with baricitinib.[37] In addition, we found that history of chronic lung disease was a risk factor for VTE across treatments, an association that has previously been found for patients with advanced chronic obstructive pulmonary disease.[38] Shared risk factors between VTE and ASCVD have been previously identified in patients with RA,[36] and this was also indicated in our analysis. It is noteworthy that other known risk factors for VTE, including oral corticosteroids and oral contraceptives or HRT use,[15,18] were not identified as predictive risk factors in the simple Cox analyses, and therefore, were not included in the subsequent multivariable analyses.

We report here that most VTE events in ORAL Surveillance occurred in patients who had residual disease activity (ie, not in CDAI-defined remission) at the last visit prior to the event, suggesting that any disease activity may be associated with an increased risk of VTE, in line with previous analyses.[39,40] Aligned with these data, it was recently reported that VTE risk across treatments in ORAL Surveillance tended to be higher in patients who had residual disease activity, as measured by CDAI, versus those who were in remission.[25] Molander et al demonstrated that the incidence and risk of VTE were higher with greater RA disease activity, as measured by Disease Activity Score 28 erythrocyte sedimentation rate.[39] Furthermore, time-averaged Disease Activity Score 28 C-reactive protein was previously identified as a significant risk factor for VTE in patients with RA.[40] Interestingly, six of the seven patients in the current analysis who were in remission and had VTE were receiving tofacitinib 10 mg BID, which may suggest that disease activity could have less of an impact on the development of VTE for this patient group, although the number of patients was too small to draw definitive conclusions. In addition to baseline risk factors and disease activity data noted above, it is noteworthy that a substantial proportion of patients with VTE, across treatment arms, were hospitalized for acute illness or surgery, or had infections within 3 months before the VTE event. Several patients also had VTE events in combination with previous/concomitant myocardial infarction and worsening of heart failure, or were heterozygous for factor V Leiden, all of which are risk factors for VTE.[18,19] Our results highlight the importance of disease management, effective disease control, and treat-to-target recommendations for patients with RA.

Rates of VTE and PE were higher with tofacitinib 10 mg BID versus TNFi in ORAL Surveillance and numerically more frequent with tofacitinib 5 mg BID versus TNFi.[23] The data we provide here suggest that risk of VTE with tofacitinib 5 mg BID versus TNFi is higher in patients aged 65 years or older. These results align with a recent analysis of ORAL Surveillance that identified age 65 years or older or ever smoking (ie, current or past) as differential risk factors for increased risk of VTE and other major safety outcomes with the combined tofacitinib doses versus TNFi.[26] In that analysis, a difference in risk of VTE in patients aged younger than 65 years who had never smoked was not detected with tofacitinib 10 mg BID versus TNFi. Notably, current or past smoking were not identified as predictive baseline risk factors in the multivariable analyses we present here, but in the general population, greater VTE risk has previously been observed in ever versus never smokers, particularly in current or past heavy smokers.[41] Pack-years of smoking could not be determined in ORAL Surveillance, but it should be noted that, across treatments, more than 90% of current and past smokers had a smoking history of more than 10 years and a median smoking duration of more than 30 years.[26] Thus, the available data point to the relevance of history of smoking for the increased risk of VTE with tofacitinib 10 mg BID versus TNFi. It is likely that older age (≥65 years) and long-term smoking history are both associated with conditions or risk factors driving the risk of VTE and PE with tofacitinib; however, we have not been able to identify these in our analyses. To further enhance our precision in identifying patients at increased risk of VTE with tofacitinib versus TNFi, we will need mechanistic understanding of any relationship between Janus kinase inhibitors and VTE events, and to do so, translational research is likely required. Moreover, it is also not clear to what extent TNFi provides protective effects against VTE events. Notably, an ongoing clinical trial is assessing risk of VTE with baricitinib versus TNFi in patients with RA and VTE risk factors,[42] and this study could potentially provide more

clarity on the risk of VTE with Janus kinase inhibitors, including risk factor identification.

Limitations of ORAL Surveillance were reported previously, including the fact that this study was not powered to compare VTE risk across treatments.[23] This also limited our ability to identify and evaluate important but uncommon risk factors of VTE. Furthermore, low numbers of VTE, DVT, and PE events in some treatment groups precluded assessments of interaction or effect modification that would be of high interest to inform a personalized medicine approach. Additionally, the risk factor analyses were exploratory in nature. Details of patient medical histories were not fully collected.

The results of this analysis of VTE in ORAL Surveillance demonstrated that, in patients with RA who were aged 50 years or older with at least one additional cardiovascular risk factor, the cumulative incidence of VTE and PE events was higher with tofacitinib 10 mg BID versus tofacitinib 5 mg BID and TNFi, and the IRs were generally consistent over time within each treatment. NNH indicated that 198 patients would need to be treated with tofacitinib 10 mg BID for one year to have one additional event of VTE versus TNFi. For tofacitinib 5 mg BID, the recommended dosage for RA, NNH versus TNFi was 763. Exploratory analyses identified history of VTE, morbid obesity, and older age as the strongest baseline risk factors for VTE across all treatments and also indicated the importance of transient VTE risk factors, including uncontrolled disease activity. These data highlight the importance of assessing risk factors for VTE when deciding whether to initiate tofacitinib or TNFi treatment in patients with active RA.

ACKNOWLEDGMENTS

The authors would like to acknowledge Arne Yndestad and Mahta Mortezavi, employees and shareholders of Pfizer, for important contributions to this work.

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. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ytterberg, Bhatt, Connell, Menon.
Acquisition of data. Greenwald, Connell.
Analysis and interpretation of data. Charles-Schoeman, Fleischmann, Mysler, Greenwald, Ytterberg, Koch, Wang, Mikuls, Chen, Connell, Woolcott, Menon, Chen, Lee, Szekanecz.

ROLE OF THE STUDY SPONSOR

Pfizer designed the study in collaboration with the academic authors. A contract research organization (ICON) collected the data. Pfizer employees, along with the academic authors, analyzed and interpreted the data, and were involved in the writing of the manuscript and the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer. Medical writing support, under the direction of the authors, was provided by Justine Juana, BHSc, CMC Connect, a division of IPG Health Medical Communications and was funded by Pfizer, New York, NY, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (Ann Intern Med 2022;175:1298–304).

REFERENCES

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010; 376:1094–1108.
2. Chung W-S, Peng CL, Lin CL, et al. Rheumatoid arthritis increases the risk of deep vein thrombosis and pulmonary thromboembolism: a nationwide cohort study. Ann Rheum Dis 2014;73:1774–1780.
3. Kim SC, Schneeweiss S, Liu J, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2013;65:1600–1607.
4. Lee JJ, Pope JE. A meta-analysis of the risk of venous thromboembolism in inflammatory rheumatic diseases. Arthritis Res Ther 2014; 16:435.
5. Holmqvist ME, Neovius M, Eriksson J, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. JAMA 2012;308:1350–1356.
6. Choi HK, Rho YH, Zhu Y, et al. The risk of pulmonary embolism and deep vein thrombosis in rheumatoid arthritis: a UK population-based outpatient cohort study. Ann Rheum Dis 2013;72:118–127.
7. Yusuf HR, Hooper WC, Grosse SD, et al. Risk of venous thromboembolism occurrence among adults with selected autoimmune diseases: a study among a U.S. cohort of commercial insurance enrollees. Thromb Res 2015;135:50–57.
8. Ketfi C, Boutigny A, Mohamedi N, et al. Risk of venous thromboembolism in rheumatoid arthritis. Joint Bone Spine 2021;88:105122.
9. Aksu K, Donmez A, Keser G. Inflammation-induced thrombosis: mechanisms, disease associations and management. Curr Pharm Des 2012;18:1478–1493.
10. Khan F, Tritschler T, Kahn SR, et al. Venous thromboembolism. Lancet 2021;398:64–77.
11. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis 2016;41:3–14.
12. Nowak M, Królak-Nowak K, Sobolewska-Włodarczyk A, et al. Elevated risk of venous thromboembolic events in patients with inflammatory myopathies. Vasc Health Risk Manag 2016;12: 233–238.
13. Falanga A, Russo L, Milesi V, et al. Mechanisms and risk factors of thrombosis in cancer. Crit Rev Oncol Hematol 2017;118:79–83.
14. Gaertner S, Cordeanu EM, Mirea C, et al. Increased risk and severity of unprovoked venous thromboembolism with clustering cardiovascular risk factors for atherosclerosis: results of the REMOTEV registry. Int J Cardiol 2018;252:169–174.
15. Rott H. Prevention and treatment of venous thromboembolism during HRT: current perspectives. Int J Gen Med 2014;7:433–440.
16. Zakai NA, McClure LA, Judd SE, et al. Racial and regional differences in venous thromboembolism in the United States in 3 cohorts. Circulation 2014;129:1502–1509.
17. Ageno W, Becattini C, Brighton T, et al. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation 2008; 117:93–102.
18. Huerta C, Johansson S, Wallander MA, et al. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med 2007;167: 935–943.
19. Ho WK, Hankey GJ, Quinlan DJ, et al. Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. Arch Intern Med 2006;166:729–736.

20. Mahmoodi BK, Cushman M, Anne Naess I, et al. Association of traditional cardiovascular risk factors with venous thromboembolism: an individual participant data meta-analysis of prospective studies. Circulation 2017;135:7–16.
21. Aviña-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71:1524–1529.
22. Gregson J, Kaptoge S, Bolton T, et al. Cardiovascular risk factors associated with venous thromboembolism. JAMA Cardiol 2019;4:163–173.
23. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med 2022;386:316–326.
24. Weitz JI, Szekanecz Z, Charles-Schoeman C, et al. Biomarkers to predict risk of venous thromboembolism in patients with rheumatoid arthritis receiving tofacitinib or tumour necrosis factor inhibitors. RMD Open 2022;8:e002571.
25. Karpouzas GA, Szekanecz Z, Baecklund E, et al. Rheumatoid arthritis disease activity and adverse events in patients receiving tofacitinib or tumor necrosis factor inhibitors: a post hoc analysis of ORAL Surveillance. Ther Adv Musculoskelet Dis 2023;15:1759720x231201047.
26. Kristensen LE, Danese S, Yndestad A, et al. Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance. Ann Rheum Dis 2023;82:901–910.
27. US Food and Drug Administration. Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate. 2019. Accessed May 30, 2022. https://www.fda.gov/media/120485/download
28. Daly L. Simple SAS macros for the calculation of exact binomial and Poisson confidence limits. Comput Biol Med 1992;22:351–361.
29. Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972;34:187–202.
30. Charles-Schoeman C, Buch MH, Dougados M, et al. 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. Ann Rheum Dis 2023;82:119–129.
31. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23(5 Suppl 39):S100–S108.
32. Mease P, Charles-Schoeman C, Cohen S, 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;79:1400–1413.
33. Taylor PC, Takeuchi T, Burmester GR, et al. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. Ann Rheum Dis 2022;81:335–343.
34. Cohen SB, van Vollenhoven RF, Winthrop KL, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. Ann Rheum Dis 2020;80:304–311.
35. Fleischmann R, Curtis JR, Charles-Schoeman C, et al. Safety profile of upadacitinib in patients at risk of cardiovascular disease: integrated post hoc analysis of the SELECT phase III rheumatoid arthritis clinical programme. Ann Rheum Dis 2023;82:1130–1141.
36. Ozen G, Pedro S, Schumacher R, et al. Risk factors for venous thromboembolism and atherosclerotic cardiovascular disease: do they differ in patients with rheumatoid arthritis? RMD Open 2021;7:e001618.
37. Taylor PC, Weinblatt ME, Burmester GR, et al. Cardiovascular safety during treatment with baricitinib in rheumatoid arthritis. Arthritis Rheumatol 2019;71:1042–1055.
38. Børvik T, Braekkan SK, Enga K, et al. COPD and risk of venous thromboembolism and mortality in a general population. Eur Respir J 2016;47:473–481.
39. Molander V, Bower H, Frisell T, et al. Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden. Ann Rheum Dis 2021;80:169–175.
40. Yoshimura M, Fujieda Y, Sugawara M, et al. Disease activity as a risk factor for venous thromboembolism in rheumatoid arthritis analysed using time-averaged DAS28CRP: a nested case-control study. Rheumatol Int 2022;42:1939–1946.
41. Cheng Y-J, Liu ZH, Yao FJ, et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med 2013;10:e1001515.
42. Clinicaltrials.gov. A study of baricitinib (LY3009104) in participants with rheumatoid arthritis (RA-BRIDGE). 2021. Accessed March 28, 2024. https://clinicaltrials.gov/ct2/show/NCT03915964