



# Venous Thromboembolism in Rheumatoid Arthritis: The Added Effect of Disease Activity to Traditional Risk Factors

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**Abstract:** Many epidemiological studies have shown an increased risk of venous thromboembolism (VTE) in patients with rheumatoid arthritis (RA). RA and VTE share some background factors, such as increasing age, smoking, and obesity. At the same time, other VTE factors, such as knee replacement and oral contraceptive pills, occur commonly in RA patients. In addition, the chronic inflammatory state of RA might hypothetically lead to endothelial injury and a hypercoagulable state. Two critical pathophysiological pathways lead to VTE. Recently, concerns increased about the increased risk of VTE in patients using Janus Kinase inhibitors. This review aims at reviewing the risk of VTE in RA and the role of traditional risk factors and disease-related inflammation and develops a conceptual framework that describes the interaction between these factors.

**Keywords:** rheumatoid arthritis, venous thromboembolism, Janus Kinase inhibitors

## Introduction

Venous thromboembolic (VTE) disease is a major health problem affecting 100 /100,000 persons, which is associated with significant disability and mortality.<sup>1</sup> Extensive epidemiological studies have indicated that patients with rheumatoid arthritis (RA) are at a higher risk of developing VTE than age- and sex-matched controls, even after adjusting for clinical risk factors and acute-phase reactants.<sup>2,3</sup> Both diseases have common background demographics such as increased age,<sup>4,5</sup> obesity,<sup>6,7</sup> smoking,<sup>8,9</sup> and certain comorbidities. In addition, the development of a VTE event in an RA patient might be triggered by immobility due to fracture occurrence, hospitalization, and joint replacement.<sup>10</sup> These factors might partially explain the increased risk, but RA inflammatory milieu might play a role in causing endothelial injury and increasing hypercoagulability.

Additionally, female RA patients commonly use oral contraceptive pills during premenopausal periods due to the teratogenicity of many treatment options. The management of RA has evolved significantly in the last three decades. This was mainly due to the approval of highly effective therapies and the developing of a “Treat To Target” strategy.<sup>11</sup> Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biological (bDMARDs) have played a major role in controlling inflammation, reducing disability, and developing morbidity and mortality.<sup>12</sup>

Recently, the introduction of Janus kinase inhibitors (JAKi) to treat RA and the observation of increased risk of VTE in the associated clinical trial program have drawn the attention of the rheumatology community to the risk of VTE in RA patients.<sup>13</sup>

VTE prevention should be aimed at high-risk patients through medical treatment, mechanical methods, and early mobilization.<sup>14–16</sup> Heparin, warfarin, and direct oral anticoagulants are the main therapeutic classes.<sup>17,18</sup>

## RA and the Virchow's Triad

Virchow's triad, comprising venous stasis, endothelial injury, and a hypercoagulable state, was first described in 1856.<sup>19</sup> In this condition, an imbalance between procoagulants and anticoagulants leads to a hypercoagulable state. Venous thrombi comprise two layers: an inner rich platelet layer surrounded by a dense red cell fibrin clot. Clots are usually formed in areas with altered blood flow, such as pockets adjacent to venous valves in the legs.<sup>20</sup> Here we dissect how RA affects each component of Virchow's triad.

### Endothelial Injury

Endothelial injury in RA patients primarily occurs secondary to inflammation. It has been linked to the positivity of antiphospholipid antibodies, human leucocyte antigen (HLA) status such as HLA-DRB1\*04:01,<sup>21</sup> and some unusual genotypes of tumor necrosis factor inhibitors (TNF) or plasminogen activator inhibitor-1 (PAI-1).<sup>22</sup>

In the early stages of RA, a pro-inflammatory state plays a major role in endothelial dysfunction by activating endothelial cells, leading to altered endothelial permeability and increased leukocyte and platelet adhesion, resulting in increased monocyte-endothelial interaction.<sup>23</sup> During inflammation, monocytes express intercellular adhesion molecules, which are induced by pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and C-reactive protein (CRP).<sup>23</sup>

The activation of coagulation factors of endothelial origins, such as the von Willebrand factor and PAI-1, may play a significant role in RA and thrombosis.<sup>24</sup>

### Hypercoagulability

In RA patients, inflammation regulates thrombotic responses by three important components: upregulating procoagulants (homocysteine and P-selectin), downregulating anticoagulants (thrombomodulin and protein C and S), and suppressing fibrinolysis.<sup>25</sup>

#### Upregulating Procoagulants

Fibrinogen, D-dimer, cytokines (such as IL-6, IL-8, and TNF), and CRP, considered inflammatory markers, are associated with an increased risk of thrombosis and may play significant roles in VTE.<sup>26</sup> Homocysteine has been increasingly observed in RA and may increase the risk of venous thrombosis.<sup>27</sup> A high homocysteine level is considered to have a modest association with atherothrombosis or venous thrombosis.<sup>28</sup> P-selectin, a member of adhesion receptors that normally generates procoagulant particles and activates platelets, has been an important predictor of VTE development.<sup>29,30</sup> Furthermore, it was found to be an important biomarker in leukocyte-endothelial interaction and RA-related thrombocytosis.<sup>31,32</sup>

#### Downregulating Anticoagulants

Natural anticoagulant mechanisms reduce the thrombotic response but may be depressed by inflammatory mediators. Thrombomodulin is a transmembrane glycoprotein synthesized by vascular endothelial cells and is distributed on the surface of the vein, artery, and capillary endothelial cells. Its gene polymorphism has been associated with an increased risk of VTE.<sup>33</sup> Prothrombotic activities are believed to exert a toxic effect on the endothelium and lead to decreased thrombomodulin expression.<sup>34</sup> Therefore, the protein C pathway is considered a major target. TNF- $\alpha$  specifically downregulates Thrombomodulin and the endothelial cell protein C receptor; while both are needed for optimal protein C activation, they are downregulated by inflammatory mediators. In addition, the protein S glycoprotein is an essential natural anticoagulant for activating the activation protein C pathway, and tissue pathway factor inhibitor can be downregulated in a chronic inflammatory state, resulting in the impaired anticoagulant function of activated protein C.<sup>35,36</sup>

#### Suppressing Fibrinolysis

The thrombin activatable fibrinolysis inhibitor (TAFI) is a proenzyme that activates the fibrinolytic system once activated by factors such as thrombin/plasmin and thrombomodulin.<sup>37</sup> TAFI has been found to be elevated in RA patients compared to controls,<sup>38</sup> especially patients with active inflammation.<sup>39</sup> Therefore, higher activated TAFI may cause a transient hypercoagulable state that leads to VTE.<sup>40</sup>

## Antiphospholipid Antibodies

The expression of antiphospholipid antibodies is considered a risk factor for VTE, arterial thrombosis, and pregnancy-related complications in patients with rheumatic diseases, especially those with background lupus or primary antiphospholipid syndrome (APS).<sup>41</sup> In the case of RA, the literature is scarce, and no solid conclusion has been drawn due to the high variability in the observed results. In a review published in 2006 by Olech and Merrill, the median prevalence of aPL antibodies in RA patients was 22% in samples not exceeding 200 patients, with a few studies showing some relation.<sup>42–44</sup> However, the functionality of these antibodies is questionable. However, their persistence is unknown, as aPL antibodies can result from infection or are induced by drugs such as TNF inhibitors (TNFi).<sup>45</sup>

## Smoking

Smoking is an important environmental risk factor for both RA and VTE.<sup>46,47</sup> Smoking primarily causes a hypercoagulable state through different mechanisms. An increase in procoagulant factors (II, V, VIII, X, and XIII), homocysteine, and tissue factor levels is unbalanced by a decrease in anti-thrombin III and tissue factor pathway inhibitor levels. Epidemiologically, Cigarette smoking (CS), intensity, and duration are directly related to the risk of RA development, even after CS cessation. Di Giuseppe et al found in a meta-analysis including three prospective and seven case-control studies that the risk of developing RA increased by 26% in CS users who smoked 1–10 pack-years and by 94% in those with more than 20 pack-years. A meta-analysis also showed that rheumatoid factor (RF)-positive smokers had a higher risk of RA than RF-negative smokers.<sup>47</sup> On the other hand, Hedström et al conducted a case-control study in a Swedish population with 3655 cases and 5883 controls and showed a dose-dependent increase in RA risk regardless of whether the anti-citrullinated peptide antibodies (ACPA) were positive or negative. When comparing the duration and intensity of CS, duration was found to have a stronger influence on the association between CS and RA.

Two closely published systematic reviews showed an increased risk of VTE in current and former smokers. Cheng et al found a relative risk (RR) of 1.23 (95% CI 1.14–1.33) for current and 1.10 (95% CI 1.03–1.17) for former smokers.<sup>46</sup> Similarly, Zhang et al described an RR of (1.24; 95% CI:1.14–1.35) for current and (1.05; 95% CI:1.01–1.10) for former smokers.<sup>9</sup>

## Hyper-Viscosity and Venous Stasis

The exact mechanisms underlying increased plasma viscosity and subsequent VTE development in RA remain unknown. Two possible factors might explain this phenomenon:

### Intrinsic Factors

Acute-phase reactants are elevated in many autoimmune diseases, including RA, contributing to increased plasma viscosity and risk of thrombosis. This includes CRP, erythrocyte sedimentation rate (ESR), coagulation factor VIII, fibrinogen, and von Willebrand factor.<sup>48</sup>

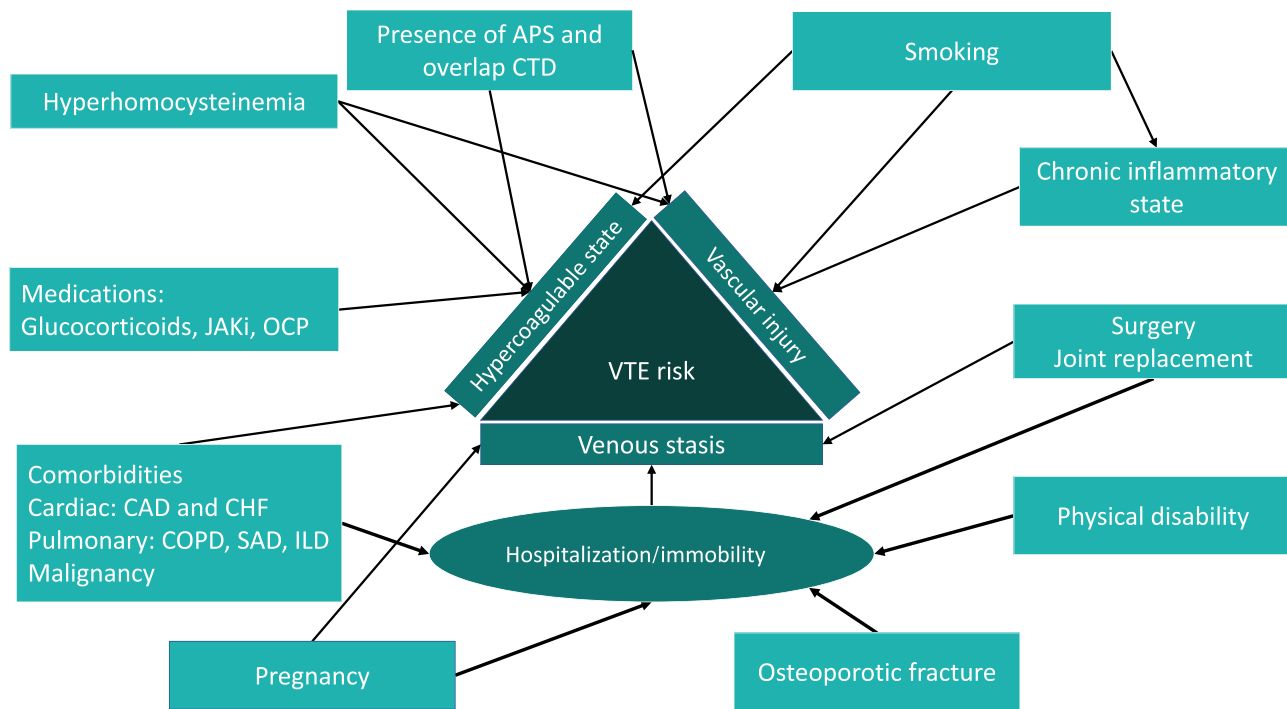
### Immobility

RA causes joint destruction that leads to disability and immobility.<sup>49</sup> Also, RA is the second cause of joint replacement after osteoarthritis,<sup>50</sup> a high-risk surgery for VTE development. Finally, RA patients are at increased risk of infection,<sup>51</sup> osteoporotic fractures,<sup>52</sup> cardiovascular,<sup>53</sup> and pulmonary diseases,<sup>54</sup> all leading to hospitalization and immobility.

Figure 1 shows the interaction between intrinsic and extrinsic risk factors for VTE in patients with RA.

## Risk of VTE in RA Patients

It has been proposed that patients with RA have an increased risk of VTE. Lee and Pope reported a cumulative incidence rate of 2.18% (95% CI:1.82% to 2.54%) and an odds ratio of 2.23 (95% CI: 2.02 to 2.47) compared to age-sex-matched populations of.<sup>55</sup> A recent meta-analysis of nine studies by Ungprastert et al showed a pooled risk ratio of VTE of 1.96 (95% CI 1.81–2.11) in patients with RA.<sup>2</sup> In another systematic review, Hu et al demonstrated similar results, with a doubled OR of VTE (2.23, 95% CI:1.79 to 2.77,  $p < 0.001$ ) compared to control<sup>3</sup> (Table 1). Although recent hospitalization is an established risk factor for VTE,<sup>1,56,57</sup> patients with RA have an increased risk of VTE, irrespective of hospitalization. This risk was well observed in a UK cohort showing a VTE relative risk of 2.16 in outpatient settings.<sup>58</sup>



**Figure 1** Conceptualization framework describing the interaction between intrinsic and extrinsic venous thromboembolism risk factors in rheumatoid arthritis patients. **Abbreviations:** APS, antiphospholipid syndrome; CTD, connective tissue disease; JAKi, Janus kinase inhibitor; OCP, oral contraceptive pills; VTE, venous thromboembolism; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive lung disease; SAD, small airway disease; ILD, interstitial lung disease.

Furthermore, the risk of VTE was increased in RA patients independent of other traditional risk factors, such as chronic comorbidities, recent fractures, and use of oral contraceptive pills.<sup>59,60</sup> In addition, the occurrence of the first VTE was associated with a threefold increased risk of cardiovascular disease in patients.<sup>61</sup> RA disease activity is associated with an increased risk of VTE.<sup>61,62</sup> In a recent Swedish cohort, the risk of VTE increased twofold in patients with evidence of disease activity compared to patients in remission.<sup>62</sup> Although it has been proposed that longer disease duration increases the risk of VTE,<sup>59,63</sup> many studies have shown that the relative risk is higher in the first year and remains relatively stable

**Table 1** Summary of Systematic Reviews Examining Venous Thromboembolism Risk in Rheumatoid Arthritis Patients

First Author	Year	Number of Studies	Inclusion Criteria	Main Outcomes
HU et al <sup>3</sup>	2021	12	Studies evaluating the incidence of VTE, DVT, and PE in RA patients	OR of DVT in RA patients relative to controls: (2.25, 95% CI: 1.70 to 2.98, p<0.001) OR of PE in RA patients relative to controls (2.15, 95% CI: 1.39 to 3.49, p=0.001). OR of VTE in RA patients relative to controls (2.23, 95% CI: 1.79 to 2.77, p<0.001)
Lee and Pope. <sup>55</sup>	2014	10	Studies evaluating the incidence of VTE, DVT, and PE in RA patients	OR of DVT in RA patients relative to controls: 2.23 (95% CI: 2.02 to 2.47) Cumulative incidence of VTE is 2.18% (95% CI: 1.82% to 2.54%)
Ungprasert et al <sup>2</sup>	2014	9	Observational studies (case-control, cross-sectional, cohort) evaluating the association between RA and VTE, DVT or PE	Pooled risk ratio for VTE 1.96 (95% CI 1.81–2.11) Pooled risk ratio for DVT= 2.08 (95% CI 1.75–2.47) Pooled risk ratio for PE= 2.17 (95% CI 2.05–2.31)

**Abbreviations:** RA, rheumatoid arthritis; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; CI, confidence interval; OR, odds ratio.

in subsequent years.<sup>56,58,60,64,65</sup> Several studies have observed an association between increased body mass index and risk of VTE.<sup>56,61,63,66,67</sup> In a recent Italian cohort, obesity was associated with a hazard ratio (HR) of 1.37 for developing VTE.<sup>63</sup> In another study by Ozen et al, obesity was found to be associated with an increased risk of VTE (HR 1.46 (95% CI), (1.13–1.87))<sup>61</sup> (Table 2).

**Table 2** Summary of Major Epidemiological Studies Evaluating Venous Thromboembolism in Rheumatoid Arthritis Patients

First Author	Year	Country	Study Design	Sample Size	Main Outcomes
Matta et al <sup>87</sup>	2009	United States	Cohort	895,873,000	Incident of DVT 0.9 in RA vs 0.4 in non-RA, RR 2.25. Incident of PE 1.6 in RA vs 0.9 in non-RA, RR 1.90. Incident of VTE 2.3 in RA vs 1.1 in non-RA, RR 1.99.
Davies et al <sup>74</sup>	2011	United Kingdom	Cohort	15,554	IR was 3.7/1000 person-year in RA with TNFi vs 3.7/1000 person-year in RA with csDMARD. Adjusted HR of VTE with TNFi group= 0.8.
Kang et al <sup>88</sup>	2012	Taiwan	Case control	25,965	OR of RA in cases of VTE= 1.92 (95% CI, 1.46–2.53; P < 0.001).
Holmqvist et al <sup>64</sup>	2012	Sweden	Prospective cohort study	215,175	Prevalent cohort: IR of VTE was 5.9/1000 person-year in RA vs 2.8/1000 person-year in non-RA, HR= 2. Incident cohort: IR of VTE was 4.5/1000 person-year in RA vs 1.6/1000 person-year in non-RA, HR= 1.6.
Choi et al <sup>58</sup>	2012	United Kingdom	Cohort	105,365	IR of DVT 2.1/1000 patient-year in RA vs 1.0/1000 patient-year in non-RA. IR of PE 1.5/1000 patient-year in RA vs 0.7/1000 patient-year in non-RA. IR for VTE 3.3/1000 patient-year in RA vs 1.5/1000 patient-year in non-RA. RR of VTE in RA after adjustment for multivariate 2.14.
Bacani et al <sup>56</sup>	2012	United States	Cohort	928	Cumulative incidence: DVT 3.1±1.0 in RA vs 1.7±0.9 in non-RA (P value= 0.034) PE 4.8±1.5 in RA vs 1.6±0.7 in non-RA (P value=0.050). VTE 6.7±1.7 in RA vs 2.8±1.1 in non-RA (P value=0.005). Rate of VTE = 7.4/1000 patient-year. HR of VTE= 3.6 (95% confidence interval [95% CI] 1.5–8.6) in RA group.
Chung et al <sup>59</sup>	2013	Taiwan	Cohort	146,190	IR of DVT 1.7/1000 person-years in RA vs 0.322/1000 person-years in non-RA, HR = 3.36. IR of PE 0.36/1000 person-years in RA vs 0.175/1000 in non-RA, HR= 2.07.
Kim et al <sup>67</sup>	2013	United States	Retrospective cohort	110,715	IR of DVT 4.5/1000 person-year in RA vs 2.1/1000 person-year in non-RA, Risk ratio= 2.2. IR of PE 2.6/1000 person-year in RA vs 0.9/1000 person-year in non-RA, Risk ratio= 2.7. IR of VTE 6.1/1000 person-year in RA vs 2.5/1000 person-year in non-RA, Risk ratio= 2.4.
Yusuf et al <sup>89</sup>	2015	United States	Cohort	296,352	IR of VTE was 4.90/1000 person-year in RA vs 1.91/1000 person-year in controls. IR of VTE was 19.74/1000 person-year in autoimmune hemolytic anemia. IR of VTE was 7.72/1000 person-year in immune thrombocytopenic purpura. IR of VTE was 9.89/1000 person-year in lupus patients.

(Continued)

Table 2 (Continued).

First Author	Year	Country	Study Design	Sample Size	Main Outcomes
Ogdie et al <sup>90</sup>	2018	United States	Retrospective Cohort	1,483,705	IR of DVT was 3.7 and 3.4/10,000 person-year in RA with DMARDs vs no DMARDs, respectively, and 2.1/10,000 person-year in non-RA. IR of PE was 1.3 and 0.9/10,000 person-year in RA with DMARDs vs no DMARDs, respectively, and 0.5/10,000 person-year in non-RA. IR of VTE was 4.7 and 4.2/10,000 person-year in RA with DMARDs vs no DMARDs, respectively, and 2.5/10,000 person-year in non-RA. HR of VTE in RA = 1.29 in no DMARD group vs 1.35 in DMARD group.
Mansour et al <sup>91</sup>	2019	Israel	Cohort	69,755	IR of VTE was 6.92% in RA vs 3.18% in non-RA. OR of VTE in RA = 2.27.
Galloway et al <sup>66</sup>	2020	United Kingdom	Cohort	266,890	HR of VTE was 1.54 in RA. HR of PE was 1.57 in RA. HR of DVT was 1.64 in RA vs HR= 1 in control. HR of VTE was 1.27, 1.73, 1.20 in UC, CD, PsA respectively. HR of PE was 1.23, 1.69, 1.34 in UC, CD, PsA respectively. HR of DVT was 1.33, 1.96, 1.34 in UC, CD, PsA respectively. vs HR = 1 in control.
Molander et al <sup>62</sup>	2020	Sweden	Cohort	262,159	IR of DVT 0.45/1000 person-year in RA vs 0.22/1000 person-year in non-RA. IR of PE 0.26/1000 person-year in RA vs 0.14/1000 person-year in non-RA. IR of VTE 0.71/1000 person-year in RA vs 0.36 in non-RA. Adjusted RR for VTE in RA = 1.88. Within RA cohort: IR of VTE was 0.52, 0.63, 0.80, 1.08 in remission, low, intermediate, and high disease activity, respectively. Adjusted RR of VTE was 1.12, 1.48, and 2.03 in low, intermediate, and high disease activity, respectively.
Chen et al <sup>72</sup>	2021	Taiwan	Cohort	28,873	IR of VTE in RA with csDMARD was 12.61/10,000 person-year vs 14.33 was 12.61/10,000 person-year in RA with bDMARDs. HR of VTE in bDMARDs was= 1.11 (not statically significant).
Dore et al <sup>92</sup>	2021	United States	Retrospective cohort		VTE incident in csDMARD naive = 0.8 (0.7 for DVT, 0.3 for PE) VTE incident in csDMARD switchers= 0.7 (0.6 for DVT, 0.3 for PE) VTE incident in bDMARD switchers= 0.9 (0.7 for DVT, 0.3 for PE).
Conforti et al <sup>63</sup>	2021	Italy	Retrospective Cohort		IR of VTE was 7.8 per 1000 person-year in the RA cohort. IR of VTE was 1 per 1000 person-year in the general population from previous data. HR for predictive factors: Age = 1.07 (P value= 0.015) BMI = 1.37 (P value= 0.025) Disease duration= 1.13 (P value= 0.006).

(Continued)

**Table 2** (Continued).

First Author	Year	Country	Study Design	Sample Size	Main Outcomes
Ozen et al <sup>61</sup>	2021	United States	Cohort		Number of VTE events = 539 HR of BMI >30 and VTE= 1.47 HR of steroid use and VTE= 1.99 HR of age >65 and VTE= 2.32 HR of RDCl and VTE= 1.20 HR of recent fracture and VTE= 1.62 HR of hospitalization and VTE= 1.09 HR of recent surgery and VTE= 1.18. HR of moderate/sever disease activity and VTE = 1.31
Li et al <sup>60</sup>	2021	Canada	Cohort	117,220	IR of DVT 2.82 per 1000 person-year in RA vs.1.94/1000 person-year in non-RA. IR of PE 1.43/1000 person-year in RA vs 1.03/1000 person-year in non-RA. IR of VTE 3.79/1000 person-year in RA vs 2.70/1000 person-year in non-RA. Fully adjusted HR of VTE = 1.28.

**Abbreviations:** RA, rheumatoid arthritis; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; CI, confidence interval; OR, odds ratio; RR, relative risk; HR, hazard ratio; IR, incidence rate; DMARDs, disease-modifying anti-rheumatic drugs; csDMARDs, conventional synthetic DMARDs; bDMARDs, biological DMARDs; TNFi, tumor necrosis factor inhibitors; UC, ulcerative colitis; CD, Crohn's disease; PsA, psoriatic arthritis; BMI, body mass index; RDCl, rheumatic disease comorbidity index.

## RA Treatment and the Risk of VTE

Glucocorticoids (GCs) play an essential role in the management of RA. Efforts have been made to limit their use as bridging therapy or during flares;<sup>68</sup> their chronic use is still significant but decreases over time.<sup>69</sup> GC use increases VTE risk 2-3-fold in different patient populations.<sup>70</sup> GCs further increase endothelial injury by decreasing nitric oxide levels and increasing adhesion molecule expression. Finally, GCs cause hypercoagulability by increasing factors II and VIII and the von Willebrand factor, critical procoagulant factors.<sup>71</sup>

bDMARDs have not been linked to an increased risk of VTE in RA.<sup>56,72–75</sup> In a large Chinese cohort studying the risk of VTE with bDMARDs compared to csDMARDs, there was no statistically significant association between biologic use and VTE (HR, 1.11 (95% CI 0.79–1.55); ( $p > 0.05$ )).<sup>72</sup> In another cohort study on the risk of VTE and TNFi use, there was no significant association between TNFi and VTE (HR of TNFi group was 0.8).<sup>74</sup> The significant effect of JAKi on different cytokine pathways may hypothetically reduce the risk of thrombosis. However, the outcome could not be predicted as some cytokines have a pleiotropic effect, and some have both pro- and anti-inflammatory effects.<sup>76</sup> The increased risk was particularly observed in the group treated with tofacitinib 10 mg twice daily in an extensive analysis that included clinical trial programs and the (Consortium of Rheumatology Researchers of North America) CORRONA registry.<sup>77</sup> The Oral Surveillance Study confirmed these findings, a randomized, open-label, non-inferiority, post-authorization, safety end-point trial that compared the long-term safety of tofacitinib 5 mg and 10 mg twice daily compared to TNFi in an enriched population of patients with increased risk for major adverse cardiovascular events and cancer (age  $\geq 50$  years and at least one cardiovascular risk factor). VTE had a numerically higher Hazard ratio for the 5 mg dosing group (HR 1.66 (0.76–3.63)) and a statistically significant Hazard ratio for the 10 mg dosing (HR 3.52 (1.74–7.12)).<sup>78</sup> These findings prompted the Food Drug Administration and the European Medicine Agency to select patients for the entire JAKi class cautiously. In contrast, multiple systematic reviews showed no increased risk of VTE in different JAKi, and variable patient populations compared to controls, even when assessing different dosing arms (Table 3).<sup>79–85</sup> These conflicting findings could be explained by the dilutional effect of low-risk patients in clinical trial programs who are classically young with high disease activity and lack significant comorbidities. In this subset of patients, the anti-cytokine effect of JAKi leads to a reduction in VTE following the control of RA-related inflammation. In patients with multiple risk factors, the impact on the JAK/STAT pathway and the inhibitory effect on some cytokines may be responsible for potentiating the risk of VTE. Therefore, it is important to stratify patients' risk prior to JAKi initiation.<sup>86</sup>



**Table 3** Systematic Reviews Assessing Venous Thromboembolism Risk in Patients Treated with Janus Kinase Inhibitors

First Author	Year	Number of Studies	Inclusion Criteria	Main Outcomes
Alves et al <sup>79</sup>	2022	42	RA RCTs of baricitinib, filgotinib, peficitinib, tofacitinib, and upadacitinib.	No differences were observed between different JAKis regarding the risk of VTE compared with placebo
Bilal et al <sup>80</sup>	2021	29	RCTs of JAK inhibitors, regardless of clinical condition, that reported adverse event data for the treatment and control groups	No association between the use of JAK inhibitors and the risk of VTE (odds ratio, 0.91; 95% CI, 0.57 to 1.47), even when cancer studies were excluded and analysis was stratified according to underlying disease.
Giménez et al <sup>81</sup>	2020	59	RCTs and non-RCTs and controlled cohort studies (prospective or retrospective) comparing oral baricitinib or tofacitinib at any dose with another active drug or placebo in which patients received at least one dose of oral baricitinib or tofacitinib for any indication.	Overall, an odds ratio (OR) for VTE events of 0.29 (95% CI 0.10–0.84) for tofacitinib. -The ORs for VTE events for baricitinib was 3.39 (95% CI 0.82–14.04) overall. -The indirect meta-analysis comparing tofacitinib with baricitinib showed an OR for VTE events of 0.086 (95% CI 0.02–0.51) for tofacitinib and a superior safety profile for VTE events. -In the meta-regression analysis, the effect was 0.02 (95% CI –0.04 to 0.08) for tofacitinib and 0.01 (95% CI –1.29 to 1.26 for baricitinib. -Plotting data for tofacitinib showed that VTE risk increased with high doses. -The effect, however, was less than 1 for the 10- and 20-mg doses, indicating a protective effect. This effect was not observed for baricitinib.
Yates et al <sup>82</sup>	2020	42	RCTs of JAKi therapy with a placebo comparator arm	IRR of VTE, PE and DVT in patients receiving JAKi were 0.68 (95% CI 0.36 to 1.29), 0.44 (95% CI 0.28 to 0.70) and 0.59 (95% CI 0.31 to 1.15), respectively.
Wang et al <sup>83</sup>	2020	20	RTCs of tofacitinib or baricitinib, or upadacitinib in RA patients	VTE data were unavailable for tofacitinib or baricitinib, but there was no increase in risk with upadacitinib (15 mg daily: RR, 2.34; 95% CI, 0.34 to 15.92).
Xie et al <sup>84</sup>	2019	29	RCTs in adult patients with immune-mediated inflammatory disorders using tofacitinib	There was a decreased rate of VTEs (OR 0.03, 95% CI 0.00–0.21) in patients initiating tofacitinib. Tofacitinib 10 twice daily was associated with an increase in VTEs risk (OR = 1.47, 95% CI 0.25–8.50) compared with the 5 mg regimen.
Xie et al	2019	25 for placebo comparison 18 for dose dependence	RTCs of tofacitinib or baricitinib, or upadacitinib in RA patients	There was no increased risk of VTEs in users of the 3 JAKi (OR 1.16 (0.48 to 2.81), p = 0.74). There was no dose dependent increase of VTE in any JAKi

**Abbreviations:** RCT, randomized controlled trial; RA, rheumatoid arthritis; JAKi, Janus kinase inhibitor; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; CI, confidence interval; OR, odds ratio; RR, relative risk; HR, hazard ratio; IR, incident rate.



## Conclusion

The increased risk of VTE in RA patients can be explained by a complex interaction between intrinsic and extrinsic factors. Therefore, Modification of risk factors, adequate disease control, and appropriate risk stratification is recommended for VTE prevention.

## Disclosure

Mohammed A. Omar received speaker honoraria from Abbvie, Actelion, Amgen, Bristol Myers Squibb, Glaxo-Smith-Kline, Hekma, Janssen, Lilly, New Bridge, Novartis, Pfizer, and Roche. The other authors have no conflicts of interest to declare.

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